



## 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          | v1               |
| This version publication date  | 02 February 2017 |
| First version publication date | 02 February 2017 |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | M10-440 |
|-----------------------|---------|

##### 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 |
|-------------------|---|

## 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                              |
| <b>Arm title</b>             | 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/m<sup>2</sup> 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

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | ABT-888 20 mg BID + TMZ QD |
|------------------|----------------------------|

Arm description:

ABT-888 20 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m<sup>2</sup> 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

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | ABT-888 40 mg BID + TMZ QD |
|------------------|----------------------------|

Arm description:

ABT-888 40 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m<sup>2</sup> 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

| <b>Number of subjects in period 1</b> | Placebo for ABT-888<br>BID + TMZ QD | ABT-888 20 mg BID<br>+ TMZ QD | ABT-888 40 mg BID<br>+ 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:<br>Placebo for ABT-888 twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m <sup>2</sup> once daily (QD) for 5 days every 28 days. |                                  |
| Reporting group title  | ABT-888 20 mg BID + TMZ QD       |
| Reporting group description:<br>ABT-888 20 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m <sup>2</sup> once daily (QD) for 5 days every 28 days.       |                                  |
| Reporting group title  | ABT-888 40 mg BID + TMZ QD       |
| Reporting group description:<br>ABT-888 40 mg twice daily (BID) for 7 days every 28 days plus temozolomide (TMZ; by body surface area) 150 mg/m <sup>2</sup> 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<br>Units: Subjects |                                  |                            |                            |

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

| Reporting group values             | Total |  |  |
|------------------------------------|-------|--|--|
| Number of subjects                 | 346   |  |  |
| Age categorical<br>Units: Subjects |       |  |  |

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

## End points

### End points reporting groups

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

| 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 <sup>[1]</sup>               | 116 <sup>[2]</sup>         | 115 <sup>[3]</sup>         |  |
| 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.

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

## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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   |

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | 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:  |                                      |
| Every 4 weeks or as needed after subject is registered as off-study, up to 18 months  |                                      |



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

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 |
|----------------|-----------|

End point timeframe:

Every cycle (28 days)

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

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 |
|----------------|-----------|

End point timeframe:

Every cycle (28 days)

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

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 |
|----------------|-----------|

End point timeframe:

Every 2 cycles (8 weeks)

| End point values                 | Placebo for<br>ABT-888 BID +<br>TMZ QD | ABT-888 20<br>mg BID + TMZ<br>QD | ABT-888 40<br>mg BID + TMZ<br>QD |  |
|----------------------------------|--|----------------------------------|----------------------------------|--|
| Subject group type               | Reporting group                        | Reporting group                  | Reporting group                  |  |
| Number of subjects analysed      | 115 <sup>[13]</sup>                    | 116 <sup>[14]</sup>              | 115 <sup>[15]</sup>              |  |
| 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 |
|-----------------|-----------------------------|

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 |
|----------------|-----------|

End point timeframe:

Every cycle (28 days)

| End point values                 | Placebo for<br>ABT-888 BID +<br>TMZ QD | ABT-888 20<br>mg BID + TMZ<br>QD | ABT-888 40<br>mg BID + TMZ<br>QD |  |
|----------------------------------|--|----------------------------------|----------------------------------|--|
| Subject group type               | Reporting group                        | Reporting group                  | Reporting group                  |  |
| Number of subjects analysed      | 115 <sup>[16]</sup>                    | 116 <sup>[17]</sup>              | 115 <sup>[18]</sup>              |  |
| 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)                |  |

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 |
|-----------------|----------------------|

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 |
|----------------|-----------|

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 <sup>[19]</sup>              | 116 <sup>[20]</sup>        | 115 <sup>[21]</sup>        |  |
| 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 |
|-----------------|---|

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 |
|----------------|-----------|

End point timeframe:

Every 2 cycles (8 weeks)

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> once daily (QD) for 5 days every 28 days.

| Serious adverse events  | Placebo for ABT-888 BID + TMZ QD | ABT-888 20 mg BID + TMZ QD | ABT-888 40 mg BID + TMZ QD |
|---|----------------------------------|----------------------------|----------------------------|
| Total subjects affected by serious adverse events                   |                                  |                            |                            |
| subjects affected / exposed   | 28 / 113 (24.78%)                | 27 / 116 (23.28%)          | 31 / 115 (26.96%)          |
| number of deaths (all causes)                                       | 4                                | 2                          | 4                          |
| 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%)                  | 1 / 116 (0.86%)            | 2 / 115 (1.74%)            |
| occurrences causally related to treatment / all                     | 0 / 2                            | 0 / 1                      | 0 / 2                      |
| deaths causally related to treatment / all                          | 0 / 0                            | 0 / 0                      | 0 / 0                      |
| Gliosarcoma   |                                  |                            |                            |
| subjects affected / exposed   | 1 / 113 (0.88%)                  | 0 / 116 (0.00%)            | 0 / 115 (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 melanoma  |                                  |                            |                            |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 2 / 113 (1.77%) | 0 / 116 (0.00%) | 0 / 115 (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 neoplasm progression                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 1 / 116 (0.86%) | 1 / 115 (0.87%) |
| 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 pleural effusion                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| 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%) | 1 / 116 (0.86%) | 0 / 115 (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%) | 1 / 116 (0.86%) | 0 / 115 (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 pain                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 1 / 115 (0.87%) |
| 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%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Vascular disorders                              |                 |                 |                 |
| Deep vein thrombosis                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypotension                                     |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                          | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Orthostatic hypotension                              |                 |                 |                 |
| subjects affected / exposed                          | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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           |
| Pelvic venous thrombosis                             |                 |                 |                 |
| subjects affected / exposed                          | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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 |                 |                 |                 |
| Death  |                 |                 |                 |
| subjects affected / exposed                          | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Disease progression                                  |                 |                 |                 |
| subjects affected / exposed                          | 2 / 113 (1.77%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 1           |
| Fatigue  |                 |                 |                 |
| subjects affected / exposed                          | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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           |
| Pain   |                 |                 |                 |
| subjects affected / exposed                          | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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 / 116 (0.86%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all           | 0 / 1           | 0 / 0           | 0 / 0           |
| Respiratory, thoracic and mediastinal disorders      |                 |                 |                 |



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

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Haemoglobin decreased                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Injury, poisoning and procedural complications  |                 |                 |                 |
| Allergic transfusion reaction                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Ankle fracture                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Facial bones fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Radius fracture                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| 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 disorders                               |                 |                 |                 |
| Angina pectoris                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Arrhythmia                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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 failure congestive                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 2 / 116 (1.72%) | 0 / 115 (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           |
| Pericardial effusion                            |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Nervous system disorders                        |                 |                 |                 |
| Aphasia   |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cerebrovascular accident                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| 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                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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           |
| Neuropathy peripheral                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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           |
| Spinal cord compression                         |                 |                 |                 |

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

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

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Melaena   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Mouth swelling                                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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 / 116 (0.86%) | 1 / 115 (0.87%) |
| 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%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Small intestinal obstruction                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Upper gastrointestinal haemorrhage              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Vomiting  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 113 (1.77%) | 2 / 116 (1.72%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 2 / 3           | 1 / 2           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hepatobiliary disorders                         |                 |                 |                 |
| Cholangitis                                     |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Cholecystitis acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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 failure acute                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Urethral prolapse                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Endocrine disorders                             |                 |                 |                 |
| Adrenal insufficiency                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 0 / 115 (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%) | 2 / 116 (1.72%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 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 / 116 (0.00%) | 0 / 115 (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           |
| Neck pain                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pathological fracture                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Appendicitis                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Bronchitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Cellulitis                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 113 (0.88%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Localised infection                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lower respiratory tract infection               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Pneumonia                                       |                 |                 |                 |



|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Post procedural infection                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Sepsis  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 1 / 116 (0.86%) | 0 / 115 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Decreased appetite                              |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 1 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Dehydration                                     |                 |                 |                 |
| subjects affected / exposed                     | 2 / 113 (1.77%) | 1 / 116 (0.86%) | 2 / 115 (1.74%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Hypercalcaemia                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 113 (0.00%) | 0 / 116 (0.00%) | 1 / 115 (0.87%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

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

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

|   |                         |                         |                         |
|---|-------------------------|-------------------------|-------------------------|
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)  | 4 / 113 (3.54%)<br>9    | 12 / 116 (10.34%)<br>28 | 10 / 115 (8.70%)<br>34  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)  | 7 / 113 (6.19%)<br>7    | 7 / 116 (6.03%)<br>7    | 6 / 115 (5.22%)<br>7    |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Cancer pain<br>subjects affected / exposed<br>occurrences (all) | 6 / 113 (5.31%)<br>7    | 0 / 116 (0.00%)<br>0    | 0 / 115 (0.00%)<br>0    |
| Tumour pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 113 (0.88%)<br>1    | 3 / 116 (2.59%)<br>4    | 6 / 115 (5.22%)<br>7    |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)   | 17 / 113 (15.04%)<br>28 | 19 / 116 (16.38%)<br>23 | 15 / 115 (13.04%)<br>21 |
| Dysgeusia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 113 (7.08%)<br>8    | 15 / 116 (12.93%)<br>16 | 11 / 115 (9.57%)<br>12  |
| Headache<br>subjects affected / exposed<br>occurrences (all)  | 30 / 113 (26.55%)<br>56 | 22 / 116 (18.97%)<br>28 | 25 / 115 (21.74%)<br>49 |
| Lethargy<br>subjects affected / exposed<br>occurrences (all)  | 7 / 113 (6.19%)<br>13   | 6 / 116 (5.17%)<br>7    | 6 / 115 (5.22%)<br>14   |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)                                       | 9 / 113 (7.96%)<br>10   | 19 / 116 (16.38%)<br>24 | 13 / 115 (11.30%)<br>23 |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)  | 5 / 113 (4.42%)<br>8    | 8 / 116 (6.90%)<br>19   | 8 / 115 (6.96%)<br>22   |
| Lymphopenia<br>subjects affected / exposed<br>occurrences (all)   | 5 / 113 (4.42%)<br>9    | 4 / 116 (3.45%)<br>9    | 6 / 115 (5.22%)<br>22   |

|  |                   |                   |                   |
|--|-------------------|-------------------|-------------------|
| Neutropenia  |                   |                   |                   |
| subjects affected / exposed                          | 7 / 113 (6.19%)   | 24 / 116 (20.69%) | 26 / 115 (22.61%) |
| occurrences (all)                                    | 9                 | 59                | 53                |
| Thrombocytopenia                                     |                   |                   |                   |
| subjects affected / exposed                          | 19 / 113 (16.81%) | 49 / 116 (42.24%) | 56 / 115 (48.70%) |
| occurrences (all)                                    | 32                | 146               | 155               |
| General disorders and administration site conditions |                   |                   |                   |
| Chest pain   |                   |                   |                   |
| subjects affected / exposed                          | 4 / 113 (3.54%)   | 5 / 116 (4.31%)   | 6 / 115 (5.22%)   |
| occurrences (all)                                    | 4                 | 6                 | 7                 |
| Chills   |                   |                   |                   |
| subjects affected / exposed                          | 4 / 113 (3.54%)   | 8 / 116 (6.90%)   | 8 / 115 (6.96%)   |
| occurrences (all)                                    | 6                 | 8                 | 8                 |
| Fatigue  |                   |                   |                   |
| subjects affected / exposed                          | 73 / 113 (64.60%) | 75 / 116 (64.66%) | 77 / 115 (66.96%) |
| occurrences (all)                                    | 130               | 139               | 161               |
| Influenza like illness                               |                   |                   |                   |
| subjects affected / exposed                          | 4 / 113 (3.54%)   | 6 / 116 (5.17%)   | 1 / 115 (0.87%)   |
| occurrences (all)                                    | 4                 | 7                 | 1                 |
| Oedema peripheral                                    |                   |                   |                   |
| subjects affected / exposed                          | 1 / 113 (0.88%)   | 9 / 116 (7.76%)   | 4 / 115 (3.48%)   |
| occurrences (all)                                    | 1                 | 12                | 4                 |
| Pain   |                   |                   |                   |
| subjects affected / exposed                          | 8 / 113 (7.08%)   | 10 / 116 (8.62%)  | 12 / 115 (10.43%) |
| occurrences (all)                                    | 10                | 17                | 16                |
| Pyrexia  |                   |                   |                   |
| subjects affected / exposed                          | 6 / 113 (5.31%)   | 7 / 116 (6.03%)   | 4 / 115 (3.48%)   |
| occurrences (all)                                    | 6                 | 7                 | 5                 |
| Gastrointestinal disorders                           |                   |                   |                   |
| Abdominal pain                                       |                   |                   |                   |
| subjects affected / exposed                          | 8 / 113 (7.08%)   | 11 / 116 (9.48%)  | 15 / 115 (13.04%) |
| occurrences (all)                                    | 9                 | 17                | 24                |
| Abdominal pain upper                                 |                   |                   |                   |
| subjects affected / exposed                          | 3 / 113 (2.65%)   | 4 / 116 (3.45%)   | 6 / 115 (5.22%)   |
| occurrences (all)                                    | 3                 | 5                 | 6                 |
| Constipation   |                   |                   |                   |

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

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

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

## 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 <sup>2</sup> /day to 10 mg/m <sup>2</sup> /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