Clinical trial results:
A Randomised, Double-Blind Study to Assess the Efficacy of Selumetinib (AZD6244, Hyd-Sulfate) in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine as First Systemic Therapy in Patients with Metastatic Uveal Melanoma (SUMIT)

Summary

EudraCT number	2013-003545-41
Trial protocol	BE GB CZ DE NL FI ES
Global end of trial date	26 October 2016

Results information

Result version number	v1 (current)
This version publication date	10 November 2017
First version publication date	10 November 2017

Trial information

Trial identification

Sponsor protocol code	D1344C00001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01974752
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AstraZeneca AB
Sponsor organisation address	Södertälje, Stockholm, Sweden, 151 85
Public contact	William Bushnell, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com
Scientific contact	William Bushnell, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2015
Global end of trial reached?	Yes
Global end of trial date	26 October 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine in terms of progression-free survival (PFS) defined as the time from randomisation until date of objective progression of disease as defined by the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1, assessed by blinded independent central review (BICR) or death (by any cause in the absence of progression).
After BICR-confirmed disease progression patients were to be unblinded and could opt to receive either open-label selumetinib (as monotherapy or in combination with dacarbazine) or an alternative treatment approach at the investigative site.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics.

Background therapy:

In combination with twice daily (BD) administration of either selumetinib or placebo, all patients received dacarbazine. Dacarbazine 1000 milligrams per square meter (mg/m2) was administered intravenously over at least 60 minutes on Day 1 of each 21-day cycle. Patients could receive up to 8 cycles of dacarbazine in the absence of BICR-confirmed disease progression, significant toxicity or occurrence of a discontinuation criterion. Further cycles of dacarbazine could also be administered at the Investigator's discretion if they felt it to be beneficial and it did not contravene local practice. Dacarbazine was sourced as marketed commercially available material/locally sourced or prescribed in accordance with the local prescribing information.

Evidence for comparator: -

Actual start date of recruitment	03 April 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	United States: 24
Country: Number of subjects enrolled	United Kingdom: 16
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Netherlands: 13
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Czech Republic: 3

Country: Number of subjects enrolled	Finland: 1
Worldwide total number of subjects	129
EEA total number of subjects	87

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)	71
From 65 to 84 years	57
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First patient enrolled: 03 April 2014; data cut-off for primary analysis: 15 May 2015; data cut-off for final update: 18 February 2016. Study performed at 29 sites in 11 countries. The study assessed the efficacy of selumetinib in combination with dacarbazine compared with placebo in combination with dacarbazine in terms of PFS.

Pre-assignment

Screening details:

152 patients were enrolled (signed informed consent). 19 patients were enrolled but failed inclusion/exclusion criteria and so were not assigned to treatment. 3 patients withdrew prior to randomisation and did not receive treatment. 1 patient was enrolled twice in error. The remaining 129 patients were randomised and received treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2

Arm description:

Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2

Arm type	Experimental
Investigational medicinal product name	Selumetinib hyd-sulfate
Investigational medicinal product code	AZD6244
Other name	ARRY-142886
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

From Day 1, patients received selumetinib 75 mg (3 x 25 mg capsules), administered orally BD, until objective disease progression confirmed by BICR, intolerable toxicity or occurrence of another discontinuation criterion.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received dacarbazine 1000 mg/m2, administered intravenously over at least 60 minutes on Day 1 of each 21-day cycle.

Arm title	Placebo + Dacarbazine 1000 mg/m2

Arm description:

Placebo + Dacarbazine 1000 mg/m2

Arm type	Placebo

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

Dosage and administration details:

From Day 1, patients received placebo to match selumetinib (3 capsules), administered orally BD, until objective disease progression confirmed by BICR, intolerable toxicity or occurrence of another discontinuation criterion.

Investigational medicinal product name	Dacarbazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Patients received dacarbazine 1000 mg/m2, administered intravenously over at least 60 minutes on Day 1 of each 21-day cycle.

Number of subjects in period 1	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	Placebo + Dacarbazine 1000 mg/m2
Started	97	32
Ongoing at primary analysis data cut-off	60	17
Received open-label study treatment	9	22
Completed	0	0
Not completed	97	32
Consent withdrawn by subject	2	4
Sponsor decision due to Protocol Amendment 3	39	6
Death	53	20
Condition under investigation worsened	-	1
Lost to follow-up	3	-
Medical deterioration	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2
Reporting group description: Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	
Reporting group title	Placebo + Dacarbazine 1000 mg/m2
Reporting group description: Placebo + Dacarbazine 1000 mg/m2	

Reporting group values	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	Placebo + Dacarbazine 1000 mg/m2	Total
Number of subjects	97	32	129
Age Categorical Units: Subjects			
<55 years	26	11	37
>=55 years To <65 years	25	9	34
>=65 years	46	12	58
Age Continuous Units: Years			
arithmetic mean	61.0	59.6	
standard deviation	± 12.28	± 11.28	-
Gender, Male/Female Units: Subjects			
Female	42	19	61
Male	55	13	68
Race, Customized Units: Subjects			
Other	1	1	2
White	96	31	127

End points

End points reporting groups

Reporting group title	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2
Reporting group description: Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	
Reporting group title	Placebo + Dacarbazine 1000 mg/m2
Reporting group description: Placebo + Dacarbazine 1000 mg/m2	

Primary: Assessment of the Efficacy of Selumetinib in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine measured as PFS using BICR according to RECIST 1.1.

End point title	Assessment of the Efficacy of Selumetinib in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine measured as PFS using BICR according to RECIST 1.1.
End point description: PFS using BICR according to RECIST 1.1. Progression is defined as a 20% increase in the sum of the longest diameter of target lesions, or a measurable increase in a non-target lesion, or the appearance of new lesions.	
End point type	Primary
End point timeframe: From randomisation, then every 6 weeks up until progression or death (whichever is sooner) assessed up to cut-off for primary analysis.	

End point values	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	Placebo + Dacarbazine 1000 mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	32		
Units: number of progression events	82	24		

Statistical analyses

Statistical analysis title	PFS using BICR: comparison between groups
Comparison groups	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2 v Placebo + Dacarbazine 1000 mg/m2
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3195
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.27

Secondary: Assessment of the Efficacy of Selumetinib in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine in terms of Objective Response Rate (ORR) by BICR

End point title	Assessment of the Efficacy of Selumetinib in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine in terms of Objective Response Rate (ORR) by BICR

End point description:

ORR at Week 6 using BICR according to RECIST 1.1.

End point type	Secondary

End point timeframe:

From randomisation, then every 6 weeks up until progression or death (whichever is sooner) assessed up cut-off for primary analysis.

End point values	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	Placebo + Dacarbazine 1000 mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	32		
Units: number of responders	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the Efficacy of Selumetinib in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine in terms of Change in Tumour Size at Week 6 by BICR

End point title	Assessment of the Efficacy of Selumetinib in Combination with Dacarbazine Compared with Placebo in Combination with Dacarbazine in terms of Change in Tumour Size at Week 6 by BICR

End point description:

Percent change in tumour size at Week 6 using BICR according to RECIST 1.1.

End point type	Secondary

End point timeframe:

From randomisation, then every 6 weeks up until progression or death (whichever is sooner) assessed up to cut-off for primary analysis.

End point values	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	Placebo + Dacarbazine 1000 mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	27		
Units: percent change				
arithmetic mean (standard deviation)	6.94 (± 18.001)	19.76 (± 38.264)		

Statistical analyses

Statistical analysis title	Change in tumour size using BICR: treatment effect
Comparison groups	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2 v Placebo + Dacarbazine 1000 mg/m2
Number of subjects included in analysis	119
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1284
Method	ANCOVA
Parameter estimate	Geometric LS mean ratio
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	1.02

Secondary: Assessment of the Overall Survival (OS) in Patients taking Selumetinib in Combination with Dacarbazine Compared with those taking Placebo in Combination with Dacarbazine

End point title	Assessment of the Overall Survival (OS) in Patients taking Selumetinib in Combination with Dacarbazine Compared with those taking Placebo in Combination with Dacarbazine
End point description:	
Overall Survival.	
End point type	Secondary
End point timeframe:	
From randomisation, up until death assessed up to cut-off for primary analysis.	

End point values	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	Placebo + Dacarbazine 1000 mg/m2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	32		
Units: Number of Overall Survival Events	34	14		

Statistical analyses

Statistical analysis title	OS: comparison between groups
Comparison groups	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2 v Placebo + Dacarbazine 1000 mg/m2
Number of subjects included in analysis	129
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4011
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.46

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to maximum duration of 22.5 months (duration from first patient enrolled to data cut-off for the final update analysis).

Adverse event reporting additional description:

Adverse events are reported until the cut-off date for the final update analysis and reflect the double-blind phase of the study, including the double-blind post follow-up (i.e. from day of first dose of study treatment (selumetinib or placebo) up to and including 30 days after last dose of study treatment in the double-blind phase).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo + Dacarbazine 1000 mg/m2

Reporting group description:

Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2

Reporting group title	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2

Reporting group description:

Placebo + Dacarbazine 1000 mg/m2

Serious adverse events	Placebo + Dacarbazine 1000 mg/m2	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 32 (6.25%)	25 / 97 (25.77%)	
number of deaths (all causes)	23	54	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
HYPOTENSION			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CHEST PAIN			

subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	0 / 32 (0.00%)	3 / 97 (3.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYSTEMIC INFLAMMATORY RESPONSE SYNDROME			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
PLEURAL EFFUSION			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	0 / 32 (0.00%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
BLOOD BILIRUBIN INCREASED			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			

subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIP FRACTURE			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
ATRIAL FLUTTER			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CARDIAC FAILURE			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
PERICARDIAL EFFUSION			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
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			
FEBRILE BONE MARROW APLASIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 32 (3.13%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
RETINAL VEIN OCCLUSION			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
subjects affected / exposed	1 / 32 (3.13%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Skin and subcutaneous tissue disorders			
URTICARIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
HAEMATURIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
NECK PAIN			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
PNEUMONIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED SEPSIS			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STREPTOCOCCAL BACTERAEMIA			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	1 / 32 (3.13%)	2 / 97 (2.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENDOCARDITIS			

subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	0 / 32 (0.00%)	1 / 97 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	1 / 32 (3.13%)	0 / 97 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + Dacarbazine 1000 mg/m2	Selumetinib 75 mg BD + Dacarbazine 1000 mg/m2	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)	97 / 97 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
TUMOUR PAIN			
subjects affected / exposed	2 / 32 (6.25%)	2 / 97 (2.06%)	
occurrences (all)	2	3	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	2 / 32 (6.25%)	22 / 97 (22.68%)	
occurrences (all)	2	23	
General disorders and administration site conditions			
ASTHENIA			
subjects affected / exposed	4 / 32 (12.50%)	20 / 97 (20.62%)	
occurrences (all)	5	21	
CHILLS			
subjects affected / exposed	1 / 32 (3.13%)	5 / 97 (5.15%)	
occurrences (all)	1	6	
FACE OEDEMA			

subjects affected / exposed	0 / 32 (0.00%)	7 / 97 (7.22%)	
occurrences (all)	0	8	
FATIGUE			
subjects affected / exposed	15 / 32 (46.88%)	44 / 97 (45.36%)	
occurrences (all)	17	55	
OEDEMA PERIPHERAL			
subjects affected / exposed	2 / 32 (6.25%)	47 / 97 (48.45%)	
occurrences (all)	2	53	
PYREXIA			
subjects affected / exposed	5 / 32 (15.63%)	8 / 97 (8.25%)	
occurrences (all)	6	9	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
subjects affected / exposed	3 / 32 (9.38%)	20 / 97 (20.62%)	
occurrences (all)	3	25	
OROPHARYNGEAL PAIN			
subjects affected / exposed	2 / 32 (6.25%)	4 / 97 (4.12%)	
occurrences (all)	2	4	
COUGH			
subjects affected / exposed	1 / 32 (3.13%)	9 / 97 (9.28%)	
occurrences (all)	1	9	
EPISTAXIS			
subjects affected / exposed	1 / 32 (3.13%)	6 / 97 (6.19%)	
occurrences (all)	1	7	
Psychiatric disorders			
INSOMNIA			
subjects affected / exposed	4 / 32 (12.50%)	8 / 97 (8.25%)	
occurrences (all)	4	8	
Investigations			
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
subjects affected / exposed	1 / 32 (3.13%)	6 / 97 (6.19%)	
occurrences (all)	2	6	
ALANINE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 32 (12.50%)	29 / 97 (29.90%)	
occurrences (all)	6	37	

ASPARTATE AMINOTRANSFERASE INCREASED			
subjects affected / exposed	4 / 32 (12.50%)	30 / 97 (30.93%)	
occurrences (all)	7	37	
BLOOD ALKALINE PHOSPHATASE INCREASED			
subjects affected / exposed	2 / 32 (6.25%)	8 / 97 (8.25%)	
occurrences (all)	3	8	
BLOOD CREATINE PHOSPHOKINASE INCREASED			
subjects affected / exposed	2 / 32 (6.25%)	36 / 97 (37.11%)	
occurrences (all)	2	41	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 32 (3.13%)	7 / 97 (7.22%)	
occurrences (all)	1	11	
PLATELET COUNT DECREASED			
subjects affected / exposed	3 / 32 (9.38%)	7 / 97 (7.22%)	
occurrences (all)	4	11	
WEIGHT DECREASED			
subjects affected / exposed	2 / 32 (6.25%)	1 / 97 (1.03%)	
occurrences (all)	2	1	
WHITE BLOOD CELL COUNT DECREASED			
subjects affected / exposed	0 / 32 (0.00%)	5 / 97 (5.15%)	
occurrences (all)	0	7	
Nervous system disorders			
PARAESTHESIA			
subjects affected / exposed	2 / 32 (6.25%)	8 / 97 (8.25%)	
occurrences (all)	4	8	
DIZZINESS			
subjects affected / exposed	3 / 32 (9.38%)	6 / 97 (6.19%)	
occurrences (all)	3	7	
DYSGEUSIA			
subjects affected / exposed	3 / 32 (9.38%)	11 / 97 (11.34%)	
occurrences (all)	4	11	
HEADACHE			
subjects affected / exposed	3 / 32 (9.38%)	16 / 97 (16.49%)	
occurrences (all)	3	17	

SYNCOPE			
subjects affected / exposed	0 / 32 (0.00%)	6 / 97 (6.19%)	
occurrences (all)	0	7	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	4 / 32 (12.50%)	19 / 97 (19.59%)	
occurrences (all)	6	23	
NEUTROPENIA			
subjects affected / exposed	11 / 32 (34.38%)	25 / 97 (25.77%)	
occurrences (all)	14	38	
THROMBOCYTOPENIA			
subjects affected / exposed	4 / 32 (12.50%)	26 / 97 (26.80%)	
occurrences (all)	4	40	
LEUKOPENIA			
subjects affected / exposed	3 / 32 (9.38%)	0 / 97 (0.00%)	
occurrences (all)	3	0	
Eye disorders			
VISION BLURRED			
subjects affected / exposed	1 / 32 (3.13%)	11 / 97 (11.34%)	
occurrences (all)	1	13	
Gastrointestinal disorders			
CONSTIPATION			
subjects affected / exposed	14 / 32 (43.75%)	38 / 97 (39.18%)	
occurrences (all)	19	47	
ABDOMINAL PAIN			
subjects affected / exposed	3 / 32 (9.38%)	11 / 97 (11.34%)	
occurrences (all)	3	12	
ABDOMINAL PAIN UPPER			
subjects affected / exposed	3 / 32 (9.38%)	8 / 97 (8.25%)	
occurrences (all)	3	8	
DIARRHOEA			
subjects affected / exposed	7 / 32 (21.88%)	44 / 97 (45.36%)	
occurrences (all)	11	89	
DRY MOUTH			
subjects affected / exposed	2 / 32 (6.25%)	9 / 97 (9.28%)	
occurrences (all)	2	9	
DYSPEPSIA			

subjects affected / exposed	2 / 32 (6.25%)	11 / 97 (11.34%)	
occurrences (all)	2	12	
GASTROINTESTINAL PAIN			
subjects affected / exposed	2 / 32 (6.25%)	0 / 97 (0.00%)	
occurrences (all)	2	0	
GASTROOESOPHAGEAL REFLUX DISEASE			
subjects affected / exposed	1 / 32 (3.13%)	5 / 97 (5.15%)	
occurrences (all)	1	5	
NAUSEA			
subjects affected / exposed	6 / 32 (18.75%)	61 / 97 (62.89%)	
occurrences (all)	12	97	
STOMATITIS			
subjects affected / exposed	3 / 32 (9.38%)	16 / 97 (16.49%)	
occurrences (all)	3	17	
VOMITING			
subjects affected / exposed	7 / 32 (21.88%)	28 / 97 (28.87%)	
occurrences (all)	8	40	
Hepatobiliary disorders			
HEPATIC PAIN			
subjects affected / exposed	3 / 32 (9.38%)	3 / 97 (3.09%)	
occurrences (all)	3	3	
Skin and subcutaneous tissue disorders			
DRY SKIN			
subjects affected / exposed	0 / 32 (0.00%)	12 / 97 (12.37%)	
occurrences (all)	0	13	
ALOPECIA			
subjects affected / exposed	1 / 32 (3.13%)	7 / 97 (7.22%)	
occurrences (all)	1	7	
DERMATITIS ACNEIFORM			
subjects affected / exposed	1 / 32 (3.13%)	30 / 97 (30.93%)	
occurrences (all)	2	41	
HYPERHIDROSIS			
subjects affected / exposed	3 / 32 (9.38%)	3 / 97 (3.09%)	
occurrences (all)	3	3	
PHOTOSENSITIVITY REACTION			

subjects affected / exposed	2 / 32 (6.25%)	0 / 97 (0.00%)	
occurrences (all)	2	0	
PRURITUS			
subjects affected / exposed	5 / 32 (15.63%)	14 / 97 (14.43%)	
occurrences (all)	6	15	
RASH			
subjects affected / exposed	2 / 32 (6.25%)	56 / 97 (57.73%)	
occurrences (all)	2	64	
SKIN FISSURES			
subjects affected / exposed	0 / 32 (0.00%)	13 / 97 (13.40%)	
occurrences (all)	0	15	
Musculoskeletal and connective tissue disorders			
NECK PAIN			
subjects affected / exposed	0 / 32 (0.00%)	6 / 97 (6.19%)	
occurrences (all)	0	6	
PAIN IN EXTREMITY			
subjects affected / exposed	1 / 32 (3.13%)	5 / 97 (5.15%)	
occurrences (all)	1	5	
ARTHRALGIA			
subjects affected / exposed	4 / 32 (12.50%)	7 / 97 (7.22%)	
occurrences (all)	6	9	
BACK PAIN			
subjects affected / exposed	0 / 32 (0.00%)	9 / 97 (9.28%)	
occurrences (all)	0	10	
MUSCULOSKELETAL CHEST PAIN			
subjects affected / exposed	3 / 32 (9.38%)	1 / 97 (1.03%)	
occurrences (all)	4	1	
MUSCULOSKELETAL PAIN			
subjects affected / exposed	3 / 32 (9.38%)	4 / 97 (4.12%)	
occurrences (all)	3	5	
MYALGIA			
subjects affected / exposed	1 / 32 (3.13%)	12 / 97 (12.37%)	
occurrences (all)	1	15	
MUSCULAR WEAKNESS			

subjects affected / exposed	0 / 32 (0.00%)	7 / 97 (7.22%)	
occurrences (all)	0	8	
Infections and infestations			
BRONCHITIS			
subjects affected / exposed	0 / 32 (0.00%)	5 / 97 (5.15%)	
occurrences (all)	0	5	
LOWER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	2 / 32 (6.25%)	0 / 97 (0.00%)	
occurrences (all)	2	0	
NASOPHARYNGITIS			
subjects affected / exposed	1 / 32 (3.13%)	5 / 97 (5.15%)	
occurrences (all)	1	6	
URINARY TRACT INFECTION			
subjects affected / exposed	3 / 32 (9.38%)	9 / 97 (9.28%)	
occurrences (all)	4	9	
PARONYCHIA			
subjects affected / exposed	0 / 32 (0.00%)	5 / 97 (5.15%)	
occurrences (all)	0	6	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
subjects affected / exposed	2 / 32 (6.25%)	4 / 97 (4.12%)	
occurrences (all)	4	6	
DECREASED APPETITE			
subjects affected / exposed	10 / 32 (31.25%)	17 / 97 (17.53%)	
occurrences (all)	10	18	
HYPERKALAEMIA			
subjects affected / exposed	2 / 32 (6.25%)	5 / 97 (5.15%)	
occurrences (all)	3	6	
HYPOALBUMINAEMIA			
subjects affected / exposed	2 / 32 (6.25%)	6 / 97 (6.19%)	
occurrences (all)	2	8	
HYPONATRAEMIA			
subjects affected / exposed	1 / 32 (3.13%)	5 / 97 (5.15%)	
occurrences (all)	1	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 April 2014	- To increase the number of centres likely to be involved in the study and to extend the estimated date of last patient enrolled and last patient completed. - To add new information on the risk of higher exposure of selumetanib for patients of Asian descent. - To increase diary card requirements for recording self-administration of study treatment (selumetinib or placebo) to allow for assessment of treatment compliance on all study days.
10 November 2014	- The timing of the primary analysis was updated to include completion of a minimum follow-up period of 14 weeks for all patients who had not yet had a PFS event (in addition to a minimum of 93 PFS events).
19 August 2015	- The results of the primary analysis demonstrated no statistically significant improvement in PFS, as determined by the BICR, when selumetinib was given in combination with dacarbazine as compared with dacarbazine alone in patients with metastatic uveal melanoma as first systemic treatment. Due to the results of the primary analysis, a decision was made that the overall survival analysis would no longer be performed. As such, patients who had discontinued randomised study treatment and were already in survival follow-up were withdrawn from the study. All patients still receiving randomised study treatment were unblinded, if this had not already happened. Patients in the selumetinib group, who in the opinion of the Investigator were receiving clinical benefit, could continue to receive study treatment. At the discretion of the Investigator, patients in the placebo group could receive open-label selumetinib (as monotherapy or in combination with dacarbazine) only following objective disease progression by site review. For patients who continued to receive treatment beyond this amendment, Investigators continued to report all serious adverse events to AstraZeneca Patient Safety until 30 days after the last dose of study treatment. - To allow Investigators to take new information into account, the risk of higher exposure of selumetinib for patients who experience hepatic impairment was added.

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.

Results reported up to data cut-off date for final update, except end points which report results up to data cut-off date for primary analysis (as per protocol plan). End point and AE results report data for double-blind, randomised phase of trial.

Notes: