



Clinical trial results:

A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Evaluating the Efficacy of ABT-888 in Combination with Temozolomide Versus Temozolomide Alone in Subjects with Metastatic Melanoma Summary

EudraCT number	2008-004941-27
Trial protocol	GB
Global end of trial date	19 January 2016

Results information

Result version number	v2 (current)
This version publication date	18 March 2017
First version publication date	02 February 2017
Version creation reason	<ul style="list-style-type: none">• Correction of full data set The correction clarifies the time frames for the endpoints.

Trial information

Trial identification

Sponsor protocol code	M10-440
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00804908
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AbbVie Deutschland GmbH & Co. KG
Sponsor organisation address	Abbott House, Vanwall Business Park, Vanwall Road, Maidenhead, Berkshire, United Kingdom, SL6-4UB
Public contact	Global Medical Servicees, AbbVie, 001 800-633-9110,
Scientific contact	Mark D McKee, MD, AbbVie, mark.mckee@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	19 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the efficacy of ABT-888 in combination with temozolomide versus temozolomide alone in subjects with metastatic melanoma.

Protection of trial subjects:

Subject read and understood the information provided about the study and gave written permission.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2009
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: 53
Country: Number of subjects enrolled	Canada: 40
Country: Number of subjects enrolled	New Zealand: 9
Country: Number of subjects enrolled	United Kingdom: 61
Country: Number of subjects enrolled	United States: 183
Worldwide total number of subjects	346
EEA total number of subjects	61

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	201
From 65 to 84 years	140

85 years and over	5
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Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 346 subjects were randomized; 2 subjects did not receive study drug and were excluded from the safety analysis.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo for ABT-888 BID + TMZ QD

Arm description:

Placebo for ABT-888 twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m² once daily (QD) for 5 days every 28 days.

Arm type	Placebo
Investigational medicinal product name	temozolomide
Investigational medicinal product code	
Other name	Temodar, Temodal
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide capsule administered orally once daily for 5 days every 28 days

Investigational medicinal product name	placebo for ABT-888
Investigational medicinal product code	
Other name	veliparib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo for ABT-888 capsule administered orally twice daily for 7 days every 28 days

Arm title	ABT-888 20 mg BID + TMZ QD
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Arm description:

ABT-888 20 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m² once daily (QD) for 5 days every 28 days.

Arm type	Active comparator
Investigational medicinal product name	temozolomide
Investigational medicinal product code	
Other name	Temodar, Temodal
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide capsule administered orally once daily for 5 days every 28 days

Investigational medicinal product name	ABT-888
Investigational medicinal product code	
Other name	veliparib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ABT-888 capsule administered orally twice daily for 7 days every 28 days

Arm title	ABT-888 40 mg BID + TMZ QD
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Arm description:

ABT-888 40 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m² once daily (QD) for 5 days every 28 days.

Arm type	Active comparator
Investigational medicinal product name	temozolomide
Investigational medicinal product code	
Other name	Temodar, Temodal
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Temozolomide capsule administered orally once daily for 5 days every 28 days

Investigational medicinal product name	ABT-888
Investigational medicinal product code	
Other name	veliparib
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

ABT-888 capsule administered orally twice daily for 7 days every 28 days

Number of subjects in period 1	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD
Started	115	116	115
Completed	0	0	1
Not completed	115	116	114
Not specified	115	116	114

Baseline characteristics

Reporting groups

Reporting group title	Placebo for ABT-888 BID + TMZ QD
Reporting group description: Placebo for ABT-888 twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m ² once daily (QD) for 5 days every 28 days.	
Reporting group title	ABT-888 20 mg BID + TMZ QD
Reporting group description: ABT-888 20 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m ² once daily (QD) for 5 days every 28 days.	
Reporting group title	ABT-888 40 mg BID + TMZ QD
Reporting group description: ABT-888 40 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m ² once daily (QD) for 5 days every 28 days.	

Reporting group values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD
Number of subjects	115	116	115
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	58.4 ± 14.13	58.6 ± 12.55	62.3 ± 13.14
Gender, Male/Female Units:			
Female	36	45	38
Male	79	71	77

Reporting group values	Total		
Number of subjects	346		
Age categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	-		
Gender, Male/Female Units:			
Female	119		
Male	227		

End points

End points reporting groups

Reporting group title	Placebo for ABT-888 BID + TMZ QD
Reporting group description: Placebo for ABT-888 twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m ² once daily (QD) for 5 days every 28 days.	
Reporting group title	ABT-888 20 mg BID + TMZ QD
Reporting group description: ABT-888 20 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m ² once daily (QD) for 5 days every 28 days.	
Reporting group title	ABT-888 40 mg BID + TMZ QD
Reporting group description: ABT-888 40 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m ² once daily (QD) for 5 days every 28 days.	

