Clinical trial results:
A randomised double blind phase 2 trial of whole brain radiotherapy with or without vandetanib in metastatic melanoma with brain metastases

Summary

EudraCT number	2011-000661-12
Trial protocol	GB
Global end of trial date	27 November 2014

Results information

Result version number	v1
This version publication date	31 March 2016
First version publication date	31 March 2016

Trial information

Trial identification

Sponsor protocol code	OCTO_022

Additional study identifiers

ISRCTN number	ISRCTN20253034
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Oxford, Block 60, Churchill Hospital, Old Road, Headington, Oxford, United Kingdom, OX3 7LE
Public contact	RADVAN Trial Coordinator, Oncology Clinical Trials Office (OCTO), +44 01865617089, RADVAN@octo-oxford.org.uk
Scientific contact	RADVAN Trial Coordinator, Oncology Clinical Trials Office (OCTO), +44 01865617089, RADVAN@octo-oxford.org.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	13 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 November 2014
Global end of trial reached?	Yes
Global end of trial date	27 November 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The principal objective of this study is to evaluate how long whole brain radiotherapy plus vandetanib is able to control the progression of melanoma brain metastases, compared with radiotherapy alone.

Protection of trial subjects:

The trial received ethical and regulatory approval, and was run in compliance with the Medicines for Human Use (Clinical Trials) Regulations 2004, and amendments thereafter, the guidelines for Good Clinical Practice, and the applicable policies of the Sponsor, the University of Oxford. Together, these regulations implement the ethical principles of the Declaration of Helsinki (2008) and the regulatory requirements for clinical trials of an investigational medicinal product as set out in the European Union (EU) Directives 001/20/EC (Clinical Trials) and 2005/28/EC (GCP). Patients also were seen for study assessments up to 30 days post end of treatment and thereafter every 2 months for clinical and radiological assessment up to a total of 12 months post randomisation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Worldwide total number of subjects	24
EEA total number of subjects	24

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)	14
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

6 eligible participants were recruited to the safety run-in phase of the trial between 1st February 2012 and 14th February 2013. Between 24th April 2013 and 17th April 2014, 18 eligible participants were recruited to the randomised phase. The TMG met on 30 April 2014 and agreed to close the RADVAN trial early to recruitment with immediate effect.

Pre-assignment

Screening details:

71 participants were screened. 47 patients were excluded/ineligible; 33 didn't meet the inclusion criteria (7 had poor performance status, 3 were unable to comply with protocol, 3 had a life expectancy <12 weeks, among other reasons), 12 patients declined to participate (of which 4 chose alternative treatment), and 2 patients did not give reasons.

Period 1

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

Blinding implementation details:

Vandetanib/placebo were both supplied as 100mg white film-coated tablets packed in high density polyethylene (HDPE) bottles.

Arms

Are arms mutually exclusive?	No
Arm title	Vandetanib plus WBRT

Arm description:

Experimental treatment arm of Vandetanib followed by WBRT

Arm type	Experimental
Investigational medicinal product name	Vandetanib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the randomisation phase received vandetanib/placebo 100 mg once daily (OD), starting 4 days (+/- 1 day) before Whole Brain Radiotherapy (WBRT) and continuing for 21 days in total, in oral tablet form. No study treatment was to be given beyond day 21, even if any doses were missed during this period.
The exposure to vandetanib is unchanged whether given in the fasted state or with food and thus a restriction on dosing with food was not required. The dose of study drug was repeated if emesis occurred within 30 minutes of taking the tablet.
If the patient inadvertently did not take the dose in the morning, he or she may have taken that day's dose any time up to 10pm that same day. The study drug could therefore be taken before or after radiotherapy treatment.
However, if a patient missed taking the scheduled dose and was unable to take the missed dose on the same day, he or she omitted the dose and took the next scheduled dose as planned. The missed dose was not made up.

Arm title	Safety of Vandetanib

Arm description:

16 patients (including those 6 patients in the safety run-in phase and 10 patients in the randomised phase) were allocated to receive vandetanib followed by WBRT.

Arm type	Safety

Investigational medicinal product name	Vandetanib
Investigational medicinal product code	L01XE12
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the safety run-in phase received vandetanib 100 mg once daily (OD), starting 4 days (+/- 1 day) before Whole Brain Radiotherapy (WBRT) and continuing for 21 days in total, in oral tablet form. No study treatment was to be given beyond day 21, even if any doses were missed during this period. The exposure to vandetanib is unchanged whether given in the fasted state or with food and thus a restriction on dosing with food was not required. The dose of study drug was repeated if emesis occurred within 30 minutes of taking the tablet.
If the patient inadvertently did not take the dose in the morning, he or she may have taken that day's dose any time up to 10pm that same day. The study drug could therefore be taken before or after radiotherapy treatment.
However, if a patient missed taking the scheduled dose and was unable to take the missed dose on the same day, he or she omitted the dose and took the next scheduled dose as planned. The missed dose was not made up.

Arm title	Placebo plus WBRT

Arm description:

Placebo followed by WBRT

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients in the randomisation phase received vandetanib/placebo 100 mg once daily (OD), starting 4 days (+/- 1 day) before Whole Brain Radiotherapy (WBRT) and continuing for 21 days in total, in oral tablet form. No study treatment was to be given beyond day 21, even if any doses were missed during this period.

Number of subjects in period 1	Vandetanib plus WBRT	Safety of Vandetanib	Placebo plus WBRT
Started	10	16	8
Completed	7	12	2
Not completed	3	4	6
Physician decision	2	2	1
Disease progression	-	-	1
Adverse event, non-fatal	1	2	1
Patient died	-	-	1
Protocol deviation	-	-	2

Baseline characteristics

Reporting groups	
Reporting group title	Vandetanib plus WBRT
Reporting group description:	
Experimental treatment arm of Vandetanib followed by WBRT	
Reporting group title	Safety of Vandetanib
Reporting group description:	
16 patients (including those 6 patients in the safety run-in phase and 10 patients in the randomised phase) were allocated to receive vandetanib followed by WBRT.	
Reporting group title	Placebo plus WBRT
Reporting group description:	
Placebo followed by WBRT	

Reporting group values	Vandetanib plus WBRT	Safety of Vandetanib	Placebo plus WBRT
Number of subjects	10	16	8
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	57.3	61.7	63.7
standard deviation	± 11.1	± 11.5	± 14.8
Gender categorical Units: Subjects			
Female	5	7	5
Male	5	9	3
Karnofsky Performance Status Units: Subjects			
100 - Normal; no evidence of disease	2	3	1
90 - Able to carry on normal activity; minor signs	5	7	5
80 - Normal activity with effort; some signs	2	5	2
70 - Cares for self; unable to carry on normal act	1	1	0
Weight Units: kg			
arithmetic mean	81	82.7	75.2
standard deviation	± 13.6	± 14.3	± 17.2

Temperature			
Units: celsius temperature			
arithmetic mean	36.4	36.3	36.5
standard deviation	± 0.6	± 0.5	± 0.5
Pulse rate			
Units: bpm			
arithmetic mean	77.2	73.8	73.3
standard deviation	± 17.8	± 16	± 14.6
Systolic blood pressure			
Units: mmHg			
arithmetic mean	131.7	136.8	135.3
standard deviation	± 13.8	± 15.1	± 76.1
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	74.3	75.6	76.1
standard deviation	± 7.8	± 11.9	± 8.7

Reporting group values	Total		
Number of subjects	24		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	12		
Male	12		
Karnofsky Performance Status			
Units: Subjects			
100 - Normal; no evidence of disease	4		
90 - Able to carry on normal activity; minor signs	12		
80 - Normal activity with effort; some signs	7		
70 - Cares for self; unable to carry on normal act	1		
Weight			
Units: kg			
arithmetic mean			

standard deviation	-		
Temperature Units: celsius temperature arithmetic mean standard deviation	-		
Pulse rate Units: bpm arithmetic mean standard deviation	-		
Systolic blood pressure Units: mmHg arithmetic mean standard deviation	-		
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	-		

End points

End points reporting groups

Reporting group title	Vandetanib plus WBRT
Reporting group description:	
Experimental treatment arm of Vandetanib followed by WBRT	
Reporting group title	Safety of Vandetanib
Reporting group description:	
16 patients (including those 6 patients in the safety run-in phase and 10 patients in the randomised phase) were allocated to receive vandetanib followed by WBRT.	
Reporting group title	Placebo plus WBRT
Reporting group description:	
Placebo followed by WBRT	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary analysis was intention-to-treat and involved all 18 patients who were randomly assigned, irrespective of the treatment they received.	
Subject analysis set title	Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
9 patients were included in the per-protocol analysis and 9 patients were excluded as they did not did not receive 21 days of treatment drug (vandetanib/Placebo) and 10 fractions of radiotherapy.	
Subject analysis set title	Safety and tolerability
Subject analysis set type	Safety analysis
Subject analysis set description:	
16 patients were randomised and received at least one dose of treatment drug (vandetanib/Placebo).	
Subject analysis set title	Safety of Vandetanib
Subject analysis set type	Safety analysis
Subject analysis set description:	
16 patients (including those 6 patients in the safety sample) were allocated to receive vandetanib.	

Primary: Progression Free Survival in brain

End point title	Progression Free Survival in brain
End point description:	
End point type	Primary
End point timeframe:	
The time from date of randomisation to date of disease progression in the brain or date of death in the absence of RECIST progression. For patients without an event, the time from randomisation to date last known alive would be the censored PFS time.	

End point values	Vandetanib plus WBRT	Safety of Vandetanib	Placebo plus WBRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	16	8	
Units: Months				
median (confidence interval 90%)	3.25 (1.55 to 5.56)	3.25 (1.81 to 5.56)	2.5 (0.2 to 4.83)	

Statistical analyses

Statistical analysis title	Difference in PFS between treatment groups
Comparison groups	Vandetanib plus WBRT v Placebo plus WBRT
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.29
upper limit	1.45

Secondary: Overall Survival

End point title	Overall Survival

End point description:

End point type	Secondary

End point timeframe:

The time from randomisation to death (event), or the time from randomisation to date last known alive for censored patients

End point values	Vandetanib plus WBRT	Safety of Vandetanib	Placebo plus WBRT	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	16	8	
Units: Months				
median (confidence interval 90%)	4.6 (1.55 to 6.28)	4.6 (1.55 to 6.28)	2.5 (0.2 to 7.2)	

Statistical analyses

Statistical analysis title	Difference in OS between treatment groups
Comparison groups	Vandetanib plus WBRT v Placebo plus WBRT

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.37
upper limit	1.96

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From randomisation to 30 days after the end of study treatment.	
Assessment type	Systematic
Dictionary used	
Dictionary name	CTCAE
Dictionary version	4.0
Reporting groups	
Reporting group title	Vandetanib
Reporting group description: Experimental treatment arm	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Safety run-in
Reporting group description: 6 safety patients who received Vandetanib before randomised part of the trial.	

Serious adverse events	Vandetanib	Placebo	Safety run-in
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 10 (50.00%)	2 / 8 (25.00%)	3 / 6 (50.00%)
number of deaths (all causes)	9	8	6
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemorrhage of brain metastases			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral edema			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disturbances			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic perforation	Additional description: Diverticular Abscess/perforation (Colonic Perforation)		
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Interstitial pneumonitis			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 10 (20.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Vandetanib	Placebo	Safety run-in
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	7 / 8 (87.50%)	6 / 6 (100.00%)
Investigations			
Electrocardiogram QT corrected interval prolonged			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			

Thromboembolic event			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Leg coldness	Additional description: Leg coldness - possible ischaemic limb		
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pericardial effusion			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Ataxia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Dysgeusia			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Edema cerebral			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Encephalopathy			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	2 / 10 (20.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	2	1	1
Intracranial hemorrhage			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Transient headaches			

subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Transient visual disturbance			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Leg twitching			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Leg numbness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Leg weakness			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Seizure			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Tremor			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 10 (30.00%)	4 / 8 (50.00%)	4 / 6 (66.67%)
occurrences (all)	5	4	4
Gait disturbance			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Gastrointestinal disorders			

Cheilitis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Dry mouth			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2
Enterocolitis infectious			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 10 (20.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	2
Vomiting			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 10 (10.00%)	2 / 8 (25.00%)	1 / 6 (16.67%)
occurrences (all)	1	2	1
Dysphonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pleural effusion			

subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pneumonitis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Sore throat			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cellulitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Excoriated skin	Additional description: Excoriated Skin Peri-anal area		
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	3 / 10 (30.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	3	0	2
Dry skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pain of skin			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rash maculo-papular			
subjects affected / exposed	1 / 10 (10.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Scalp pain			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin rash			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash forehead			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	0	0	2

Skin reaction			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 10 (20.00%)	0 / 8 (0.00%)	2 / 6 (33.33%)
occurrences (all)	2	0	3
Insomnia			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Migraines with shapes in eyes			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 10 (0.00%)	1 / 8 (12.50%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Infections and infestations			
Infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mucosal infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	3 / 6 (50.00%)
occurrences (all)	0	0	3
Upper respiratory infection			
subjects affected / exposed	0 / 10 (0.00%)	0 / 8 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Urinary tract infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 8 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 February 2013	Protocol amendment to remove the exclusion criterion of no more than 3 extra-cranial organ sites involved with melanoma and removal of the neuro-cognitive tests. Both changes were made to maximise recruitment.
11 August 2014	Protocol amendment to describe the early closing of recruitment to the trial due to the inability of the trial to achieve its sample size in a timely manner and to reduce the follow-up period.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 April 2014	Recruitment to the trial closed on 30 April 2014 with 24 patients recruited (6 to the safety cohort and 18 to the randomised trial) following significant difficulties encountered in recruiting from this patient population. This decision was made by the Trial Management Group (TMG) and agreed by the Independent Early Phase Trial Oversight Committee (IEPTOC) following concerns that slow recruitment would lead to an inability to answer the research question in a timely manner.	-

Notes:

Limitations and caveats

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

Early termination of the trial due to failure to recruit patients has led to a small number of patients analysed. This meant there was a lack of statistical power to detect differences between treatment arms.

Notes: