



Clinical trial results:

A double blind randomised phase 2 trial of docetaxel with or without AZD6244 in wt BRAF advanced melanoma

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2009-018153-23 |
| Trial protocol | GB |
| Global end of trial date | 20 February 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 14 March 2021 |
| First version publication date | 14 March 2021 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | OCTO_015 |
|-----------------------|----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University of Oxford |
| Sponsor organisation address | Joint Research Office, 1st floor, Boundary Brook House, Churchill Drive, Headington,, Oxford, United Kingdom, OX3 7GB |
| Public contact | Linda Collins, OCTO, octo-dock-mek@oncology.ox.ac.uk |
| Scientific contact | Linda Collins, OCTO, octo-dock-mek@oncology.ox.ac.uk |

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 | 01 October 2012 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 01 October 2012 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 February 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of AZD6244 in combination with docetaxel, compared with docetaxel alone, in first line treatment of patients with wild type BRAF advanced malignant melanoma.

Protection of trial subjects:

The protocol was conducted in compliance with the UK Clinical Trials Regulations, the Principles of Good Clinical Practice (GCP) and the applicable policies of the sponsoring organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of investigational medicinal products under the European Union Clinical Trials Directive.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 26 October 2010 |
| 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 | United Kingdom: 83 |
| Worldwide total number of subjects | 83 |
| EEA total number of subjects | 83 |

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) | 50 |
| From 65 to 84 years | 33 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Eighty-three patients were recruited to DOC-MEK from 26October2010 to 22May2012 from 16 centres. 41 were recruited in the AZD6244 arm (docetaxel plus selumetinib) and 42 in the Placebo arm (docetaxel plus placebo)

The 16 centres were across the UK under the auspices of the NCRI Melanoma Clinical Study Group.

Pre-assignment

Screening details:

Assessed for eligibility (n=260)

Excluded (n=177): Reasons for exclusion: Not meeting inclusion criteria (n=134), Declined to participate (n=30), Other reasons (n = 13)

Randomised (n=83)

Did not start treatment (n=4)

Pre-assignment period milestones

| | |
|------------------------------|----|
| Number of subjects started | 83 |
| Number of subjects completed | 83 |

Period 1

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

Blinding implementation details:

A placebo (matched to selumetinib) was used in the control group to ensure this blinding.

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Doc + AZD6244 |

Arm description:

Patients receive docetaxel with AZD6244 (selumetinib). Docetaxel 75 mg/m² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles. Selumetinib 75 mg was given orally twice daily on a continuous schedule until disease progression or unacceptable toxicity.

| | |
|--|---------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | AZD6244/selumetinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oromucosal capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Selumetinib 75 mg was given orally twice daily on a continuous schedule until disease progression or unacceptable toxicity.

| | |
|--|-----------------|
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel 75 mg/m² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles.

| | |
|------------------|---------------|
| Arm title | Doc + placebo |
|------------------|---------------|

Arm description:

Patients receive docetaxel with AZD6244 (selumetinib). Docetaxel 75 mg/m² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles. placebo (matched to selumetinib) was given orally twice daily on a continuous schedule until disease progression or unacceptable toxicity.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Docetaxel |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Docetaxel 75 mg/m² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles.

| Number of subjects in period 1 | Doc + AZD6244 | Doc + placebo |
|---------------------------------------|---------------|---------------|
| Started | 41 | 42 |
| Completed | 38 | 41 |
| Not completed | 3 | 1 |
| Did not start allocated intervention | 3 | - |
| Did not start treatment | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|---------------|
| Reporting group title | Doc + AZD6244 |
| Reporting group description: | |
| Patients receive docetaxel with AZD6244 (selumetinib). Docetaxel 75 mg/m ² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles. Selumetinib 75 mg was given orally twice daily on a continuous schedule until disease progression or unacceptable toxicity. | |
| Reporting group title | Doc + placebo |
| Reporting group description: | |
| Patients receive docetaxel with AZD6244 (selumetinib). Docetaxel 75 mg/m ² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles. placebo (matched to selumetinib) was given orally twice daily on a continuous schedule until disease progression or unacceptable toxicity. | |

| Reporting group values | Doc + AZD6244 | Doc + placebo | Total |
|--|---------------|---------------|-------|
| Number of subjects | 41 | 42 | 83 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | | | 0 |
| Preterm newborn infants (gestational age < 37 wks) | | | 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.5 | 59.2 | |
| standard deviation | ± 12.0 | ± 13.3 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 15 | 25 |
| Male | 31 | 27 | 58 |
| Stage | | | |
| Units: Subjects | | | |
| M1c | 33 | 32 | 65 |
| M0 or M1a or M1b | 8 | 10 | 18 |
| ECOG Performance Score | | | |
| Units: Subjects | | | |
| PS = 0 | 28 | 34 | 62 |
| PS=1 | 13 | 8 | 21 |
| Smoking status | | | |
| Units: Subjects | | | |
| Yes | 4 | 3 | 7 |
| No, but smoked in the past | 22 | 27 | 49 |
| Never smoked | 15 | 12 | 27 |

| | | | |
|--|--------------|------------|----|
| LDH | | | |
| Units: Subjects | | | |
| Above Upper limit normal | 20 | 27 | 47 |
| BBelow Upper limit normal | 21 | 15 | 36 |
| ECG (at screening) | | | |
| Units: Subjects | | | |
| Abnormal | 4 | 4 | 8 |
| Normal | 37 | 37 | 74 |
| Not evaluated | 0 | 1 | 1 |
| Urinalysis | | | |
| Units: Subjects | | | |
| Abnormal | 9 | 8 | 17 |
| Normal | 30 | 30 | 60 |
| Not evaluated | 2 | 4 | 6 |
| Conmeds | | | |
| Number of pts reporting taking con meds at baseline | | | |
| Units: Subjects | | | |
| Yes for conmeds at baseline | 35 | 33 | 68 |
| No | 6 | 9 | 15 |
| Vital signs-Temperature | | | |
| Out of 40 (active) and 40 (placebo) patients with data | | | |
| Units: degrees Celsius | | | |
| median | 36.2 | 36.5 | |
| full range (min-max) | 35.2 to 37.3 | 35 to 37.4 | - |
| Vital signs- Pulse rate | | | |
| Available data: 41 active, 41 placebo | | | |
| Units: bpm | | | |
| median | 70 | 72 | |
| full range (min-max) | 56 to 100 | 42 to 120 | - |
| Vital signs- Systolic BP | | | |
| Available data: 41 active, 41 placebo | | | |
| Units: mmHg | | | |
| median | 137 | 136 | |
| full range (min-max) | 97 to 192 | 113 to 175 | - |
| Vital signs- diastolic BP | | | |
| Available data, 41 active, 41 placebo | | | |
| Units: mmHg | | | |
| median | 85 | 82 | |
| full range (min-max) | 56 to 115 | 68 to 95 | - |
| Height | | | |
| Out of 40 active and 40 placebo with data | | | |
| Units: metres | | | |
| arithmetic mean | 1.74 | 1.7 | |
| standard deviation | ± 0.1 | ± 0.1 | - |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 88.4 | 83 | |
| standard deviation | ± 19 | ± 19.5 | - |
| BSA | | | |
| Units: msquared | | | |
| arithmetic mean | 2.022 | 1.939 | |

| | | | |
|---|------------|------------|---|
| standard deviation | ± 0.232 | ± 0.260 | - |
| Biochemistry-ALT | | | |
| Out of 41 active and 41 placebo with data | | | |
| Units: U/L | | | |
| median | 26 | 22 | |
| full range (min-max) | 7 to 93 | 6 to 54 | - |
| Biochemistry-AST | | | |
| Available data for 37 active and 38 placebo patients. | | | |
| Units: U/L | | | |
| median | 24 | 22 | |
| full range (min-max) | 12 to 104 | 14 to 58 | - |
| Bilirubin | | | |
| Data availability 41 active and 41 placebo patients. | | | |
| Units: umol/L | | | |
| median | 10 | 8 | |
| full range (min-max) | 4 to 21 | 2 to 18 | - |
| Biochemistry Creatine clearance | | | |
| Available data for 40 active and 41 placebo patients | | | |
| Units: ml/min | | | |
| median | 111 | 94 | |
| full range (min-max) | 54 to 233 | 39 to 194 | - |
| Haematology-Haemoglobin | | | |
| Data available for 41 active and 41 placebo patients | | | |
| Units: g/dL | | | |
| median | 14 | 14 | |
| full range (min-max) | 10 to 16 | 10 to 17 | - |
| Haematology- White cell count | | | |
| Data available for 41 active and 41 placebo patients | | | |
| Units: x10 ⁹ /L | | | |
| median | 8 | 7 | |
| full range (min-max) | 4 to 15 | 5 to 13 | - |
| Haematology- Neutrophils | | | |
| Data available for 41 active and 41 placebo patients | | | |
| Units: x10 ⁹ /L | | | |
| median | 5 | 5 | |
| full range (min-max) | 2 to 11 | 2 to 11 | - |
| Haematology- Platelets | | | |
| Data available for 41 active and 41 placebo patients | | | |
| Units: x10 ⁹ /L | | | |
| median | 259 | 255 | |
| full range (min-max) | 147 to 681 | 177 to 754 | - |
| Target lesion Sum LD | | | |
| Units: mm | | | |
| median | 98 | 56 | |
| full range (min-max) | 16 to 243 | 11 to 450 | - |

End points

End points reporting groups

| | |
|---|--------------------------------------|
| Reporting group title | Doc + AZD6244 |
| Reporting group description: Patients receive docetaxel with AZD6244 (selumetinib). Docetaxel 75 mg/m ² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles. Selumetinib 75 mg was given orally twice daily on a continuous schedule until disease progression or unacceptable toxicity. | |
| Reporting group title | Doc + placebo |
| Reporting group description: Patients receive docetaxel with AZD6244 (selumetinib). Docetaxel 75 mg/m ² was administered intravenously on day 1 of a 21-day cycle up to a maximum of six cycles. placebo (matched to selumetinib) was given orally twice daily on a continuous schedule until disease progression or unacceptable toxicity. | |
| Subject analysis set title | Intention-to-treat population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Includes all patients who were randomly assigned. | |
| Subject analysis set title | Sensitivity population |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Patients that had CT scans as per protocol. Doc + Placebo = 33 and Doc+AZD6244 = 28 | |
| Subject analysis set title | Sensitivity population- per protocol |
| Subject analysis set type | Full analysis |
| Subject analysis set description: This includes 77 patients. Four patients who did not start treatment and two patients who were later found to be ineligible are excluded. | |

Primary: Progression Free Survival

| | |
|--|---------------------------|
| End point title | Progression Free Survival |
| End point description: The primary endpoint is Progression Free Survival (PFS). This is defined as time from date of randomisation to the first of date of progression (using CT scan, x-ray, MRI scan and clinical examination) using modified RECIST criteria or date of death (events). For patients without an event, the time from date of randomisation to date last known alive will be the censored PFS time. | |
| End point type | Primary |
| End point timeframe: From first patient randomised to date last known alive before 01 Oct 2012. | |

| End point values | Doc + AZD6244 | Doc + placebo | Intention-to-treat population | |
|-----------------------------|-------------------|-------------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 41 ^[1] | 42 ^[2] | 83 ^[3] | |
| Units: Patients | 32 | 36 | 68 | |

Notes:

[1] - Count given is the number of events

[2] - Count given is the number of events

[3] - Count given is the number of events

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Cox Proportional Hazards analysis |
| Statistical analysis description: Adjusted for M status and performance status | |
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.13 ^[4] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.753 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.498 |
| upper limit | 1.138 |

Notes:

[4] - p value < 0.1 one-sided considered to be significant.

Secondary: Progression free survival at 6 months

| | |
|--|---------------------------------------|
| End point title | Progression free survival at 6 months |
| End point description: PFS at 6 months is defined as the percentage progression free survival at 6 months from the PFS Kaplan Meier graph. This would allow all patients randomised to be included. | |
| End point type | Secondary |
| End point timeframe: At 6 months | |

| | | | | |
|----------------------------------|-----------------|-----------------|--|--|
| End point values | Doc + AZD6244 | Doc + placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 41 | 42 | | |
| Units: % | | | | |
| number (confidence interval 90%) | 40 (27 to 53) | 26 (15 to 38) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | PFS rate |
| Statistical analysis description: Progression free survival rate at 6 months was estimated from the KM plot. | |
| Comparison groups | Doc + AZD6244 v Doc + placebo |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.187 |
| Method | Logrank |
| Parameter estimate | Difference in PFS rate (%) |
| Point estimate | 14 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 31.4 |

Notes:

[5] - Result is the estimated difference in PFS rate (%)

Secondary: Overall survival

| | |
|--|------------------|
| End point title | Overall survival |
| End point description: | |
| This is defined as the time from randomisation to death (event) or time from randomisation to date last known alive (censored time). | |
| End point type | Secondary |
| End point timeframe: | |
| Trial duration i.e. from start of recruitment to 01 Oct 2012 . Patients without an event at the time of the datalock on 01 Oct 2012 were censored at their last known alive time (date last seen). | |

| End point values | Doc + AZD6244 | Doc + placebo | Intention-to-treat population | |
|-----------------------------|-----------------|-----------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 41 | 42 | 83 | |
| Units: Patients | 20 | 17 | 37 | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Cox Proportional Hazards analysis |
| Statistical analysis description: | |
| Unadjusted | |
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.169 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.373 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.797 |
| upper limit | 2.369 |

Secondary: Objective response rate

| | |
|---|-------------------------|
| End point title | Objective response rate |
| End point description: | |
| Best overall response recorded from the start date of treatment until disease progression. The numerator of the objective response rate is the number of patients achieving a CR or PR. The denominator is all patients randomised. | |
| End point type | Secondary |
| End point timeframe: | |
| From the start date of treatment until disease progression. | |

| End point values | Doc + AZD6244 | Doc + placebo | Intention-to-treat population | |
|-----------------------------|-----------------|-----------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 41 | 42 | 83 | |
| Units: Patients | 13 | 6 | 19 | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Chi squared test |
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.059 |
| Method | Chi-squared |

Secondary: Lab analysis

| | |
|---|--------------|
| End point title | Lab analysis |
| End point description: | |
| This secondary endpoint includes multiple lab based measures: vital signs (temperature, pulse rate and blood pressure), weight, biochemistry, haematology and urinalysis measures, physical examination outcomes (general appearance, skin etc.) and ECG measures. Analysis was descriptive- data were graphed on a per- patient basis. The measurement type is not 'number' as selected above but it is the relevant unit for each measure, for example for temperature, the data points graphed are in degrees Celsius. | |
| End point type | Secondary |

End point timeframe:

Trial duration.

| | | | | |
|-----------------------------|-------------------------------|--|--|--|
| End point values | Intention-to-treat population | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 83 | | | |
| Units: multiple measures | | | | |
| number (not applicable) | 83 | | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Lab data- all graphs/DOCMEK_StatisticalReport _V4. |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival-updated

| | |
|-----------------|--------------------------|
| End point title | Overall survival-updated |
|-----------------|--------------------------|

End point description:

time from randomisation to death (event) or time from randomisation to date last known alive (censored time).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

OS analysis was carried out at the final analysis time point on data taken on 01Oct2012. Another data extraction was taken on 05Mar2013 in order to carry out posthoc analyses, OS was analysed again on this data which has more death events.

| | | | | |
|-----------------------------|-----------------|-----------------|-------------------------------|--|
| End point values | Doc + AZD6244 | Doc + placebo | Intention-to-treat population | |
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 41 | 42 | 83 | |
| Units: Patients | 26 | 28 | 54 | |

Statistical analyses

| | |
|-----------------------------------|----------------------|
| Statistical analysis title | Cox Regression model |
|-----------------------------------|----------------------|

Statistical analysis description:

Adjusted for with Mstatus and Performance Score

| | |
|-------------------|-------------------------------|
| Comparison groups | Doc + placebo v Doc + AZD6244 |
|-------------------|-------------------------------|

| | |
|---|-------------------|
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.318 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.15 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.71 |
| upper limit | 1.84 |

Secondary: Overall survival-updated sensitivity

| | |
|---|--------------------------------------|
| End point title | Overall survival-updated sensitivity |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| This is OS analysis done on a later timepoint to the final analysis and has a few more events (see OS-updated), this is on the per protocol population. | |

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|-----------------|-----------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 37 | 40 | 77 | |
| Units: Patients | 23 | 26 | 49 | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Cox Regression model |
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.348 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.12 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.68 |
| upper limit | 1.87 |

Other pre-specified: Progression Free survival- sensitivity analysis

| | |
|-----------------|---|
| End point title | Progression Free survival- sensitivity analysis |
|-----------------|---|

End point description:

Survival is from date of randomisation to the first of date of progression (using CT scan, x-ray, MRI scan and clinical examination) using modified RECIST criteria or date of death (events). For patients without an event, the time from date of randomisation to date last known alive will be the censored PFS time.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Trial duration i.e. from start of recruitment to 01 Oct 2012 . Patients without an event at the time of the datalock on 01 Oct 2012 were censored at their last known alive time (date last seen).

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population | |
|-----------------------------|-------------------|-------------------|------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 28 ^[6] | 33 ^[7] | 61 ^[8] | |
| Units: Patients | 24 | 27 | 51 | |

Notes:

[6] - only pts with ct scans as per protocol

[7] - only pts with ct scans as per protocol

[8] - Doc + Placebo = 33 and Doc+AZD6244 = 28

Statistical analyses

| | |
|----------------------------|-----------------------------------|
| Statistical analysis title | Cox Proportional Hazards analysis |
|----------------------------|-----------------------------------|

Statistical analysis description:

Adjusted for mstatus, performance status

| | |
|---|-------------------------------|
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 61 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.468 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.022 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.649 |
| upper limit | 1.612 |

Other pre-specified: Progression Free Survival- Sensitivity analysis (per-protocol)

| | |
|-----------------|--|
| End point title | Progression Free Survival- Sensitivity analysis (per-protocol) |
|-----------------|--|

End point description:

Survival is from date of randomisation to the first of date of progression (using CT scan, x-ray, MRI scan

and clinical examination) using modified RECIST criteria or date of death (events). For patients without an event, the time from date of randomisation to date last known alive will be the censored PFS time.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Trial duration i.e. from start of recruitment to 01 Oct 2012 . Patients without an event at the time of the datalock on 01 Oct 2012 were censored at their last known alive time (date last seen).

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|-----------------|-----------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 37 | 40 | 77 | |
| Units: Patients | 28 | 34 | 62 | |

Statistical analyses

| | |
|---|-----------------------------------|
| Statistical analysis title | Cox Proportional Hazards analysis |
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 77 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.106 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.721 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.468 |
| upper limit | 1.09 |

Other pre-specified: Progression Free Survival- Sensitivity analysis adjusted

| | |
|-----------------|--|
| End point title | Progression Free Survival- Sensitivity analysis adjusted |
|-----------------|--|

End point description:

Survival is from date of randomisation to the first of date of progression (using CT scan, x-ray, MRI scan and clinical examination) using modified RECIST criteria or date of death (events). For patients without an event, the time from date of randomisation to date last known alive will be the censored PFS time.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Trial duration i.e. from start of recruitment to 01 Oct 2012 . Patients without an event at the time of the datalock on 01 Oct 2012 were censored at their last known alive time (date last seen).

| End point values | Doc + AZD6244 | Doc + placebo | Intention-to-treat population | |
|-----------------------------|-----------------|-----------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 41 | 42 | 83 | |
| Units: Patients | 32 | 36 | 68 | |

Statistical analyses

| Statistical analysis title | Cox Proportional Hazards analysis |
|--|-----------------------------------|
| Statistical analysis description: Adjusted for mstatus, performance status, LDH, target lesion sum and time interval between randomisation and baseline CT scan | |
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.113 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.723 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.465 |
| upper limit | 1.123 |

Other pre-specified: Progression Free survival- centre effect

| End point title | Progression Free survival- centre effect |
|---|--|
| End point description: Survival is from date of randomisation to the first of date of progression (using CT scan, x-ray, MRI scan and clinical examination) using modified RECIST criteria or date of death (events). For patients without an event, the time from date of randomisation to date last known alive will be the censored PFS time. | |
| End point type | Other pre-specified |
| End point timeframe: Trial duration i.e. from start of recruitment to 01 Oct 2012 . Patients without an event at the time of the datalock on 01 Oct 2012 were censored at their last known alive time (date last seen). | |

| End point values | Doc + AZD6244 | Doc + placebo | Intention-to-treat population | |
|-----------------------------|-----------------|-----------------|-------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 41 | 42 | 83 | |
| Units: Patients | 32 | 36 | 68 | |

Statistical analyses

| | |
|-----------------------------------|-----------------------------------|
| Statistical analysis title | Cox Proportional Hazards analysis |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

Centre effects were limited to the three biggest recruiters and all other centres are combined.

| | |
|---|-------------------------------|
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.305 |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 1.348 |
| Confidence interval | |
| level | 90 % |
| sides | 2-sided |
| lower limit | 0.602 |
| upper limit | 3.016 |

Post-hoc: Progression Free Survival - Sensitivity analysis interval

| | |
|-----------------|---|
| End point title | Progression Free Survival - Sensitivity analysis interval |
|-----------------|---|

End point description:

Survival is from date of randomisation to the first of date of progression (using CT scan, x-ray, MRI scan and clinical examination) using modified RECIST criteria or date of death (events). For patients without an event, the time from date of randomisation to date last known alive will be the censored PFS time.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Trial duration i.e. from start of recruitment to 01 Oct 2012 . Patients without an event at the time of the datalock on 01 Oct 2012 were censored at their last known alive time (date last seen).

| | | | | |
|-----------------------------|-----------------|-----------------|-------------------------------|--|
| End point values | Doc + AZD6244 | Doc + placebo | Intention-to-treat population | |
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 41 | 42 | 83 | |
| Units: Patients | 32 | 36 | 68 | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Survival analysis with interval censoring |
| Statistical analysis description: Patients are assessed periodically for the response so progression is known only to have occurred at some time between visits, the exact time is not known. We carried out interval censored analysis as a sensitivity analysis to demonstrate if allowing for interval censoring gives a different interpretation of the primary outcome. | |
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 83 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.302 ^[9] |
| Method | Survival analysis with interval censorin |

Notes:

[9] - Generalized log rank test compares between treatment groups. P-value given are from applying the Zhao & Sun. 2004 method is SAS version 9.2.

Post-hoc: Progression free survival- NRAS

| | |
|---|---------------------------------|
| End point title | Progression free survival- NRAS |
| End point description: On 05Mar2013 (post final analysis) we had 64/83 (77%) patients with NRAS data available. The main analysis included the per-protocol sample. A sensitivity analysis will be carried out for patients who had changed BRAF status on re-testing carried out with the NRAS test. The ITT sample is not relevant to this analysis and NRAS is not available on all randomised patients. We have N = 77/83 (93%) in the PP-sample of which 60/77 (78%) have NRAS data and 75/83 in the sensitivity analysis sample of which 58/75 (77%) have NRAS data. | |
| End point type | Post-hoc |

End point timeframe:

Trial duration. NRAS mutational analysis for all patients has been derived from archival melanoma tumour tissue samples. Progression times used was from the trial.