Primary: Progression-Free Survival (PFS): Time to event

End point title	Progression-Free Survival (PFS): Time to event
End point description: PFS: the number of days from the date that the subject was randomized to the date the subject experienced a confirmed event of disease progression (radiological, as determined by the central imaging center; or clinical, as determined by the investigator), or to the date of death (all causes of mortality) if disease progression was not reached. All events were included whether the subject was still taking or had discontinued study drug. Events of death were included for subjects who had not experienced a confirmed event of disease progression, provided the death occurred within 8 weeks of the last available disease progression assessment. The distribution of PFS, as determined by the central imaging center (radiological)/ investigator (clinical), was estimated for each treatment group using Kaplan-Meier methodology. Point estimates and 95% confidence intervals (95% CIs) for the quartiles for the PFS distribution are provided. 9999=Not calculable due to insufficient progression events.	
End point type	Primary
End point timeframe: Every Cycle (28 Days) until disease progression was observed or another reason for discontinuation of assessments was identified by the investigator. The maximum observed followup duration at the progression-free survival analysis time was 9.7 months.	

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[1]	116 ^[2]	115 ^[3]	
Units: days				
number (confidence interval 95%)				
25th Percentile	54 (50 to 56)	56 (53 to 58)	53 (51 to 56)	
50th Percentile	60 (57 to 111)	113 (92 to 168)	110 (57 to 125)	
75th Percentile	163 (113 to 283)	225 (169 to 9999)	226 (173 to 9999)	

Notes:

[1] - ITT population defined as all randomized subjects.

[2] - ITT population defined as all randomized subjects.

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Comparisons between treatment groups were performed using a log-rank test stratified by baseline lactate dehydrogenase (LDH) status (0 to 1 ULN; >1 to ≤ 2 ULN) and history of previously treated brain metastases (with, without). Hochberg testing procedure for multiplicity adjustment.	
Comparison groups	Placebo for ABT-888 BID + TMZ QD v ABT-888 40 mg BID + TMZ QD
Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.233
Method	stratified log-rank

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Comparisons between treatment groups were performed using a log-rank test stratified by baseline lactate dehydrogenase (LDH) status (0 to 1 ULN; >1 to ≤ 2 ULN) and history of previously treated brain metastases (with, without). Hochberg testing procedure for multiplicity adjustment.	
Comparison groups	Placebo for ABT-888 BID + TMZ QD v ABT-888 20 mg BID + TMZ QD
Number of subjects included in analysis	231
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.071
Method	stratified log-rank

Secondary: Overall Survival (OS): Time to Event

End point title	Overall Survival (OS): Time to Event
End point description:	
OS: the number of days from the date the subject was randomized to the date of death. All deaths were included, whether the subject was still taking or had discontinued study drug. If a subject had not died and was lost to follow-up, data were censored at the last study visit or contact date, or date the subject was last known to be alive, whichever was later; if the subject was not lost to follow-up, data were censored at the last study visit or contact date, whichever was later. The distribution of OS was estimated for each treatment group using Kaplan-Meier methodology. Point estimates and 95% CIs for the quartiles for the OS distribution are provided. Per protocol, because neither the ABT-888 20 mg BID + TMZ nor ABT-888 40 mg BID + TMZ groups were statistically significantly better than the Placebo + TMZ group for the primary endpoint of PFS, confirmatory statistical testing was not continued for any secondary endpoints. 9999-Not calculable due to insufficient survival events.	
End point type	Secondary

End point timeframe:

Per protocol, survival follow-up information was to be obtained every 3 months for up to 18 months after the final visit for the subject. The maximum observed follow-up at the overall survival analysis time was 21.0 months.

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[4]	116 ^[5]	115 ^[6]	
Units: days				
number (confidence interval 95%)				
25th Percentile	207 (155 to 241)	204 (175 to 247)	181 (154 to 266)	
50th Percentile	390 (299 to 436)	327 (274 to 399)	412 (346 to 483)	
75th Percentile	559 (476 to 598)	9999 (492 to 9999)	9999 (9999 to 9999)	

Notes:

[4] - ITT population defined as all randomized subjects.

[5] - ITT population defined as all randomized subjects.

[6] - ITT population defined as all randomized subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: 12-Month Overall Survival (OS) Rate

End point title	12-Month Overall Survival (OS) Rate
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End point description:

The 12-month overall survival rate was defined as the percentage of participants surviving at 12 months. The distribution of 12-month OS rate was estimated using Kaplan-Meier methodology. Point estimates and 95% CIs for the quartiles for the PFS distribution are provided. Per protocol, because neither the ABT-888 20 mg BID + TMZ nor ABT-888 40 mg BID + TMZ treatment groups were statistically significantly better than the Placebo + TMZ treatment group for the primary endpoint of PFS, confirmatory statistical testing was not continued for any secondary endpoints, regardless of the observed P values.

End point type	Secondary
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End point timeframe:

Per protocol, survival was to be assessed every 4 weeks or as needed after participant is registered as off-study for up to 18 months. The maximum observed follow-up at the overall survival analysis time was 21.0 months.

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[7]	116 ^[8]	115 ^[9]	
Units: percentage of subjects				
number (confidence interval 95%)	52.6 (43.1 to 61.3)	43.5 (34.3 to 52.3)	54.1 (44.5 to 62.7)	

Notes:

[7] - ITT population defined as all randomized participants.

[8] - ITT population defined as all randomized participants.

[9] - ITT population defined as all randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: 6-month Progression-Free Survival Rate

End point title	6-month Progression-Free Survival Rate
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End point description:

The 6-month progression-free survival rate was defined as the percentage of participants without disease progression at 6 months. The distribution of 6-month progression-free survival rate, as determined by the central imaging center (radiological)/ investigator (clinical), was estimated using Kaplan-Meier methodology. Point estimates and 95% CIs for the quartiles for the PFS distribution are provided. Per protocol, because neither the ABT-888 20 mg BID + TMZ nor ABT-888 40 mg BID + TMZ treatment groups were statistically significantly better than the Placebo + TMZ treatment group for the primary endpoint of PFS, confirmatory statistical testing was not continued for any secondary endpoints, regardless of the observed P values.

End point type	Secondary
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End point timeframe:

Every Cycle (28 Days) until disease progression was observed or another reason for discontinuation of assessments was identified by the investigator. The maximum observed followup duration at the progression-free survival analysis time was 9.7 months.

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[10]	116 ^[11]	115 ^[12]	
Units: percentage of subjects				
number (confidence interval 95%)	19.1 (10.9 to 29)	32.8 (22 to 44.1)	30.7 (20.3 to 41.7)	

Notes:

[10] - ITT population defined as all randomized participants.

[11] - ITT population defined as all randomized participants.

[12] - ITT population defined as all randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title	Objective Response Rate
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End point description:

The objective response rate was defined as the percentage of participants with a confirmed CR or PR based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Per protocol, because neither the ABT-888 20 mg BID + TMZ nor ABT-888 40 mg BID + TMZ treatment groups were statistically significantly better than the Placebo + TMZ treatment group for the primary endpoint of PFS, confirmatory statistical testing was not continued for any secondary endpoints, regardless of the observed P values.

End point type	Secondary
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End point timeframe:

Every 2 cycles (8 weeks) until disease progression was observed or another reason for discontinuation of assessments was identified by the investigator. The maximum observed followup duration at the progression-free survival analysis time was 9.7 months.

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[13]	116 ^[14]	115 ^[15]	
Units: percentage of subjects				
number (confidence interval 95%)	7 (3.1 to 13.2)	10.3 (5.5 to 17.4)	9.6 (4.9 to 16.5)	

Notes:

[13] - All subjects in the ITT population (defined as all randomized participants) with measurable disease.

[14] - All subjects in the ITT population (defined as all randomized participants) with measurable disease.

[15] - All subjects in the ITT population (defined as all randomized participants) with measurable disease.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Disease Progression

End point title	Time to Disease Progression
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End point description:

The distribution of time to disease progression, as determined by the central imaging center (radiological)/ investigator (clinical), was estimated for each treatment group using Kaplan-Meier methodology. Point estimates and 95% CIs for the quartiles for the PFS distribution are provided. Per protocol, because neither the ABT-888 20 mg BID + TMZ nor ABT-888 40 mg BID + TMZ treatment groups were statistically significantly better than the Placebo + TMZ treatment group for the primary endpoint of PFS, confirmatory statistical testing was not continued for any secondary endpoints, regardless of the observed P values. 9999=Not calculable due to insufficient progression events

End point type	Secondary
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End point timeframe:

Every Cycle (28 Days), until disease progression was observed or another reason for discontinuation of assessments was identified by the investigator. The maximum observed followup duration at the progression-free survival analysis time was 9.7 months.

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[16]	116 ^[17]	115 ^[18]	
Units: days				
number (confidence interval 95%)				
25th Percentile	54 (50 to 56)	56 (53 to 57)	53 (51 to 56)	
50th Percentile	60 (57 to 111)	113 (92 to 168)	110 (57 to 125)	

75th Percentile	163 (113 to 283)	225 (169 to 9999)	226 (173 to 9999)	
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Notes:

[16] - ITT population defined as all randomized participants.

[17] - ITT population defined as all randomized participants.

[18] - ITT population defined as all randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate

End point title	Disease Control Rate
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End point description:

The disease control rate was defined as the percentage of subjects who had at least stable disease (complete response, partial response, or stable disease) through the end of Week 8. Per protocol, because neither the ABT-888 20 mg BID + TMZ nor ABT-888 40 mg BID + TMZ treatment groups were statistically significantly better than the Placebo + TMZ treatment group for the primary endpoint of PFS, confirmatory statistical testing was not continued for any secondary endpoints, regardless of the observed P values.

End point type	Secondary
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End point timeframe:

Week 8

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[19]	116 ^[20]	115 ^[21]	
Units: percentage of subjects				
number (confidence interval 95%)	48.7 (39.3 to 58.2)	62.9 (53.5 to 71.7)	59.1 (49.6 to 68.2)	

Notes:

[19] - ITT population defined as all randomized participants.

[20] - ITT population defined as all randomized participants.

[21] - ITT population defined as all randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to neurological/brain metastases progression

End point title	Time to neurological/brain metastases progression
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End point description:

Time to neurological/brain metastases progression, defined as the number of days from randomization to the date the subject experienced an event of neurological/brain metastases progression, was estimated using Kaplan-Meier methodology. Point estimates and 95% CIs for the quartiles for the distribution are provided. All events of progression were included, whether the event occurred while the subject was still taking study drug. If a subject did not experience an event, data were censored at the date of the last available brain CT scan; for subjects with no postbaseline brain CT scans, data were censored at randomization. Per protocol, because neither the ABT-888 20 mg BID+TMZ nor ABT-888 40 mg BID+TMZ groups were statistically significantly better than the Placebo + TMZ group for the primary endpoint of PFS, confirmatory statistical testing was not continued for any secondary endpoints, regardless of the observed P values. 9999=Not calculable due to insufficient progression events.

End point type	Secondary
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End point timeframe:

Every 2 cycles (8 weeks) until disease progression was observed or another reason for discontinuation of assessments was identified by the investigator. The maximum observed followup duration at the progression-free survival analysis time was 9.7 months.

End point values	Placebo for ABT-888 BID + TMZ QD	ABT-888 20 mg BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	115 ^[22]	116 ^[23]	115 ^[24]	
Units: days				
number (confidence interval 95%)				
25th Percentile	60 (34 to 9999)	119 (48 to 9999)	184 (51 to 9999)	
50th Percentile	9999 (60 to 9999)	9999 (119 to 9999)	184 (184 to 9999)	
75th Percentile	9999 (9999 to 9999)	9999 (119 to 9999)	9999 (184 to 9999)	

Notes:

[22] - ITT population defined as all randomized participants.

[23] - ITT population defined as all randomized participants.

[24] - ITT population defined as all randomized participants.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs (TEAEs) were collected from first dose of study drug until 30 days after the last dose of study drug (up to 5.6 years); SAEs were collected from the time informed consent was obtained (up to 5.7 years).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo for ABT-888 BID + TMZ QD
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Reporting group description:

Placebo for ABT-888 twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m² once daily (QD) for 5 days every 28 days.

Reporting group title	ABT-888 40 mg BID + TMZ QD
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Reporting group description:

ABT-888 40 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m² once daily (QD) for 5 days every 28 days.

Reporting group title	ABT-888 20 mg BID + TMZ QD
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Reporting group description:

ABT-888 20 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m² once daily (QD) for 5 days every 28 days.

Serious adverse events	Placebo for ABT-888 BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	ABT-888 20 mg BID + TMZ QD
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 113 (24.78%)	31 / 115 (26.96%)	27 / 116 (23.28%)
number of deaths (all causes)	4	4	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	2 / 113 (1.77%)	2 / 115 (1.74%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gliosarcoma			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Malignant neoplasm progression			

subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Malignant melanoma			
subjects affected / exposed	2 / 113 (1.77%)	0 / 115 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Metastatic malignant melanoma			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastatic pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal adenocarcinoma			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Hypotension			

subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
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 venous thrombosis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	2 / 113 (1.77%)	1 / 115 (0.87%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Death			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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 / 113 (0.88%)	1 / 115 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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			

Dyspnoea			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Haemothorax			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Pleural effusion			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Pulmonary artery thrombosis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 113 (0.00%)	4 / 115 (3.48%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary thrombosis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			

Haemoglobin decreased			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
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			
Allergic transfusion reaction			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Facial bones fracture			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Limb crushing injury			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Arrhythmia			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pericardial effusion			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	2 / 116 (1.72%)
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 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Ataxia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Dizziness			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Neuropathy peripheral			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Spinal cord compression			

subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	0 / 116 (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
Tremor			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 113 (1.77%)	3 / 115 (2.61%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow failure			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Febrile neutropenia			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			

subjects affected / exposed	1 / 113 (0.88%)	3 / 115 (2.61%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	4 / 113 (3.54%)	4 / 115 (3.48%)	3 / 116 (2.59%)
occurrences causally related to treatment / all	4 / 4	2 / 4	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Melaena			

subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Intestinal obstruction			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth swelling			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Nausea			
subjects affected / exposed	2 / 113 (1.77%)	1 / 115 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	2 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	2 / 113 (1.77%)	1 / 115 (0.87%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	2 / 3	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
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			
Cholecystitis acute			

subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangitis			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Nephrolithiasis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure acute			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral prolapse			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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			
Back pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	2 / 116 (1.72%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Neck pain			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	0 / 116 (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
Pathological fracture			
subjects affected / exposed	1 / 113 (0.88%)	1 / 115 (0.87%)	0 / 116 (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
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 113 (0.88%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised infection			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Pneumonia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Post procedural infection			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 113 (0.00%)	0 / 115 (0.00%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Hypercalcaemia			
subjects affected / exposed	0 / 113 (0.00%)	1 / 115 (0.87%)	0 / 116 (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
Dehydration			
subjects affected / exposed	2 / 113 (1.77%)	2 / 115 (1.74%)	1 / 116 (0.86%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo for ABT-888 BID + TMZ QD	ABT-888 40 mg BID + TMZ QD	ABT-888 20 mg BID + TMZ QD
Total subjects affected by non-serious adverse events			
subjects affected / exposed	112 / 113 (99.12%)	113 / 115 (98.26%)	116 / 116 (100.00%)
Investigations			
Haemoglobin decreased			
subjects affected / exposed	6 / 113 (5.31%)	3 / 115 (2.61%)	3 / 116 (2.59%)
occurrences (all)	13	4	5

Weight decreased subjects affected / exposed occurrences (all)	7 / 113 (6.19%) 7	6 / 115 (5.22%) 7	7 / 116 (6.03%) 7
Platelet count decreased subjects affected / exposed occurrences (all)	4 / 113 (3.54%) 9	10 / 115 (8.70%) 34	12 / 116 (10.34%) 28
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain subjects affected / exposed occurrences (all)	6 / 113 (5.31%) 7	0 / 115 (0.00%) 0	0 / 116 (0.00%) 0
Tumour pain subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	6 / 115 (5.22%) 7	3 / 116 (2.59%) 4
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	17 / 113 (15.04%) 28	15 / 115 (13.04%) 21	19 / 116 (16.38%) 23
Dysgeusia subjects affected / exposed occurrences (all)	8 / 113 (7.08%) 8	11 / 115 (9.57%) 12	15 / 116 (12.93%) 16
Lethargy subjects affected / exposed occurrences (all)	7 / 113 (6.19%) 13	6 / 115 (5.22%) 14	6 / 116 (5.17%) 7
Headache subjects affected / exposed occurrences (all)	30 / 113 (26.55%) 56	25 / 115 (21.74%) 49	22 / 116 (18.97%) 28
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	9 / 113 (7.96%) 10	13 / 115 (11.30%) 23	19 / 116 (16.38%) 24
Leukopenia subjects affected / exposed occurrences (all)	5 / 113 (4.42%) 8	8 / 115 (6.96%) 22	8 / 116 (6.90%) 19
Neutropenia subjects affected / exposed occurrences (all)	7 / 113 (6.19%) 9	26 / 115 (22.61%) 53	24 / 116 (20.69%) 59

Lymphopenia subjects affected / exposed occurrences (all)	5 / 113 (4.42%) 9	6 / 115 (5.22%) 22	4 / 116 (3.45%) 9
Thrombocytopenia subjects affected / exposed occurrences (all)	19 / 113 (16.81%) 32	56 / 115 (48.70%) 155	49 / 116 (42.24%) 146
General disorders and administration site conditions			
Chest pain subjects affected / exposed occurrences (all)	4 / 113 (3.54%) 4	6 / 115 (5.22%) 7	5 / 116 (4.31%) 6
Chills subjects affected / exposed occurrences (all)	4 / 113 (3.54%) 6	8 / 115 (6.96%) 8	8 / 116 (6.90%) 8
Influenza like illness subjects affected / exposed occurrences (all)	4 / 113 (3.54%) 4	1 / 115 (0.87%) 1	6 / 116 (5.17%) 7
Fatigue subjects affected / exposed occurrences (all)	73 / 113 (64.60%) 130	77 / 115 (66.96%) 161	75 / 116 (64.66%) 139
Pain subjects affected / exposed occurrences (all)	8 / 113 (7.08%) 10	12 / 115 (10.43%) 16	10 / 116 (8.62%) 17
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 113 (0.88%) 1	4 / 115 (3.48%) 4	9 / 116 (7.76%) 12
Pyrexia subjects affected / exposed occurrences (all)	6 / 113 (5.31%) 6	4 / 115 (3.48%) 5	7 / 116 (6.03%) 7
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 113 (2.65%) 3	6 / 115 (5.22%) 6	4 / 116 (3.45%) 5
Abdominal pain subjects affected / exposed occurrences (all)	8 / 113 (7.08%) 9	15 / 115 (13.04%) 24	11 / 116 (9.48%) 17
Constipation			

subjects affected / exposed	62 / 113 (54.87%)	62 / 115 (53.91%)	60 / 116 (51.72%)
occurrences (all)	103	112	84
Diarrhoea			
subjects affected / exposed	24 / 113 (21.24%)	26 / 115 (22.61%)	27 / 116 (23.28%)
occurrences (all)	30	50	45
Dry mouth			
subjects affected / exposed	6 / 113 (5.31%)	0 / 115 (0.00%)	3 / 116 (2.59%)
occurrences (all)	6	0	3
Dyspepsia			
subjects affected / exposed	12 / 113 (10.62%)	8 / 115 (6.96%)	8 / 116 (6.90%)
occurrences (all)	13	12	10
Nausea			
subjects affected / exposed	75 / 113 (66.37%)	82 / 115 (71.30%)	83 / 116 (71.55%)
occurrences (all)	148	183	162
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 113 (0.00%)	2 / 115 (1.74%)	10 / 116 (8.62%)
occurrences (all)	0	3	10
Vomiting			
subjects affected / exposed	53 / 113 (46.90%)	30 / 115 (26.09%)	42 / 116 (36.21%)
occurrences (all)	90	52	75
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 113 (14.16%)	18 / 115 (15.65%)	28 / 116 (24.14%)
occurrences (all)	22	24	33
Dyspnoea			
subjects affected / exposed	11 / 113 (9.73%)	17 / 115 (14.78%)	17 / 116 (14.66%)
occurrences (all)	13	18	17
Epistaxis			
subjects affected / exposed	5 / 113 (4.42%)	10 / 115 (8.70%)	1 / 116 (0.86%)
occurrences (all)	5	13	1
Oropharyngeal pain			
subjects affected / exposed	6 / 113 (5.31%)	5 / 115 (4.35%)	7 / 116 (6.03%)
occurrences (all)	7	7	7
Skin and subcutaneous tissue disorders			

Dry skin			
subjects affected / exposed	5 / 113 (4.42%)	8 / 115 (6.96%)	2 / 116 (1.72%)
occurrences (all)	7	12	2
Erythema			
subjects affected / exposed	2 / 113 (1.77%)	3 / 115 (2.61%)	7 / 116 (6.03%)
occurrences (all)	2	3	11
Night sweats			
subjects affected / exposed	7 / 113 (6.19%)	3 / 115 (2.61%)	7 / 116 (6.03%)
occurrences (all)	7	3	7
Hyperhidrosis			
subjects affected / exposed	6 / 113 (5.31%)	2 / 115 (1.74%)	3 / 116 (2.59%)
occurrences (all)	8	2	3
Pruritus			
subjects affected / exposed	15 / 113 (13.27%)	6 / 115 (5.22%)	7 / 116 (6.03%)
occurrences (all)	16	9	8
Rash			
subjects affected / exposed	6 / 113 (5.31%)	11 / 115 (9.57%)	10 / 116 (8.62%)
occurrences (all)	8	15	11
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 113 (10.62%)	14 / 115 (12.17%)	12 / 116 (10.34%)
occurrences (all)	14	15	12
Anxiety			
subjects affected / exposed	7 / 113 (6.19%)	5 / 115 (4.35%)	6 / 116 (5.17%)
occurrences (all)	8	5	6
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	13 / 113 (11.50%)	14 / 115 (12.17%)	17 / 116 (14.66%)
occurrences (all)	21	24	20
Back pain			
subjects affected / exposed	10 / 113 (8.85%)	14 / 115 (12.17%)	21 / 116 (18.10%)
occurrences (all)	12	21	29
Groin pain			
subjects affected / exposed	3 / 113 (2.65%)	6 / 115 (5.22%)	4 / 116 (3.45%)
occurrences (all)	4	6	4
Muscle spasms			

subjects affected / exposed	1 / 113 (0.88%)	6 / 115 (5.22%)	2 / 116 (1.72%)
occurrences (all)	1	8	2
Musculoskeletal chest pain			
subjects affected / exposed	6 / 113 (5.31%)	1 / 115 (0.87%)	7 / 116 (6.03%)
occurrences (all)	10	1	8
Musculoskeletal pain			
subjects affected / exposed	11 / 113 (9.73%)	9 / 115 (7.83%)	11 / 116 (9.48%)
occurrences (all)	11	16	11
Myalgia			
subjects affected / exposed	7 / 113 (6.19%)	8 / 115 (6.96%)	4 / 116 (3.45%)
occurrences (all)	7	13	4
Pain in extremity			
subjects affected / exposed	11 / 113 (9.73%)	10 / 115 (8.70%)	13 / 116 (11.21%)
occurrences (all)	12	12	15
Infections and infestations			
Sinusitis			
subjects affected / exposed	5 / 113 (4.42%)	3 / 115 (2.61%)	7 / 116 (6.03%)
occurrences (all)	5	3	8
Upper respiratory tract infection			
subjects affected / exposed	7 / 113 (6.19%)	10 / 115 (8.70%)	8 / 116 (6.90%)
occurrences (all)	7	10	8
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	37 / 113 (32.74%)	36 / 115 (31.30%)	26 / 116 (22.41%)
occurrences (all)	53	56	30
Hyperglycaemia			
subjects affected / exposed	6 / 113 (5.31%)	5 / 115 (4.35%)	4 / 116 (3.45%)
occurrences (all)	8	8	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 December 2008	The main purpose of this amendment was to clarify inclusion criteria (men must agree to contraception) and modify the starting dose of temozolomide (TMZ) from 200 mg/m ² /day to 10 mg/m ² /day.
22 May 2009	The main purpose of this amendment was to increase the number of subjects from 180 to 300 and clarify inclusion (history of brain metastases, prior and excluded anticancer therapy) and exclusion (prior whole brain radiation therapy [WBRT]) criteria.
22 April 2010	The main purpose of this amendment was to clarify ABT-888 dosing, time frame for collection of survival and post-treatment therapy information, update the actual number of subjects enrolled from 300 to 346, clarify the frequency of brain magnetic resonance imaging for subjects with a history of previously treated metastasis, and clarify discontinuation criteria.
15 March 2012	The main purpose of this amendment was to decrease the number of required study procedures (tumor assessments, serial biopsies, and pharmacodynamic sampling no longer required); clarify the final visit date and assessments to be performed at final visit; and define the stop date for collection of survival assessments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported