Clinical trial results:
INTELLANCE-2: ABT-414 Alone or ABT-414 plus Temozolomide Versus Lomustine or Temozolomide for Recurrent Glioblastoma: A Randomized Phase 2 Study of the EORTC Brain Tumor Group

Summary

EudraCT number	2014-004438-24
Trial protocol	NL DE HU AT FI GB IE ES BE CZ FR PL IT
Global end of trial date	24 June 2019

Results information

Result version number	v1
This version publication date	05 January 2020
First version publication date	05 January 2020

Trial information

Trial identification

Sponsor protocol code	M14-483

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02343406
WHO universal trial number (UTN)	-
Other trial identifiers	1410-BTG: EORTC Protocol Number

Notes:

Sponsors

Sponsor organisation name	AbbVie
Sponsor organisation address	1 North Waukegan Road, North Chicago, IL, United States, 60064
Public contact	Global Medical Services, AbbVie, 001 800-633-9110,
Scientific contact	Jim Looman, AbbVie, jim.looman@abbvie.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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The study objectives were to assess whether depatuxizumab mafodotin (ABT-414) alone or in combination with temozolomide (TMZ) improved overall survival (OS), progression-free survival (PFS), tumor response, quality of life, neurological deterioration-free survival (NDFS), and steroid use compared to standard treatment with lomustine single agent or TMZ re-challenge in adult subjects ≥ 18 years of age with centrally-confirmed recurrent epidermal growth factor receptor (EGFR)-amplified glioblastoma. The safety, pharmacokinetics, and efficacy of depatuxizumab mafodotin in children <18 years of age was evaluated in a pediatric substudy. The EMEA-001732-PIP02-15 pediatric investigation plan was withdrawn on 07 July 2019 due to the discontinuation of the depatuxizumab mafodotin research program.

Protection of trial subjects:

Participant and/or legal guardian read and understood information provided about the study and gave written permission.

Background therapy:

Due to the risk of eye toxicity, each administration of depatuxizumab mafodotin was to be given with a steroid ophthalmic solution. The recommended type, dose, and schedule of eye drops was as follows: dexamethasone 0.1% solution, 2 drops (gtts) in each eye (OU) every 8 (q8) hours to start 48 hours prior to depatuxizumab mafodotin dosing and continue for a total of 7 days (or 21 doses total). The type of ophthalmic solution used may have varied depending on the availability of the solution at each location. A modification to the eye drop dosing or schedule based on ongoing clinical experience may have been suggested.

Evidence for comparator: -

Actual start date of recruitment	01 December 2014
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	Australia: 20
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 16
Country: Number of subjects enrolled	Czech Republic: 3
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 9
Country: Number of subjects enrolled	Ireland: 7
Country: Number of subjects enrolled	Italy: 25

Country: Number of subjects enrolled	Korea, Republic of: 12
Country: Number of subjects enrolled	Netherlands: 32
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Singapore: 2
Country: Number of subjects enrolled	Spain: 19
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	United States: 27
Worldwide total number of subjects	275
EEA total number of subjects	202

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)	4
Adolescents (12-17 years)	2
Adults (18-64 years)	204
From 65 to 84 years	65
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study included a 30-day screening period.

Pre-assignment

Screening details:

Randomized adult subjects: histologically confirmed glioblastoma with unequivocal first progression after radiation therapy, concurrent/adjuvant TMZ chemotherapy, and presence of EGFR amplification.
Pediatric subjects: histologically proven high grade glioma, grade IV glioma, or DIPG and presence of EGFR amplification.

Period 1

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

Blinding implementation details:

In the subject disposition table, "Completed" and "Not completed" refer to study drug treatment, and the reasons not completed listings refer to study drug treatment.

Arms

Are arms mutually exclusive?	Yes
Arm title	ABT-414/temozolomide

Arm description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks in combination with temozolomide (TMZ) to adult subjects

Arm type	Experimental
Investigational medicinal product name	Depatuxizumab mafodotin
Investigational medicinal product code	
Other name	ABT-414
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous administration (1.25 mg/kg or 1.0 mg/kg body weight) over 30 to 40 minutes once every 2 weeks until one of the treatment withdrawal criteria was met. The dose was 1.25 mg/kg in the original protocol (Version 1) and Version 2, Amendment 1, and was lowered to 1.0 mg/kg in protocol Version 3, Amendment 2.

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

Dosage and administration details:

150 mg/m^2 on Days 1-5 for the first 28-day cycle, with dose escalation to 200 mg/m^2 in subsequent cycles in case of adequate tolerance until one of the treatment withdrawal criteria was met.

Arm title	ABT-414_adult

Arm description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to adult subjects

Arm type	Experimental

Investigational medicinal product name	Depatuxizumab mafodotin
Investigational medicinal product code	
Other name	ABT-414
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous administration (1.25 mg/kg or 1.0 mg/kg body weight) over 30 to 40 minutes once every 2 weeks until one of the treatment withdrawal criteria was met. The dose was 1.25 mg/kg in the original protocol (Version 1) and Version 2, Amendment 1, and was lowered to 1.0 mg/kg in protocol Version 3, Amendment 2.

Arm title	Control_lomustine

Arm description:

Adult subjects relapsing during temozolomide (TMZ) treatment or within the first 16 weeks after the first day of the last TMZ cycle received lomustine on Day 1 of every 42-day treatment period until one of the treatment withdrawal criteria was met, up to a maximum of 1 year.

Arm type	Active comparator
Investigational medicinal product name	Lomustine
Investigational medicinal product code	
Other name	Gleostine
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

110 mg/m^2 on Day 1 of every 42-day treatment period. Treatment continued until one of the treatment withdrawal criteria was met, for a maximum of one year.

Arm title	Control_ temozolomide

Arm description:

Adult subjects relapsing 16 weeks or more after the first day of the last temozolomide (TMZ) cycle received TMZ on Day 1 to Day 5 for the first 28-day cycle, with dose escalation in subsequent cycles in case of adequate tolerance and treatment continuing until one of the treatment withdrawal criteria was met.

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

Dosage and administration details:

150 mg/m^2 on Day 1 to Day 5 for the first 28-day cycle, with dose escalation to 200 mg/m^2 in subsequent cycles in case of adequate tolerance. Treatment continued until one of the treatment withdrawal criteria was met.

Arm title	ABT-414_ pediatric

Arm description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to pediatric subjects. Temozolomide (TMZ) was only allowed for pediatric subjects if its use was in accordance with local clinical practice, and was not considered an investigational product for the study (unless this was a local requirement).

Arm type	Experimental
Investigational medicinal product name	Depatuxizumab mafodotin
Investigational medicinal product code	
Other name	ABT-414
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Intravenous administration (1.0 mg/kg body weight for subjects who are 6 to 17 years old at the date of first depatuxizumab mafodotin dose, or 1.3 mg/kg for subjects who are 0 to 5 years old) over 30 to 40 minutes or as directed by the administration guidelines once every 2 weeks until one of the treatment withdrawal criteria was met, for a maximum of one year. If depatuxizumab mafodotin was used in combination with temozolomide (TMZ), depatuxizumab mafodotin was dosed on Day 1 and Day 15 of the TMZ cycle (assuming a standard regimen of 200 mg/m^2/day for 5 days of each 28-day cycle; for other TMZ schedules, timing of the depatuxizumab mafodotin dosing schedule were to be discussed with the medical monitor).

Number of subjects in period 1[1]	ABT-414/temozolomide	ABT-414_adult	Control_lomustine
Started	88	86	60
Completed	0	0	2
Not completed	88	86	58
Other primary malignancy	-	1	-
Adverse event, non-fatal	15	8	6
Death	2	1	-
Other, not specified	8	1	1
Start of a new anti-cancer treatment	-	1	-
Progressive disease	56	70	43
Withdrawal by subject	7	4	8

Number of subjects in period 1[1]	Control_ temozolomide	ABT-414_ pediatric
Started	26	6
Completed	0	1
Not completed	26	5
Other primary malignancy	-	-
Adverse event, non-fatal	3	-
Death	-	-
Other, not specified	4	-
Start of a new anti-cancer treatment	1	-
Progressive disease	15	5
Withdrawal by subject	3	-

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: Nine of the 275 enrolled adult subjects did not have a screen failure form reported and were not randomized. A total of 260 adult and 6 pediatric subjects were randomized.

Baseline characteristics

Reporting groups	
Reporting group title	ABT-414/temozolomide
Reporting group description:	
Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks in combination with temozolomide (TMZ) to adult subjects	
Reporting group title	ABT-414_adult
Reporting group description:	
Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to adult subjects	
Reporting group title	Control_lomustine
Reporting group description:	
Adult subjects relapsing during temozolomide (TMZ) treatment or within the first 16 weeks after the first day of the last TMZ cycle received lomustine on Day 1 of every 42-day treatment period until one of the treatment withdrawal criteria was met, up to a maximum of 1 year.	
Reporting group title	Control_ temozolomide
Reporting group description:	
Adult subjects relapsing 16 weeks or more after the first day of the last temozolomide (TMZ) cycle received TMZ on Day 1 to Day 5 for the first 28-day cycle, with dose escalation in subsequent cycles in case of adequate tolerance and treatment continuing until one of the treatment withdrawal criteria was met.	
Reporting group title	ABT-414_ pediatric
Reporting group description:	
Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to pediatric subjects. Temozolomide (TMZ) was only allowed for pediatric subjects if its use was in accordance with local clinical practice, and was not considered an investigational product for the study (unless this was a local requirement).	

Reporting group values	ABT-414/temozolomide	ABT-414_adult	Control_lomustine
Number of subjects	88	86	60
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	57.9	58.1	57.8
standard deviation	± 8.15	± 9.18	± 10.62
Gender categorical			
Units: Subjects			
Female	29	36	19
Male	59	50	41

Reporting group values	Control_ temozolomide	ABT-414_ pediatric	Total
Number of subjects	26	6	266
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	55.9	10.5	

standard deviation	± 11.04	± 5.43	-

Gender categorical Units: Subjects			
Female	9	5	98
Male	17	1	168

End points

End points reporting groups

Reporting group title	ABT-414/temozolomide

Reporting group description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks in combination with temozolomide (TMZ) to adult subjects

Reporting group title	ABT-414_adult

Reporting group description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to adult subjects

Reporting group title	Control_lomustine

Reporting group description:

Adult subjects relapsing during temozolomide (TMZ) treatment or within the first 16 weeks after the first day of the last TMZ cycle received lomustine on Day 1 of every 42-day treatment period until one of the treatment withdrawal criteria was met, up to a maximum of 1 year.

Reporting group title	Control_ temozolomide

Reporting group description:

Adult subjects relapsing 16 weeks or more after the first day of the last temozolomide (TMZ) cycle received TMZ on Day 1 to Day 5 for the first 28-day cycle, with dose escalation in subsequent cycles in case of adequate tolerance and treatment continuing until one of the treatment withdrawal criteria was met.

Reporting group title	ABT-414_ pediatric

Reporting group description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to pediatric subjects. Temozolomide (TMZ) was only allowed for pediatric subjects if its use was in accordance with local clinical practice, and was not considered an investigational product for the study (unless this was a local requirement).

Subject analysis set title	Control (Temozolomide/Lomustine)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Adult subjects relapsing during temozolomide (TMZ) treatment or within the first 16 weeks after the first day of the last TMZ cycle who received lomustine on Day 1 of every 42-day treatment period until one of the treatment withdrawal criteria was met, up to a maximum of 1 year OR adult subjects relapsing 16 weeks or more after the first day of the last temozolomide (TMZ) cycle who received TMZ on Day 1 to Day 5 for the first 28-day cycle, with dose escalation in subsequent cycles in case of adequate tolerance and treatment continuing until one of the treatment withdrawal criteria was met.

Primary: Pediatric study: Maximum observed serum concentration (Cmax) of ABT-414

End point title	Pediatric study: Maximum observed serum concentration (Cmax) of ABT-414[1][2]

End point description:

Cmax is the peak concentration that a drug achieves in a specified compartment after the drug has been administrated and before administration of a second dose.

End point type	Primary

End point timeframe:

Samples collected Cycle 1 Days 1, 2,3,5,8,15; Cycle 2 Day 1; Cycle 3 Day 1; Cycle 5 Day 1; Day 1 of every two cycles starting with Cycle 5; and 35 days after the last dose

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: Statistical analysis was not applicable for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	5[3]			
Units: µg/mL				
arithmetic mean (standard deviation)	31.4 (± 15.0)			

Notes:

[3] - Pediatric subjects with available data

Statistical analyses

No statistical analyses for this end point

Primary: Adult study: Progression-Free Survival (PFS)

End point title	Adult study: Progression-Free Survival (PFS)[4]

End point description:

Progression-free survival was assessed per response assessment in neuro-oncology criteria (RANO) criteria and assessed by an independent review committee and was defined as the length of time during and after the treatment of a disease, that the participant lived with the disease but did not get worse.

End point type	Primary

End point timeframe:

Measured every 8 weeks from date of randomization until the date of first objective progression or subject's death, whichever occurred first, up to 2 years

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Progression-Free Survival was analyzed using the data sets reported in this end point.

End point values	ABT-414/temozolomide	ABT-414_adult	Control (Temozolomide /Lomustine)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	88[5]	86[6]	86[7]	
Units: months				
number (confidence interval 95%)				
25th quartile	1.8 (1.7 to 2.0)	1.5 (1.1 to 1.7)	1.6 (1.3 to 1.7)	
50th quartile	2.7 (2.0 to 3.8)	1.9 (1.8 to 2.0)	1.9 (1.9 to 2.2)	
75th quartile	4.9 (3.9 to 9.3)	3.5 (2.1 to 3.9)	4.2 (3.4 to 5.8)	

Notes:

[5] - All randomized adult participants

[6] - All randomized adult participants

[7] - All randomized adult participants

Statistical analyses

Statistical analysis title	ABT-414/temozolomide vs Control (TMZ/Lomustine)
Comparison groups	ABT-414/temozolomide v Control (Temozolomide/Lomustine)
Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.123
Method	Log rank test
Parameter estimate	Cox proportional hazard
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.07

Statistical analysis title	ABT-414_adult vs Control (TMZ/Lomustine)
Comparison groups	ABT-414_adult v Control (Temozolomide/Lomustine)
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.117
Method	Log rank test
Parameter estimate	Cox proportional hazard
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.84

Primary: Pediatric study: Area Under the Concentration-time-curve (AUC) observed for unconjugated Cys-mcMMAF

End point title	Pediatric study: Area Under the Concentration-time-curve (AUC) observed for unconjugated Cys-mcMMAF[8][9]

End point description:

AUC is a measure of how long and how much drug or drug metabolite is present in the body after dosing. The AUC of Cys-mcMMAF, a toxic metabolite of depatuxizumab mafodotin, in the pediatric population was measured following treatment to confirm that this was comparable to adults, and that the dosing levels are appropriate for a pediatric population.

End point type	Primary

End point timeframe:

Samples collected Cycle 1 Days 1, 2, 3, 5, 8

Notes:

[8] - 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: Statistical analysis was not applicable for this endpoint.

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	5[10]			
Units: ng*h/mL				
arithmetic mean (standard deviation)	14.1 (± 6.22)			

Notes:

[10] - Pediatric subjects with available data

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric study: Area Under the Concentration-time Curve (AUC) observed for ABT-414

End point title	Pediatric study: Area Under the Concentration-time Curve (AUC) observed for ABT-414[11][12]

End point description:

AUC is a measure of how long and how much drug is present in the body after dosing. The AUC of depatuxizumab mafodotin (ABT-414) in the pediatric population was measured following treatment to confirm that this was comparable to adults, and that the dosing levels are appropriate for a pediatric population.

End point type	Primary

End point timeframe:

Samples collected Cycle 1 Days 1, 2,3,5,8,15; Cycle 2 Day 1; Cycle 3 Day 1; Cycle 5 Day 1; Day 1 of every two cycles starting with Cycle 5; and 35 days after the last dose

Notes:

[11] - 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: Statistical analysis was not applicable for this endpoint.

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	5[13]			
Units: µg*h/mL				
arithmetic mean (standard deviation)	3170 (± 1320)			

Notes:

[13] - Pediatric subjects with available data

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric study: Half-life (t1/2) observed for ABT-414

End point title	Pediatric study: Half-life (t1/2) observed for ABT-414[14][15]

End point description:

Half-life is the calculated time it takes for half of the drug to leave the body.

End point type	Primary

End point timeframe:

Samples collected Cycle 1 Days 1, 2,3,5,8,15; Cycle 2 Day 1; Cycle 3 Day 1; Cycle 5 Day 1; Day 1 of every two cycles starting with Cycle 5; and 35 days after the last dose

Notes:

[14] - 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: Statistical analysis was not applicable for this endpoint.

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	4[16]			
Units: days				
arithmetic mean (standard deviation)	9.0 (± 1.5)			

Notes:

[16] - Pediatric subjects with available data

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric study: Maximum observed plasma concentration (Cmax) of Cys-mcMMAF

End point title	Pediatric study: Maximum observed plasma concentration (Cmax) of Cys-mcMMAF[17][18]

End point description:

Cmax is the peak concentration that a drug or drug metabolite achieves in a specified compartment after the drug has been administrated and before administration of a second dose. Cys-mcMMAF is a toxic metabolite of depatuxizumab mafodotin.

End point type	Primary

End point timeframe:

Samples collected Cycle 1 Days 1, 2, 3, 5, 8

Notes:

[17] - 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: Statistical analysis was not applicable for this endpoint.

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	5[19]			
Units: ng/mL				
arithmetic mean (standard deviation)	0.272 (± 0.0983)			

Notes:

[19] - Pediatric subjects with available data

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric study: Half-life (t1/2) observed for Cys-mcMMAF

End point title	Pediatric study: Half-life (t1/2) observed for Cys-mcMMAF[20][21]

End point description:

Half-life is the calculated time it takes for half of the drug or drug metabolite to leave the body. Cys-mcMMAF is a toxic metabolite of depatuxizumab mafodotin.

End point type	Primary

End point timeframe:

Samples collected Cycle 1 Days 1, 2, 3, 5, 8

Notes:

[20] - 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: Statistical analysis was not applicable for this endpoint.

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	2[22]			
Units: days				
arithmetic mean (standard deviation)	11.2 (± 22.9)			

Notes:

[22] - Pediatric subjects with available data

Statistical analyses

No statistical analyses for this end point

Primary: Pediatric study: Percentage of participants with adverse events from the first visit until 49 days after the last dose of study drug

End point title	Pediatric study: Percentage of participants with adverse events from the first visit until 49 days after the last dose of study drug[23][24]

End point description:

The severity of each adverse event was rated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0)

End point type	Primary

End point timeframe:

From participant's first visit until 49 days after the participant's last dose of study drug

Notes:

[23] - 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: Statistical analysis was not applicable for this endpoint.

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	6[25]			
Units: Percentage of participants				
number (not applicable)	100			

Notes:

[25] - Pediatric subjects (safety population)

Statistical analyses

No statistical analyses for this end point

Primary: Adult study: Overall Survival (OS)

End point title	Adult study: Overall Survival (OS)[26]

End point description:

Overall Survival (OS) was defined as time from randomization to death due to any cause, regardless of whether the event occurred on or off study drug (depatuxizumab mafodotin/temozolomide/lomustine).

End point type	Primary

End point timeframe:

From the date of randomization up to the date of participant's death; participants who completed treatment were to be assessed every 12 weeks, up to 28 months.

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Overall survival was analyzed using the data sets reported in this end point.

End point values	ABT-414/temozolomide	ABT-414_adult	Control (Temozolomide /Lomustine)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	88[27]	86[28]	86[29]	
Units: months				
number (confidence interval 95%)				
25th quartile	5.7 (4.0 to 6.8)	4.6 (3.5 to 5.5)	4.9 (4.1 to 5.4)	
50th quartile	9.6 (7.4 to 11.8)	7.9 (6.1 to 8.7)	8.2 (5.9 to 9.5)	
75th quartile	16.9 (14.4 to 999)	15.5 (10.2 to 19.0)	12.6 (10.2 to 14.9)	

Notes:

[27] - All randomized adult participants; 999= not calculable

[28] - All randomized adult participants

[29] - All randomized adult participants

Statistical analyses

Statistical analysis title	ABT-414/temozolomide vs Control (TMZ/Lomustine)

Statistical analysis description:

Stratified at randomization by regions of the world (North America, Europe and Australia, Asia/Other Regions), WHO performance status (0, > 0), timing of relapse (< 16 weeks, ≥ 16 weeks after first day of last TMZ cycle).

Comparison groups	ABT-414/temozolomide v Control (Temozolomide/Lomustine)

Number of subjects included in analysis	174
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.062
Method	Log rank test
Parameter estimate	Cox proportional hazard
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	1.02

Statistical analysis title	ABT-414_adult vs Control (TMZ/Lomustine)

Statistical analysis description:

Stratified at randomization by regions of the world (North America, Europe and Australia, Asia/Other Regions), WHO performance status (0, > 0), timing of relapse (< 16 weeks, ≥ 16 weeks after first day of last TMZ cycle).

Comparison groups	ABT-414_adult v Control (Temozolomide/Lomustine)
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.835
Method	Log rank test
Parameter estimate	Cox proportional hazard
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	1.48

Secondary: Adult study: Objective Response Rate (ORR)

End point title	Adult study: Objective Response Rate (ORR)[30]

End point description:

The objective response rate (ORR) included best overall responses – complete response (CR) and partial response (PR) – assessed by the independent review committee per response assessment in neuro-oncology criteria (RANO) criteria from the date of randomization until disease progression or death, whichever came first. All objective responses (CR and PR) must be have been confirmed by repeat MRI 4 weeks after the first time when CR or PR is identified. Any subject who did not meet CR or PR including those who did not have post-baseline radiological assessments was considered a nonresponder.

End point type	Secondary

End point timeframe:

Every 8 weeks at each assessment of disease, up to 28 months

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Objective Response Rate was analyzed using the data sets reported in this end point.

End point values	ABT-414/temozolomide	ABT-414_adult	Control (Temozolomide/Lomustine)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	49[31]	39[32]	45[33]	
Units: Percentage of participants				
number (confidence interval 95%)	14.3 (5.9 to 27.2)	7.7 (1.6 to 20.9)	4.4 (0.5 to 15.1)	

Notes:

[31] - Subjects with measurable disease at baseline

[32] - Subjects with measurable disease at baseline

[33] - Subjects with measurable disease at baseline

Statistical analyses

Statistical analysis title	ABT-414/temozolomide vs Control (TMZ/Lomustine)
Comparison groups	ABT-414/temozolomide v Control (Temozolomide/Lomustine)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	= 0.06
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	16.16

Notes:

[34] - Comparison is based on Cochran-Mantel-Haenszel method with stratification factors. Stratified at randomization by regions of the world (North America, Europe and Australia, Asia/Other Regions), WHO performance status (0, > 0), timing of relapse (< 16 weeks, ≥ 16 weeks after first day of last TMZ cycle).

Statistical analysis title	ABT-414_adult vs Control (TMZ/Lomustine)
Comparison groups	ABT-414_adult v Control (Temozolomide/Lomustine)
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other[35]
P-value	= 0.767
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.21

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	12.49

Notes:

[35] - Comparison is based on Cochran-Mantel-Haenszel method with stratification factors. Stratified at randomization by regions of the world (North America, Europe and Australia, Asia/Other Regions), WHO performance status (0, > 0), timing of relapse (< 16 weeks, ≥ 16 weeks after first day of last TMZ cycle).

Secondary: Pediatric study: Overall Survival

End point title	Pediatric study: Overall Survival[36]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, the pediatric substudy OS analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

From the date of enrollment to the date of death; participants who completed treatment were to be assessed every 12 weeks, up to 28 months.

Notes:

[36] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[37]			
Units: months				
number (confidence interval 95%)	(to)			

Notes:

[37] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric study: Objective Response Rate (ORR)

End point title	Pediatric study: Objective Response Rate (ORR)[38]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, the pediatric substudy ORR analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

Evaluated every 8 weeks (+/- 7 days) at each assessment of disease according to response assessment

in neuro-oncology criteria (RANO), until progression or withdrawal up to approximately 52 weeks

Notes:

[38] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[39]			
Units: Percentage of participants				
number (confidence interval 95%)	(to)			

Notes:

[39] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric study: Percentage of Participants With Changes in Neurological Status and Function

End point title	Pediatric study: Percentage of Participants With Changes in Neurological Status and Function[40]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, the pediatric neurological status and function data analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

Baseline, Day 1 and 15 of each cycle, every 6 months for 5 years thereafter, and then annually

Notes:

[40] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[41]			
Units: Percentage of participants				
number (not applicable)				

Notes:

[41] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Secondary: Adult study: Overall Survival in the Subgroup with Epidermal Growth Factor Receptor (EGFRvIII) Mutation

End point title	Adult study: Overall Survival in the Subgroup with Epidermal Growth Factor Receptor (EGFRvIII) Mutation[42]

End point description:

Overall Survival (OS) was defined as time from randomization to death due to any cause, regardless of whether the event occurred on or off study drug (depatuxizumab mafodotin/temozolomide/lomustine) for all randomized participants that had the Epidermal Growth Factor Receptor (EGFRvIII) mutation.

End point type	Secondary

End point timeframe:

From the date of randomization up to the date of participant's death; participants who completed treatment were to be assessed every 12 weeks, up to 28 months.

Notes:

[42] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Overall survival was analyzed using the data sets reported in this end point.

End point values	ABT-414/temozolomide	ABT-414_adult	Control (Temozolomide /Lomustine)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	39[43]	36[44]	47[45]	
Units: months				
number (confidence interval 95%)				
25th quartile	6.3 (3.1 to 7.4)	5.0 (3.1 to 5.9)	4.7 (3.0 to 5.8)	
50th quartile	9.4 (7.1 to 11.0)	8.4 (5.5 to 9.0)	7.5 (5.1 to 9.6)	
75th quartile	14.4 (10.3 to 999)	13.9 (8.7 to 999)	12.4 (9.5 to 16.2)	

Notes:

[43] - Randomized subjects with EGFRvIII-mutated tumors; 999=not calculable

[44] - Randomized subjects with EGFRvIII-mutated tumors; 999=not calculable

[45] - EGFRvIII-mutated population: randomized subjects with EGFRvIII-mutated tumors

Statistical analyses

Statistical analysis title	ABT-414/temozolomide vs Control (TMZ/Lomustine)
Comparison groups	ABT-414/temozolomide v Control (Temozolomide/Lomustine)
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.127
Method	Log rank test
Parameter estimate	Cox proportional hazard
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.13

Statistical analysis title	ABT-414_adult vs Control (TMZ/Lomustine)
Comparison groups	ABT-414_adult v Control (Temozolomide/Lomustine)
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.64
Method	Log rank test
Parameter estimate	Cox proportional hazard
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	1.49

Secondary: Pediatric study: Best Tumor Response Rate

End point title	Pediatric study: Best Tumor Response Rate[46]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, the pediatric best tumor response rate data analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

Evaluated every 8 weeks (+/- 7 days) at each assessment of disease according to response assessment in neuro-oncology criteria (RANO), until progression or withdrawal up to approximately 52 weeks

Notes:

[46] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[47]			
Units: Percentage of participants				
number (confidence interval 95%)	(to)			

Notes:

[47] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric study: Duration of Response

End point title	Pediatric study: Duration of Response[48]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, pediatric duration of response data analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

Evaluated every 8 weeks (+/- 7 days) at each assessment of disease according to response assessment in neuro-oncology criteria (RANO), until progression or withdrawal up to approximately 52 weeks

Notes:

[48] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[49]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[49] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric study: Time to Progression

End point title	Pediatric study: Time to Progression[50]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, pediatric time to progression data analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

Evaluated every 8 weeks (+/- 7 days) from the date of enrollment until the date of first objective progression or participant’s death, whichever occurs first, up to approximately 52 weeks

Notes:

[50] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[51]			
Units: months				
median (confidence interval 95%)	(to)			

Notes:

[51] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric study: Progression-Free Survival (PFS)

End point title	Pediatric study: Progression-Free Survival (PFS)[52]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, pediatric progression-free survival data analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

Evaluated every 8 weeks (+/- 7 days) from the date of enrollment until the date of first objective progression or participant’s death, whichever occurs first, up to approximately 52 weeks

Notes:

[52] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[53]			
Units: months				
number (confidence interval 95%)	(to)			

Notes:

[53] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Secondary: Pediatric study: Mean Change in Pediatric Quality of Life Inventory (PedsQL) Scores

End point title	Pediatric study: Mean Change in Pediatric Quality of Life Inventory (PedsQL) Scores[54]

End point description:

The pediatric data collection for this study was still ongoing when INTELLANCE-1 (EudraCT number 2015-001166-26; NCT02573324) interim efficacy results overall indicated no survival benefit to adding depatuxizumab mafodotin to standard radiotherapy/ temozolomide therapy in newly diagnosed glioblastoma multiforme patients. Based on the INTELLANCE-1 results, AbbVie decided to stop further

enrollment of pediatric patients into the pediatric substudy and to stop the collection of efficacy data. Because of this decision not to summarize except for safety data, mean change in pediatric quality of life inventory scores data analysis was not summarized due to the small number of pediatric subjects enrolled in the study.

