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/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.	
Reporting group title	Doc + placebo
Reporting group 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.	

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/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.	
Reporting group title	Doc + placebo
Reporting group 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.	
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			
Anaemia	Additional description: Anaemia		
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	
Febrile Neutropenia	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	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever	Additional description: Fever		
subjects affected / exposed	5 / 38 (13.16%)	2 / 41 (4.88%)	
occurrences causally related to treatment / all	5 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic Reaction	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	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal Vascular Disorder	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	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric Haemorrhage	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	
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	28 / 38 (73.68%)	32 / 41 (78.05%)	
occurrences (all)	58	60	
Fever	Additional description: Fever		
subjects affected / exposed	7 / 38 (18.42%)	3 / 41 (7.32%)	
occurrences (all)	9	3	
Immune system disorders			
Allergic Reaction	Additional description: Allergic Reaction		
subjects affected / exposed	4 / 38 (10.53%)	5 / 41 (12.20%)	
occurrences (all)	5	7	
Respiratory, thoracic and mediastinal disorders			
Dyspnea	Additional description: Dyspnea		
subjects affected / exposed	4 / 38 (10.53%)	6 / 41 (14.63%)	
occurrences (all)	4	6	
Epistaxis	Additional description: Epistaxis		
subjects affected / exposed	9 / 38 (23.68%)	4 / 41 (9.76%)	
occurrences (all)	13	7	
Cough	Additional description: Cough		
subjects affected / exposed	3 / 38 (7.89%)	3 / 41 (7.32%)	
occurrences (all)	3	5	
Psychiatric disorders			
Depression	Additional description: Depression		
subjects affected / exposed	6 / 38 (15.79%)	0 / 41 (0.00%)	
occurrences (all)	8	0	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	1 / 38 (2.63%)	4 / 41 (9.76%)	
occurrences (all)	2	6	
Investigations			
Neutrophil Count Decreased	Additional description: Neutrophil Count Decreased		
subjects affected / exposed	4 / 38 (10.53%)	13 / 41 (31.71%)	
occurrences (all)	6	15	
Platelet Count Decreased	Additional description: Platelet Count Decreased		
subjects affected / exposed	0 / 38 (0.00%)	1 / 41 (2.44%)	
occurrences (all)	0	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	Additional description: Alopecia		
subjects affected / exposed	20 / 38 (52.63%)	21 / 41 (51.22%)	
occurrences (all)	21	22	
Palmar-Plantar Erythrodysesthesia Syndrome	Additional description: Palmar-Plantar Erythrodysesthesia Syndrome		
subjects affected / exposed	5 / 38 (13.16%)	1 / 41 (2.44%)	
occurrences (all)	6	1	
Periorbital Edema	Additional description: Periorbital Edema		
subjects affected / exposed	6 / 38 (15.79%)	0 / 41 (0.00%)	
occurrences (all)	7	0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	4 / 38 (10.53%)	10 / 41 (24.39%)	
occurrences (all)	7	13	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	5 / 38 (13.16%)	8 / 41 (19.51%)	
occurrences (all)	7	11	
Pain - Other	Additional description: Pain - Other		
subjects affected / exposed	17 / 38 (44.74%)	12 / 41 (29.27%)	
occurrences (all)	43	19	
Infections and infestations			
Nail Infection	Additional description: Nail Infection		
subjects affected / exposed	3 / 38 (7.89%)	0 / 41 (0.00%)	
occurrences (all)	3	0	
Upper Respiratory Infection	Additional description: Upper Respiratory Infection		
subjects affected / exposed	4 / 38 (10.53%)	1 / 41 (2.44%)	
occurrences (all)	4	1	
Mucosal Infection	Additional description: Mucosal Infection		
subjects affected / exposed	2 / 38 (5.26%)	5 / 41 (12.20%)	
occurrences (all)	2	6	
Bronchial Infection	Additional description: Bronchial Infection		
subjects affected / exposed	0 / 38 (0.00%)	5 / 41 (12.20%)	
occurrences (all)	0	5	
Wound Infection	Additional description: Wound Infection		
subjects affected / exposed	2 / 38 (5.26%)	1 / 41 (2.44%)	
occurrences (all)	2	1	
Urinary Tract Infection	Additional description: Urinary Tract Infection		

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