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|--------------------|--------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 29 ^[10] | 31 ^[11] | 60 ^[12] | |
| Units: Patients | 25 | 28 | 53 | |

Notes:

[10] - PP population with NRAS data

[11] - PP population with NRAS data

[12] - pp sample with NRAS data

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Cox Regression model |
| Statistical analysis description: The impact of NRAS mutation status (Mutated/Wild type]) on effectiveness of treatment in PFS was assessed by adding an interaction term with treatment in the COX model. What we mean by interaction is that the effect of the treatment may be different, depending on NRAS mutation status. Model also adjusted for stratification variables | |
| Comparison groups | Doc + AZD6244 v Doc + placebo v Sensitivity population- per protocol |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 120 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.824 ^[13] |
| Method | Regression, Cox |

Notes:

[13] - p-value is for interaction term

HRs (95% CI) for active vs placebo arms are below for wild type and mutated NRAS respectively

0.63 (0.25, 1.53)

0.71 (0.349, 1.44)

Post-hoc: Progression free survival- NRAS sensitivity

| | |
|-----------------|---|
| End point title | Progression free survival- NRAS sensitivity |
|-----------------|---|

End point description:

On 05Mar2013 (post final analysis) we had 64/83 (77%) patients with NRAS data available. The main analysis included the per-protocol sample. A sensitivity analysis (results here) will be carried out for patients who had changed BRAF status on re-testing carried out with the NRAS test. The ITT sample is not relevant to this analysis and NRAS is not available on all randomised patients. We have N = 77/83 (93%) in the PP-sample of which 60/77 (78%) have NRAS data and 75/83 in the sensitivity analysis sample of which 58/75 (77%) have NRAS data.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Trial duration. NRAS mutational analysis for all patients has been derived from archival melanoma tumour tissue samples. Progression times used was from the trial.

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|--------------------|--------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 28 ^[14] | 30 ^[15] | 58 ^[16] | |
| Units: Patients | 24 | 27 | 51 | |

Notes:

[14] - PP population with NRAS data minus one pt with BRAF mutation

[15] - PP population with NRAS data minus one pt with BRAF mutation

[16] - PP sample with NRAS data, further excludes 2 samples found to have BRAF mutation on retesting

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Cox Regression model |
|----------------------------|----------------------|

Statistical analysis description:

Model with interaction term and stratification variables

| | |
|---|-------------------------------|
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 58 |
| Analysis specification | Post-hoc |
| Analysis type | superiority |
| P-value | = 0.797 ^[17] |
| Method | Regression, Cox |

Notes:

[17] - p-value is for interaction term. HRs (95% CI) between active vs placebo treatment groups are below

0.61 (0.24, 1.58) - wild type

0.71 (0.350, 1.45) -mutated NRAS

Post-hoc: Overall survival-NRAS

| | |
|-----------------|-----------------------|
| End point title | Overall survival-NRAS |
|-----------------|-----------------------|

End point description:

On 05Mar2013 (post final analysis) we had 64/83 (77%) patients with NRAS data available. The main analysis included the per-protocol sample. A sensitivity analysis will be carried out for patients who had changed BRAF status on re-testing carried out with the NRAS test. The ITT sample is not relevant to this analysis and NRAS is not available on all randomised patients. We have N = 77/83 (93%) in the PP-sample of which 60/77 (78%) have NRAS data and 75/83 in the sensitivity analysis sample of which 58/75 (77%) have NRAS data.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Trial duration. NRAS mutational analysis for all patients has been derived from archival melanoma tumour tissue samples. Progression times used was from the trial.

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|-----------------|-----------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 29 | 31 | 60 ^[18] | |
| Units: Patients | 18 | 20 | 38 | |

Notes:

[18] - with NRAS data only

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Cox Regression model |
|----------------------------|----------------------|

Statistical analysis description:

The impact of NRAS mutation status (Mutated/Wild type)] on OS was assessed by adding an interaction term with treatment in the Cox model. Model has interaction term and stratification variables

| | |
|-------------------|-------------------------------|
| Comparison groups | Doc + AZD6244 v Doc + placebo |
|-------------------|-------------------------------|

| | |
|---|----|
| Number of subjects included in analysis | 60 |
|---|----|

| | |
|------------------------|----------|
| Analysis specification | Post-hoc |
|------------------------|----------|

| | |
|---------------|-----------------------------|
| Analysis type | superiority ^[19] |
|---------------|-----------------------------|

| | |
|---------|-------------------------|
| P-value | = 0.072 ^[20] |
|---------|-------------------------|

| | |
|--------|-----------------|
| Method | Regression, Cox |
|--------|-----------------|

Notes:

[19] - HRs (95%CI) between active vs placebo groups below
0.51 (0.16, 1.60)- WT
1.97 (0.73, 5.33)-mutated NRAS

[20] - p-value is for interaction term

Post-hoc: Overall survival-NRAS sensitivity

| | |
|-----------------|-----------------------------------|
| End point title | Overall survival-NRAS sensitivity |
|-----------------|-----------------------------------|

End point description:

On 05Mar2013 (post final analysis) we had 64/83 (77%) patients with NRAS data available. The main analysis included the per-protocol sample. A sensitivity analysis will be carried out for patients who had changed BRAF status on re-testing carried out with the NRAS test. The ITT sample is not relevant to this

analysis and NRAS is not available on all randomised patients. We have N = 77/83 (93%) in the PP-sample of which 60/77 (78%) have NRAS data and 75/83 in the sensitivity analysis sample of which 58/75 (77%) have NRAS data.

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Trial duration. NRAS mutational analysis for all patients has been derived from archival melanoma tumour tissue samples. Progression times used was from the trial.

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|-----------------|-----------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 28 | 30 | 58 ^[21] | |
| Units: Patients | 18 | 19 | 37 | |

Notes:

[21] - This excludes the patients in the per-protocol sample found to have BRAF mutation on retesting

Statistical analyses

| | |
|----------------------------|----------------------|
| Statistical analysis title | Cox Regression model |
|----------------------------|----------------------|

Statistical analysis description:

Model with interaction term and stratification variables

| | |
|---|-------------------------------|
| Comparison groups | Doc + AZD6244 v Doc + placebo |
| Number of subjects included in analysis | 58 |
| Analysis specification | Post-hoc |
| Analysis type | superiority ^[22] |
| P-value | = 0.12 |
| Method | Regression, Cox |

Notes:

[22] - Hazard ratio (95%CI) for AZD6244 vs Placebo groups

0.60 (0.18, 1.97)- WT

1.99 (0.73, 5.38)- mutated NRAS

Post-hoc: Objective response rate for mutated NRAS patients

| | |
|-----------------|---|
| End point title | Objective response rate for mutated NRAS patients |
|-----------------|---|

End point description:

Best overall response as reported for evaluable/measurable scans including target, non-target and new lesion for NRAS mutated patients in PP population

| | |
|----------------|----------|
| End point type | Post-hoc |
|----------------|----------|

End point timeframe:

Trial duration

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|--------------------|--------------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 20 ^[23] | 17 ^[24] | | |
| Units: Patients | | | | |
| Complete response | 1 | 0 | 1 | |
| Partial response | 6 | 2 | 8 | |
| Stable disease | 7 | 9 | 16 | |
| Progressive disease | 2 | 6 | 8 | |
| Not applicable | 4 | 0 | 4 | |

Notes:

[23] - Mutated only

[24] - Mutated only

Statistical analyses

No statistical analyses for this end point

Post-hoc: Objective response rate for WT NRAS patients

| | |
|------------------------|---|
| End point title | Objective response rate for WT NRAS patients |
| End point description: | Best overall response as reported for evaluable/measurable scans including target, non-target and new lesion for NRAS wild type patients in PP population |
| End point type | Post-hoc |
| End point timeframe: | |
| Trial duration | |

| End point values | Doc + AZD6244 | Doc + placebo | Sensitivity population- per protocol | |
|-----------------------------|-------------------|-----------------|--------------------------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 9 ^[25] | 14 | | |
| Units: Patients | | | | |
| Complete response | 0 | 0 | 0 | |
| Partial response | 2 | 2 | 4 | |
| Stable disease | 4 | 4 | 8 | |
| Progressive disease | 3 | 8 | 11 | |
| Not applicable* | 0 | 0 | 0 | |

Notes:

[25] - WT total=23

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event monitoring starts from the time the patient receives any of the research procedures until they complete the trial.

Adverse event reporting additional description:

In addition to the AEs entered below, there are 99 (nonserious) events where the System Organ Class was classed as "Other" so cannot be entered. 3 AEs on placebo arm were fatal but were part of the 99 that had no SOC.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Docetaxel+AZD6244 |
|-----------------------|-------------------|

Reporting group description: -

| | |
|-----------------------|--------------------|
| Reporting group title | Docetaxel+ Placebo |
|-----------------------|--------------------|

Reporting group description: -

| Serious adverse events | Docetaxel+AZD6244 | Docetaxel+ Placebo | |
|---|--|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 29 / 38 (76.32%) | 20 / 41 (48.78%) | |
| number of deaths (all causes) | 23 | 27 | |
| number of deaths resulting from adverse events | 2 | 0 | |
| Investigations | | | |
| Neutrophil Count Decreased | Additional description: Neutrophil Count Decreased | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac Arrest | Additional description: Cardiac Arrest | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nervous system disorders | | | |
| Presyncope | Additional description: Presyncope | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|---|------------------|------------------|
| Blood and lymphatic system disorders | | | |
| | Additional description: Anaemia | | |
| | subjects affected / exposed | 0 / 38 (0.00%) | 1 / 41 (2.44%) |
| | occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| Anaemia | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | Additional description: Febrile Neutropenia | | |
| | subjects affected / exposed | 20 / 38 (52.63%) | 13 / 41 (31.71%) |
| | occurrences causally related to treatment / all | 25 / 25 | 15 / 16 |
| Febrile Neutropenia | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | | | |
| | | | |
| | | | |
| General disorders and administration site conditions | | | |
| | Additional description: Fever | | |
| | subjects affected / exposed | 5 / 38 (13.16%) | 2 / 41 (4.88%) |
| | occurrences causally related to treatment / all | 5 / 6 | 1 / 2 |
| Fever | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | | | |
| | | | |
| | | | |
| Immune system disorders | | | |
| | Additional description: Allergic Reaction | | |
| | subjects affected / exposed | 1 / 38 (2.63%) | 0 / 41 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| Allergic Reaction | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | | | |
| | | | |
| | | | |
| Eye disorders | | | |
| | Additional description: Retinal Vascular Disorder | | |
| | subjects affected / exposed | 1 / 38 (2.63%) | 0 / 41 (0.00%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| Retinal Vascular Disorder | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | | | |
| | | | |
| | | | |
| Gastrointestinal disorders | | | |
| | Additional description: Gastric Haemorrhage | | |
| | subjects affected / exposed | 2 / 38 (5.26%) | 0 / 41 (0.00%) |
| | occurrences causally related to treatment / all | 2 / 2 | 0 / 0 |
| Gastric Haemorrhage | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| | | | |
| | | | |
| | | | |
| Vomiting | Additional description: Vomiting | | |
| | subjects affected / exposed | 1 / 38 (2.63%) | 1 / 41 (2.44%) |
| | occurrences causally related to treatment / all | 1 / 1 | 0 / 1 |
| | deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Diarrhoea | Additional description: Diarrhoea | | |
| | | | |
| | | | |
| | | | |

| | | | |
|---|--|----------------|--|
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal Pain | Additional description: Abdominal Pain | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnea | Additional description: Dyspnea | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | Additional description: Arthralgia | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle Weakness Lower Limb | Additional description: Muscle Weakness Lower Limb | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Other - Source Unknown | Additional description: Other - Source Unknown | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis Infectious | Additional description: Enterocolitis Infectious | | |
| subjects affected / exposed | 0 / 38 (0.00%) | 1 / 41 (2.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin Infection | Additional description: Skin Infection | | |

| | | | |
|---|---|----------------|--|
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lung Infection | Additional description: Lung Infection | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 2 / 41 (4.88%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper Respiratory Infection | Additional description: Upper Respiratory Infection | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | Additional description: Sepsis | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 41 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Docetaxel+AZD6244 | Docetaxel+ Placebo | |
|---|--|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 35 / 38 (92.11%) | 40 / 41 (97.56%) | |
| Vascular disorders | | | |
| Flushing | Additional description: Flushing | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 6 / 41 (14.63%) | |
| occurrences (all) | 4 | 7 | |
| Thromboembolic Event | Additional description: Thromboembolic Event | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 41 (2.44%) | |
| occurrences (all) | 1 | 1 | |
| General disorders and administration site conditions | | | |
| Localized Edema | Additional description: Localized Edema | | |
| subjects affected / exposed | 16 / 38 (42.11%) | 9 / 41 (21.95%) | |
| occurrences (all) | 24 | 13 | |
| Fatigue | Additional description: Fatigue | | |

| | | | |
|--|---|------------------------|--|
| subjects affected / exposed occurrences (all) | 28 / 38 (73.68%) 58 | 32 / 41 (78.05%) 60 | |
| Fever | Additional description: Fever | | |
| subjects affected / exposed occurrences (all) | 7 / 38 (18.42%) 9 | 3 / 41 (7.32%) 3 | |
| Immune system disorders | | | |
| Allergic Reaction | Additional description: Allergic Reaction | | |
| subjects affected / exposed occurrences (all) | 4 / 38 (10.53%) 5 | 5 / 41 (12.20%) 7 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnea | Additional description: Dyspnea | | |
| subjects affected / exposed occurrences (all) | 4 / 38 (10.53%) 4 | 6 / 41 (14.63%) 6 | |
| Epistaxis | Additional description: Epistaxis | | |
| subjects affected / exposed occurrences (all) | 9 / 38 (23.68%) 13 | 4 / 41 (9.76%) 7 | |
| Cough | Additional description: Cough | | |
| subjects affected / exposed occurrences (all) | 3 / 38 (7.89%) 3 | 3 / 41 (7.32%) 5 | |
| Psychiatric disorders | | | |
| Depression | Additional description: Depression | | |
| subjects affected / exposed occurrences (all) | 6 / 38 (15.79%) 8 | 0 / 41 (0.00%) 0 | |
| Insomnia | Additional description: Insomnia | | |
| subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 2 | 4 / 41 (9.76%) 6 | |
| Investigations | | | |
| Neutrophil Count Decreased | Additional description: Neutrophil Count Decreased | | |
| subjects affected / exposed occurrences (all) | 4 / 38 (10.53%) 6 | 13 / 41 (31.71%) 15 | |
| Platelet Count Decreased | Additional description: Platelet Count Decreased | | |
| subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 41 (2.44%) 3 | |
| Nervous system disorders | | | |
| Peripheral Sensory Neuropathy | Additional description: Peripheral Sensory Neuropathy | | |

| | | | |
|--------------------------------------|---|------------------|--|
| subjects affected / exposed | 9 / 38 (23.68%) | 14 / 41 (34.15%) | |
| occurrences (all) | 11 | 17 | |
| Dizziness | Additional description: Dizziness | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 4 / 41 (9.76%) | |
| occurrences (all) | 11 | 4 | |
| Dysgeusia | Additional description: Dysgeusia | | |
| subjects affected / exposed | 14 / 38 (36.84%) | 13 / 41 (31.71%) | |
| occurrences (all) | 19 | 18 | |
| Headache | Additional description: Headache | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 4 / 41 (9.76%) | |
| occurrences (all) | 3 | 5 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | Additional description: Anaemia | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 4 / 41 (9.76%) | |
| occurrences (all) | 6 | 5 | |
| Febrile Neutropenia | Additional description: Febrile Neutropenia | | |
| subjects affected / exposed | 8 / 38 (21.05%) | 5 / 41 (12.20%) | |
| occurrences (all) | 11 | 6 | |
| Eye disorders | | | |
| Blurred Vision | Additional description: Blurred Vision | | |
| subjects affected / exposed | 4 / 38 (10.53%) | 1 / 41 (2.44%) | |
| occurrences (all) | 5 | 1 | |
| Dry Eye | Additional description: Dry Eye | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 1 / 41 (2.44%) | |
| occurrences (all) | 3 | 1 | |
| Floaters | Additional description: Floaters | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 0 / 41 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Watering Eyes | Additional description: Watering Eyes | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 5 / 41 (12.20%) | |
| occurrences (all) | 7 | 5 | |
| Gastrointestinal disorders | | | |
| Nausea | Additional description: Nausea | | |
| subjects affected / exposed | 19 / 38 (50.00%) | 15 / 41 (36.59%) | |
| occurrences (all) | 30 | 18 | |
| Constipation | Additional description: Constipation | | |

| | | | |
|--|--|------------------|--|
| subjects affected / exposed | 11 / 38 (28.95%) | 11 / 41 (26.83%) | |
| occurrences (all) | 13 | 15 | |
| Flatulence | Additional description: Flatulence | | |
| subjects affected / exposed | 1 / 38 (2.63%) | 1 / 41 (2.44%) | |
| occurrences (all) | 3 | 2 | |
| Dyspepsia | Additional description: Dyspepsia | | |
| subjects affected / exposed | 5 / 38 (13.16%) | 10 / 41 (24.39%) | |
| occurrences (all) | 8 | 13 | |
| Diarrhoea | Additional description: Diarrhoea | | |
| subjects affected / exposed | 33 / 38 (86.84%) | 20 / 41 (48.78%) | |
| occurrences (all) | 82 | 29 | |
| Dry Mouth | Additional description: Dry Mouth | | |
| subjects affected / exposed | 6 / 38 (15.79%) | 3 / 41 (7.32%) | |
| occurrences (all) | 9 | 3 | |
| Vomiting | Additional description: Vomiting | | |
| subjects affected / exposed | 11 / 38 (28.95%) | 8 / 41 (19.51%) | |
| occurrences (all) | 15 | 9 | |
| Abdominal Pain | Additional description: Abdominal Pain | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 2 / 41 (4.88%) | |
| occurrences (all) | 3 | 2 | |
| Mucositis Oral | Additional description: Mucositis Oral | | |
| subjects affected / exposed | 21 / 38 (55.26%) | 17 / 41 (41.46%) | |
| occurrences (all) | 36 | 27 | |
| Skin and subcutaneous tissue disorders | | | |
| Other Rash | Additional description: Other Rash | | |
| subjects affected / exposed | 2 / 38 (5.26%) | 0 / 41 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nail Ridging | Additional description: Nail Ridging | | |
| subjects affected / exposed | 7 / 38 (18.42%) | 9 / 41 (21.95%) | |
| occurrences (all) | 8 | 12 | |
| Rash Acneiform | Additional description: Rash Acneiform | | |
| subjects affected / exposed | 31 / 38 (81.58%) | 20 / 41 (48.78%) | |
| occurrences (all) | 56 | 26 | |
| Dry Skin | Additional description: Dry Skin | | |
| subjects affected / exposed | 3 / 38 (7.89%) | 1 / 41 (2.44%) | |
| occurrences (all) | 5 | 1 | |

| | | | |
|--|--|------------------|--|
| Alopecia subjects affected / exposed occurrences (all) | Additional description: Alopecia | | |
| | 20 / 38 (52.63%) | 21 / 41 (51.22%) | |
| | 21 | 22 | |
| Palmar-Plantar Erythrodysesthesia Syndrome subjects affected / exposed occurrences (all) | Additional description: Palmar-Plantar Erythrodysesthesia Syndrome | | |
| | 5 / 38 (13.16%) | 1 / 41 (2.44%) | |
| | 6 | 1 | |
| Periorbital Edema subjects affected / exposed occurrences (all) | Additional description: Periorbital Edema | | |
| | 6 / 38 (15.79%) | 0 / 41 (0.00%) | |
| | 7 | 0 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Pain - Other subjects affected / exposed occurrences (all) | Additional description: Arthralgia | | |
| | 4 / 38 (10.53%) | 10 / 41 (24.39%) | |
| | 7 | 13 | |
| | Additional description: Myalgia | | |
| | 5 / 38 (13.16%) | 8 / 41 (19.51%) | |
| | 7 | 11 | |
| | Additional description: Pain - Other | | |
| | 17 / 38 (44.74%) | 12 / 41 (29.27%) | |
| | 43 | 19 | |
| Infections and infestations Nail Infection subjects affected / exposed occurrences (all) Upper Respiratory Infection subjects affected / exposed occurrences (all) Mucosal Infection subjects affected / exposed occurrences (all) Bronchial Infection subjects affected / exposed occurrences (all) Wound Infection subjects affected / exposed occurrences (all) Urinary Tract Infection | Additional description: Nail Infection | | |
| | 3 / 38 (7.89%) | 0 / 41 (0.00%) | |
| | 3 | 0 | |
| | Additional description: Upper Respiratory Infection | | |
| | 4 / 38 (10.53%) | 1 / 41 (2.44%) | |
| | 4 | 1 | |
| | Additional description: Mucosal Infection | | |
| | 2 / 38 (5.26%) | 5 / 41 (12.20%) | |
| | 2 | 6 | |
| | Additional description: Bronchial Infection | | |
| | 0 / 38 (0.00%) | 5 / 41 (12.20%) | |
| | 0 | 5 | |
| | Additional description: Wound Infection | | |
| | 2 / 38 (5.26%) | 1 / 41 (2.44%) | |
| | 2 | 1 | |
| | Additional description: Urinary Tract Infection | | |

| | | | |
|--|---|-----------------------|--|
| subjects affected / exposed occurrences (all) | 2 / 38 (5.26%) 2 | 1 / 41 (2.44%) 1 | |
| Other Infection | Additional description: Other Infection | | |
| subjects affected / exposed occurrences (all) | 3 / 38 (7.89%) 6 | 1 / 41 (2.44%) 1 | |
| Skin Infection | Additional description: Skin Infection | | |
| subjects affected / exposed occurrences (all) | 5 / 38 (13.16%) 7 | 3 / 41 (7.32%) 4 | |
| Metabolism and nutrition disorders | | | |
| Hypoalbuminemia | Additional description: Hypoalbuminemia | | |
| subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 1 | 0 / 41 (0.00%) 0 | |
| Anorexia | Additional description: Anorexia | | |
| subjects affected / exposed occurrences (all) | 9 / 38 (23.68%) 12 | 8 / 41 (19.51%) 11 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 01 April 2011 | Inclusion of the use of generic docetaxel as well as the brand Taxotere |
| 05 July 2012 | Addition of an independent Data and Safety Management Committee. |
| 25 March 2013 | Inclusion of the use of open label AZD6244 (selumetinib) |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/24567366>

<http://www.ncbi.nlm.nih.gov/pubmed/31839677>