End point type	Secondary

End point timeframe:

Baseline, Week 16 on treatment, and 6 months

Notes:

[54] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This is a pediatric substudy-specific endpoint.

End point values	ABT-414_ pediatric			
Subject group type	Reporting group			
Number of subjects analysed	0[55]			
Units: units on a scale				
arithmetic mean (standard deviation)	()			

Notes:

[55] - Pediatric data except safety were not summarized when INTELLANCE-1 deemed futile

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) and serious adverse events (TESAEs) were collected from the time of study drug administration until 35 days (adults) or 49 days (pediatric subjects) after the last dose of study drug, up to 125 weeks.

Adverse event reporting additional description:

Serious and non-serious adverse events occurring after the subject signed the study-specific informed consent and prior to the initial dose of study drug were to be collected only if they were considered by the Investigator to be causally related to required study procedures.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	ABT-414/temozolomide

Reporting group description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks in combination with temozolomide (TMZ) to adult subjects

Reporting group title	ABT-414_adult

Reporting group description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to adult subjects

Reporting group title	Control_lomustine

Reporting group description:

Adult subjects relapsing during temozolomide (TMZ) treatment or within the first 16 weeks after the first day of the last TMZ cycle received lomustine on Day 1 of every 42-day treatment period until one of the treatment withdrawal criteria was met, up to a maximum of 1 year.

Reporting group title	Control_ temozolomide

Reporting group description:

Adult subjects relapsing 16 weeks or more after the first day of the last temozolomide (TMZ) cycle received TMZ on Day 1 to Day 5 for the first 28-day cycle, with dose escalation in subsequent cycles in case of adequate tolerance and treatment continuing until one of the treatment withdrawal criteria was met.

Reporting group title	ABT-414_ pediatric

Reporting group description:

Depatuxizumab mafodotin (ABT-414) administered once every 2 weeks to pediatric subjects. Temozolomide (TMZ) was only allowed for pediatric subjects if its use was in accordance with local clinical practice, and was not considered an investigational product for the study (unless this was a local requirement).

Serious adverse events	ABT-414/temozolomide	ABT-414_adult	Control_lomustine
Total subjects affected by serious adverse events			
subjects affected / exposed	39 / 88 (44.32%)	30 / 84 (35.71%)	19 / 56 (33.93%)
number of deaths (all causes)	80	80	52
number of deaths resulting from adverse events	12	9	3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT NEOPLASM PROGRESSION			

subjects affected / exposed	11 / 88 (12.50%)	7 / 84 (8.33%)	2 / 56 (3.57%)
occurrences causally related to treatment / all	0 / 16	0 / 10	0 / 4
deaths causally related to treatment / all	0 / 7	0 / 6	0 / 2
METASTASES TO PERITONEUM			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
NEOPLASM PROGRESSION			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TUMOUR HAEMORRHAGE			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBGALEAL HAEMATOMA			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FATIGUE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PYREXIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
HYPOXIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA ASPIRATION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONITIS			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
PULMONARY EMBOLISM			
subjects affected / exposed	3 / 88 (3.41%)	0 / 84 (0.00%)	2 / 56 (3.57%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			
COMPLETED SUICIDE			

subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
CONFUSIONAL STATE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDAL IDEATION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BODY TEMPERATURE INCREASED			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
FALL			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HIP FRACTURE			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PELVIC FRACTURE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
APHASIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
APRAXIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BRAIN OEDEMA			
subjects affected / exposed	2 / 88 (2.27%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CEREBROVASCULAR ACCIDENT			

subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
EPILEPSY			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERALISED TONIC-CLONIC SEIZURE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 88 (0.00%)	2 / 84 (2.38%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	2 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
HEADACHE			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPARESIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEMIPLEGIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYDROCEPHALUS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MUSCLE SPASTICITY			

subjects affected / exposed	2 / 88 (2.27%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	0 / 88 (0.00%)	2 / 84 (2.38%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NEUROLOGICAL DECOMPENSATION			
subjects affected / exposed	0 / 88 (0.00%)	3 / 84 (3.57%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PARTIAL SEIZURES			
subjects affected / exposed	1 / 88 (1.14%)	2 / 84 (2.38%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEIZURE			
subjects affected / exposed	9 / 88 (10.23%)	3 / 84 (3.57%)	4 / 56 (7.14%)
occurrences causally related to treatment / all	1 / 9	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
STATUS EPILEPTICUS			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUBDURAL HYGROMA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SYNCOPE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TRANSIENT ISCHAEMIC ATTACK			

subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
CORNEAL EPITHELIAL MICROCYSTS			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONSTIPATION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA			

subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIVERTICULAR PERFORATION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NAUSEA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VOMITING			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
HEPATIC STEATOSIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
BACK PAIN			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
DIVERTICULITIS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PNEUMONIA			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SEPSIS			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
WOUND INFECTION			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DEHYDRATION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPONATRAEMIA			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Control_ temozolomide	ABT-414_ pediatric	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 21 (23.81%)	3 / 6 (50.00%)	
number of deaths (all causes)	21	5	

number of deaths resulting from adverse events	1	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
MALIGNANT NEOPLASM PROGRESSION			
subjects affected / exposed	2 / 21 (9.52%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
METASTASES TO PERITONEUM			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEOPLASM PROGRESSION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR HAEMORRHAGE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBGALEAL HAEMATOMA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
DISEASE PROGRESSION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
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			
HYPOXIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

COMPLETED SUICIDE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDAL IDEATION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUICIDE ATTEMPT			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BODY TEMPERATURE INCREASED			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
CLAVICLE FRACTURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HUMERUS FRACTURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LUMBAR VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC FRACTURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
APHASIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
APRAXIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN OEDEMA			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERALISED TONIC-CLONIC SEIZURE			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPLEGIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDROCEPHALUS			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCLE SPASTICITY			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVOUS SYSTEM DISORDER			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROLOGICAL DECOMPENSATION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARTIAL SEIZURES			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEIZURE			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STATUS EPILEPTICUS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL HYGROMA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
CORNEAL EPITHELIAL MICROCYSTS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULAR PERFORATION			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
NAUSEA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATIC STEATOSIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
NEPHROLITHIASIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

BACK PAIN			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
DIVERTICULITIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY TRACT INFECTION VIRAL			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SEPSIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	ABT-414/temozolomide	ABT-414_adult	Control_lomustine
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 88 (95.45%)	76 / 84 (90.48%)	46 / 56 (82.14%)
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	9 / 88 (10.23%)	6 / 84 (7.14%)	4 / 56 (7.14%)
occurrences (all)	18	9	5
HYPOTENSION			
subjects affected / exposed	1 / 88 (1.14%)	3 / 84 (3.57%)	0 / 56 (0.00%)
occurrences (all)	1	3	0
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	6 / 88 (6.82%)	3 / 84 (3.57%)	4 / 56 (7.14%)
occurrences (all)	9	4	7
FATIGUE			
subjects affected / exposed	33 / 88 (37.50%)	27 / 84 (32.14%)	13 / 56 (23.21%)
occurrences (all)	60	39	16
GAIT DISTURBANCE			
subjects affected / exposed	4 / 88 (4.55%)	3 / 84 (3.57%)	2 / 56 (3.57%)
occurrences (all)	5	5	2
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	4 / 88 (4.55%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences (all)	4	0	1
OEDEMA PERIPHERAL			
subjects affected / exposed	7 / 88 (7.95%)	2 / 84 (2.38%)	4 / 56 (7.14%)
occurrences (all)	9	2	5
PYREXIA			
subjects affected / exposed	5 / 88 (5.68%)	4 / 84 (4.76%)	1 / 56 (1.79%)
occurrences (all)	5	4	1
Respiratory, thoracic and mediastinal disorders			

COUGH			
subjects affected / exposed	5 / 88 (5.68%)	2 / 84 (2.38%)	3 / 56 (5.36%)
occurrences (all)	7	2	3
DYSPHONIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
DYSPNOEA			
subjects affected / exposed	8 / 88 (9.09%)	1 / 84 (1.19%)	1 / 56 (1.79%)
occurrences (all)	8	1	1
EPISTAXIS			
subjects affected / exposed	2 / 88 (2.27%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	3	0	0
NASAL CONGESTION			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
OROPHARYNGEAL PAIN			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
PRODUCTIVE COUGH			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
ANXIETY			
subjects affected / exposed	5 / 88 (5.68%)	2 / 84 (2.38%)	1 / 56 (1.79%)
occurrences (all)	6	2	1
DEPRESSION			
subjects affected / exposed	4 / 88 (4.55%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences (all)	4	1	0
DISINHIBITION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
INSOMNIA			
subjects affected / exposed	8 / 88 (9.09%)	6 / 84 (7.14%)	2 / 56 (3.57%)
occurrences (all)	10	7	2
Investigations			

ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	11 / 88 (12.50%)	12 / 84 (14.29%)	3 / 56 (5.36%)
occurrences (all)	24	17	4
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	9 / 88 (10.23%)	13 / 84 (15.48%)	2 / 56 (3.57%)
occurrences (all)	12	15	2
BLOOD CULTURE POSITIVE			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	4 / 88 (4.55%)	8 / 84 (9.52%)	0 / 56 (0.00%)
occurrences (all)	6	15	0
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	7 / 88 (7.95%)	4 / 84 (4.76%)	6 / 56 (10.71%)
occurrences (all)	11	4	13
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	8 / 56 (14.29%)
occurrences (all)	0	1	11
PLATELET COUNT DECREASED			
subjects affected / exposed	21 / 88 (23.86%)	9 / 84 (10.71%)	15 / 56 (26.79%)
occurrences (all)	46	17	31
WEIGHT DECREASED			
subjects affected / exposed	4 / 88 (4.55%)	7 / 84 (8.33%)	3 / 56 (5.36%)
occurrences (all)	4	9	4
WEIGHT INCREASED			
subjects affected / exposed	6 / 88 (6.82%)	6 / 84 (7.14%)	3 / 56 (5.36%)
occurrences (all)	8	9	3
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	3 / 88 (3.41%)	2 / 84 (2.38%)	5 / 56 (8.93%)
occurrences (all)	7	2	15
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	4 / 88 (4.55%)	4 / 84 (4.76%)	3 / 56 (5.36%)
occurrences (all)	5	5	3

Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
SINUS BRADYCARDIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
APHASIA			
subjects affected / exposed	9 / 88 (10.23%)	9 / 84 (10.71%)	3 / 56 (5.36%)
occurrences (all)	10	10	3
ATAXIA			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	2 / 56 (3.57%)
occurrences (all)	1	1	2
BALANCE DISORDER			
subjects affected / exposed	2 / 88 (2.27%)	1 / 84 (1.19%)	3 / 56 (5.36%)
occurrences (all)	3	1	3
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
DIZZINESS			
subjects affected / exposed	7 / 88 (7.95%)	2 / 84 (2.38%)	1 / 56 (1.79%)
occurrences (all)	9	2	1
DYSARTHRIA			
subjects affected / exposed	1 / 88 (1.14%)	3 / 84 (3.57%)	3 / 56 (5.36%)
occurrences (all)	1	3	4
ENCEPHALOPATHY			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
HEADACHE			
subjects affected / exposed	21 / 88 (23.86%)	20 / 84 (23.81%)	8 / 56 (14.29%)
occurrences (all)	31	21	8
HEMIPARESIS			
subjects affected / exposed	2 / 88 (2.27%)	7 / 84 (8.33%)	7 / 56 (12.50%)
occurrences (all)	2	7	9
HYDROCEPHALUS			

subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
PERIPHERAL MOTOR NEUROPATHY			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	3 / 56 (5.36%)
occurrences (all)	0	0	4
SEIZURE			
subjects affected / exposed	6 / 88 (6.82%)	7 / 84 (8.33%)	5 / 56 (8.93%)
occurrences (all)	13	11	9
SOMNOLENCE			
subjects affected / exposed	3 / 88 (3.41%)	3 / 84 (3.57%)	3 / 56 (5.36%)
occurrences (all)	3	3	6
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	7 / 88 (7.95%)	4 / 84 (4.76%)	5 / 56 (8.93%)
occurrences (all)	7	13	7
LEUKOPENIA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	5 / 56 (8.93%)
occurrences (all)	1	0	11
LYMPHOPENIA			
subjects affected / exposed	9 / 88 (10.23%)	8 / 84 (9.52%)	9 / 56 (16.07%)
occurrences (all)	17	16	13
NEUTROPENIA			
subjects affected / exposed	2 / 88 (2.27%)	1 / 84 (1.19%)	10 / 56 (17.86%)
occurrences (all)	2	3	12
THROMBOCYTOPENIA			
subjects affected / exposed	19 / 88 (21.59%)	7 / 84 (8.33%)	19 / 56 (33.93%)
occurrences (all)	55	11	34
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
CATARACT			
subjects affected / exposed	4 / 88 (4.55%)	5 / 84 (5.95%)	0 / 56 (0.00%)
occurrences (all)	4	5	0
CORNEAL EPITHELIAL MICROCYSTS			

subjects affected / exposed	25 / 88 (28.41%)	12 / 84 (14.29%)	0 / 56 (0.00%)
occurrences (all)	64	22	0
CORNEAL OPACITY			
subjects affected / exposed	1 / 88 (1.14%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences (all)	1	3	0
DRY EYE			
subjects affected / exposed	20 / 88 (22.73%)	22 / 84 (26.19%)	1 / 56 (1.79%)
occurrences (all)	36	33	1
EYE IRRITATION			
subjects affected / exposed	6 / 88 (6.82%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences (all)	8	1	0
EYE PAIN			
subjects affected / exposed	7 / 88 (7.95%)	11 / 84 (13.10%)	0 / 56 (0.00%)
occurrences (all)	10	20	0
EYELID PTOSIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
KERATITIS			
subjects affected / exposed	16 / 88 (18.18%)	27 / 84 (32.14%)	0 / 56 (0.00%)
occurrences (all)	24	45	0
KERATOPATHY			
subjects affected / exposed	15 / 88 (17.05%)	7 / 84 (8.33%)	0 / 56 (0.00%)
occurrences (all)	24	8	0
LACRIMATION INCREASED			
subjects affected / exposed	9 / 88 (10.23%)	3 / 84 (3.57%)	0 / 56 (0.00%)
occurrences (all)	10	5	0
OCULAR DISCOMFORT			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
PHOTOPHOBIA			
subjects affected / exposed	12 / 88 (13.64%)	8 / 84 (9.52%)	0 / 56 (0.00%)
occurrences (all)	14	11	0
PUNCTATE KERATITIS			
subjects affected / exposed	3 / 88 (3.41%)	6 / 84 (7.14%)	0 / 56 (0.00%)
occurrences (all)	6	6	0
PUPILLARY REFLEX IMPAIRED			

subjects affected / exposed	0 / 88 (0.00%)	2 / 84 (2.38%)	0 / 56 (0.00%)
occurrences (all)	0	3	0
VISION BLURRED			
subjects affected / exposed	30 / 88 (34.09%)	17 / 84 (20.24%)	1 / 56 (1.79%)
occurrences (all)	52	27	1
VISUAL IMPAIRMENT			
subjects affected / exposed	3 / 88 (3.41%)	5 / 84 (5.95%)	0 / 56 (0.00%)
occurrences (all)	3	6	0
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 88 (0.00%)	2 / 84 (2.38%)	1 / 56 (1.79%)
occurrences (all)	0	2	1
ABDOMINAL PAIN			
subjects affected / exposed	2 / 88 (2.27%)	2 / 84 (2.38%)	0 / 56 (0.00%)
occurrences (all)	2	2	0
ABDOMINAL PAIN UPPER			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
CONSTIPATION			
subjects affected / exposed	23 / 88 (26.14%)	8 / 84 (9.52%)	2 / 56 (3.57%)
occurrences (all)	28	9	2
DIARRHOEA			
subjects affected / exposed	8 / 88 (9.09%)	6 / 84 (7.14%)	3 / 56 (5.36%)
occurrences (all)	9	6	3
NAUSEA			
subjects affected / exposed	21 / 88 (23.86%)	8 / 84 (9.52%)	6 / 56 (10.71%)
occurrences (all)	33	8	6
PROCTALGIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
VOMITING			
subjects affected / exposed	19 / 88 (21.59%)	5 / 84 (5.95%)	3 / 56 (5.36%)
occurrences (all)	23	5	4
Skin and subcutaneous tissue disorders			
DERMATITIS DIAPER			

subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
DRY SKIN			
subjects affected / exposed	1 / 88 (1.14%)	5 / 84 (5.95%)	0 / 56 (0.00%)
occurrences (all)	1	5	0
ERYTHEMA			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
HYPERKERATOSIS			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
PRURITUS			
subjects affected / exposed	2 / 88 (2.27%)	1 / 84 (1.19%)	0 / 56 (0.00%)
occurrences (all)	2	1	0
RASH			
subjects affected / exposed	7 / 88 (7.95%)	2 / 84 (2.38%)	1 / 56 (1.79%)
occurrences (all)	7	3	1
Renal and urinary disorders			
URINARY INCONTINENCE			
subjects affected / exposed	1 / 88 (1.14%)	3 / 84 (3.57%)	3 / 56 (5.36%)
occurrences (all)	1	3	3
Endocrine disorders			
CUSHINGOID			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	6 / 88 (6.82%)	3 / 84 (3.57%)	3 / 56 (5.36%)
occurrences (all)	7	3	3
BACK PAIN			
subjects affected / exposed	7 / 88 (7.95%)	7 / 84 (8.33%)	4 / 56 (7.14%)
occurrences (all)	8	7	4
MUSCLE SPASMS			
subjects affected / exposed	0 / 88 (0.00%)	1 / 84 (1.19%)	1 / 56 (1.79%)
occurrences (all)	0	1	1
MUSCULAR WEAKNESS			

subjects affected / exposed	4 / 88 (4.55%)	3 / 84 (3.57%)	2 / 56 (3.57%)
occurrences (all)	4	3	2
MUSCULOSKELETAL PAIN			
subjects affected / exposed	5 / 88 (5.68%)	2 / 84 (2.38%)	0 / 56 (0.00%)
occurrences (all)	6	2	0
PAIN IN EXTREMITY			
subjects affected / exposed	6 / 88 (6.82%)	1 / 84 (1.19%)	1 / 56 (1.79%)
occurrences (all)	7	1	1
PAIN IN JAW			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	1 / 56 (1.79%)
occurrences (all)	0	0	1
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	7 / 88 (7.95%)	6 / 84 (7.14%)	1 / 56 (1.79%)
occurrences (all)	8	6	1
EYE INFECTION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
INFLUENZA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
NASOPHARYNGITIS			
subjects affected / exposed	5 / 88 (5.68%)	1 / 84 (1.19%)	3 / 56 (5.36%)
occurrences (all)	6	1	3
ORAL CANDIDIASIS			
subjects affected / exposed	2 / 88 (2.27%)	2 / 84 (2.38%)	1 / 56 (1.79%)
occurrences (all)	2	2	1
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 88 (1.14%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	1	0	0
VAGINAL INFECTION			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
VULVOVAGINAL CANDIDIASIS			

subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	10 / 88 (11.36%)	5 / 84 (5.95%)	2 / 56 (3.57%)
occurrences (all)	11	7	2
HYPERGLYCAEMIA			
subjects affected / exposed	5 / 88 (5.68%)	3 / 84 (3.57%)	1 / 56 (1.79%)
occurrences (all)	8	3	1
HYPERKALAEMIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
HYPERMAGNESAEMIA			
subjects affected / exposed	0 / 88 (0.00%)	0 / 84 (0.00%)	0 / 56 (0.00%)
occurrences (all)	0	0	0
HYPOKALAEMIA			
subjects affected / exposed	7 / 88 (7.95%)	2 / 84 (2.38%)	1 / 56 (1.79%)
occurrences (all)	12	2	1

Non-serious adverse events	Control_ temozolomide	ABT-414_ pediatric	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)	6 / 6 (100.00%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
HYPOTENSION			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	2 / 21 (9.52%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
FATIGUE			
subjects affected / exposed	5 / 21 (23.81%)	2 / 6 (33.33%)	
occurrences (all)	6	6	

GAIT DISTURBANCE			
subjects affected / exposed	2 / 21 (9.52%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
INFLUENZA LIKE ILLNESS			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
OEDEMA PERIPHERAL			
subjects affected / exposed	4 / 21 (19.05%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
PYREXIA			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
COUGH			
subjects affected / exposed	3 / 21 (14.29%)	2 / 6 (33.33%)	
occurrences (all)	3	2	
DYSPHONIA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
DYSPNOEA			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
EPISTAXIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
NASAL CONGESTION			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
OROPHARYNGEAL PAIN			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
PRODUCTIVE COUGH			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Psychiatric disorders			

ANXIETY			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
DEPRESSION			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
DISINHIBITION			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
INSOMNIA			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	4	
BLOOD CULTURE POSITIVE			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	10	
PLATELET COUNT DECREASED			
subjects affected / exposed	2 / 21 (9.52%)	1 / 6 (16.67%)	
occurrences (all)	6	29	
WEIGHT DECREASED			

subjects affected / exposed	0 / 21 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	8	
WEIGHT INCREASED			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	1 / 21 (4.76%)	2 / 6 (33.33%)	
occurrences (all)	1	8	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Cardiac disorders			
BRADYCARDIA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
SINUS BRADYCARDIA			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Nervous system disorders			
APHASIA			
subjects affected / exposed	3 / 21 (14.29%)	0 / 6 (0.00%)	
occurrences (all)	3	0	
ATAXIA			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	3	
BALANCE DISORDER			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
DIZZINESS			
subjects affected / exposed	3 / 21 (14.29%)	1 / 6 (16.67%)	
occurrences (all)	3	1	

DYSARTHRIA			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
ENCEPHALOPATHY			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
HEADACHE			
subjects affected / exposed	2 / 21 (9.52%)	2 / 6 (33.33%)	
occurrences (all)	2	3	
HEMIPARESIS			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
HYDROCEPHALUS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
PERIPHERAL MOTOR NEUROPATHY			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
SEIZURE			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
SOMNOLENCE			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
LEUKOPENIA			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences (all)	4	0	
LYMPHOPENIA			
subjects affected / exposed	4 / 21 (19.05%)	0 / 6 (0.00%)	
occurrences (all)	8	0	
NEUTROPENIA			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
THROMBOCYTOPENIA			
subjects affected / exposed	8 / 21 (38.10%)	0 / 6 (0.00%)	
occurrences (all)	11	0	
Ear and labyrinth disorders			
EAR PAIN			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Eye disorders			
CATARACT			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
CORNEAL EPITHELIAL MICROCYSTS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
CORNEAL OPACITY			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
DRY EYE			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
EYE IRRITATION			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
EYE PAIN			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
EYELID PTOSIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
KERATITIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
KERATOPATHY			

subjects affected / exposed	0 / 21 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	3	
LACRIMATION INCREASED			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
OCULAR DISCOMFORT			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
PHOTOPHOBIA			
subjects affected / exposed	0 / 21 (0.00%)	3 / 6 (50.00%)	
occurrences (all)	0	4	
PUNCTATE KERATITIS			
subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
PUPILLARY REFLEX IMPAIRED			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
VISION BLURRED			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	5	
VISUAL IMPAIRMENT			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
ABDOMINAL PAIN			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
CONSTIPATION			
subjects affected / exposed	6 / 21 (28.57%)	0 / 6 (0.00%)	
occurrences (all)	6	0	

DIARRHOEA			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
NAUSEA			
subjects affected / exposed	6 / 21 (28.57%)	2 / 6 (33.33%)	
occurrences (all)	7	3	
PROCTALGIA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
VOMITING			
subjects affected / exposed	6 / 21 (28.57%)	3 / 6 (50.00%)	
occurrences (all)	6	5	
Skin and subcutaneous tissue disorders			
DERMATITIS DIAPER			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
DRY SKIN			
subjects affected / exposed	2 / 21 (9.52%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
ERYTHEMA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
HYPERKERATOSIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
PRURITUS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
RASH			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
Renal and urinary disorders			
URINARY INCONTINENCE			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	
Endocrine disorders			

CUSHINGOID			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
BACK PAIN			
subjects affected / exposed	2 / 21 (9.52%)	1 / 6 (16.67%)	
occurrences (all)	2	1	
MUSCLE SPASMS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
MUSCULAR WEAKNESS			
subjects affected / exposed	2 / 21 (9.52%)	0 / 6 (0.00%)	
occurrences (all)	2	0	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	2	
PAIN IN JAW			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Infections and infestations			
CONJUNCTIVITIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
EYE INFECTION			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
INFLUENZA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
NASOPHARYNGITIS			

subjects affected / exposed	0 / 21 (0.00%)	0 / 6 (0.00%)	
occurrences (all)	0	0	
ORAL CANDIDIASIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
VAGINAL INFECTION			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
VULVOVAGINAL CANDIDIASIS			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	2	
HYPERGLYCAEMIA			
subjects affected / exposed	1 / 21 (4.76%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
HYPERKALAEMIA			
subjects affected / exposed	0 / 21 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	6	
HYPERMAGNESAEMIA			
subjects affected / exposed	0 / 21 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
HYPOKALAEMIA			
subjects affected / exposed	1 / 21 (4.76%)	1 / 6 (16.67%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 April 2015	• Updates to selection criteria to exclude subjects with coeliac diseases and wheat allergy, plus subjects with planned live vaccinations • Requirement that national prescribing information should be followed for all concomitant medications
13 July 2015	• Depatuxizumab mafodotin starting dose reduced from 1.25 mg/kg to 1.0 mg/kg • Clarification of timings of electrocardiograms (ECGs) for subjects receiving depatuxizumab mafodotin and types of samples required for translational research
25 November 2015	• Requirement for dose adjustment (depatuxizumab mafodotin, TMZ, lomustine) if ≥ 10% change in body weight, addition of depatuxizumab mafodotin 20 mg vial strength • Clarification that subjects who discontinued lomustine treatment for non hematologic toxicity should not discontinue the entire study • Requirement for reporting of clinically significant laboratory values outside the reference range as adverse events (AEs) • Clarification that AEs deemed related to glioblastoma or the progression of glioblastoma will be considered expected for this study and not have expedited reporting
01 July 2016	• Update to allow subjects with radiological pseudoprogression to resume study treatment • Addition of ± 2-day dosing window for depatuxizumab mafodotin on Day 1 and Day 15 • End of study definition updated to include 35 days after all subjects have completed treatment • Addition of pediatric sub-study
18 January 2017	• Updates to withdrawal criteria in the event that a subject withdraws consent from all further data collection • Addition of process for optional collection of images of ocular AEs, window (± 7 days) for magnetic resonance imaging (MRI) scan after end of treatment, and clarifications to align with Statistical Analysis Plan version 1.0. • Multiple updates to Appendix I (pediatric sub-study) including addition of background and introduction information; exclusion of subjects < 3 years of age until favorable results of a juvenile repeated mouse toxicity study are available; restriction of treatment duration to 12 months; addition of Quality of Life measurements, WHO performance evaluation replaced by Karnofsky/Lansky; updates to (serious) adverse event/progression/survival collection during long term follow-up; added language for data safety monitoring; and updates to the statistical analysis plan
24 May 2018	• Addition of precautionary safety measures regarding hepatotoxicity including updates to safety information, guidelines for dose modifications due to hepatic laboratory abnormalities, and guidelines for management and evaluation of severe hepatic laboratory abnormalities • Addition of eligibility criteria regarding liver function for pediatric sub-study

04 January 2019	• Updated safety profile of depatuxizumab mafodotin (additional safety information; updated information on monitoring and management of intraocular pressure; addition of a follow up visit at 49 days after last treatment administration (End of Study) with extension of the safety monitoring period) • In the pediatric sub-study, safety primary endpoint updated to include subjects with adverse events up until 49 days post last dose and requirement for a follow-up ophthalmology assessment at Day 49 day visit; addition of live attenuated vaccines prohibited during the study and for a period of 49 days after the end of depatuxizumab mafodotin administration; amended enrollment criteria for pediatric sub-study with regards to liver function; amended enrollment criteria for pediatric sub-study with regards to pregnancy and contraception language

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported