Clinical trial results:
A Randomised Trial Evaluating the VEGF Inhibitor, Bevacizumab (Avastin), as Adjuvant Therapy following Resection of AJCC Stage IIB (T3bN0M0 & T4aN0M0), IIC (T4bN0M0) and III (TxN1-3M0) Cutaneous Melanoma

Summary

EudraCT number	2006-005505-64
Trial protocol	GB
Global end of trial date	31 March 2022

Results information

Result version number	v1 (current)
This version publication date	08 April 2023
First version publication date	08 April 2023

Trial information

Trial identification

Sponsor protocol code	AVAST-M

Additional study identifiers

ISRCTN number	ISRCTN81261306
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Hills Road, Cambridge, United Kingdom, CB2 0QQ
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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	15 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2022
Global end of trial reached?	Yes
Global end of trial date	31 March 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objective:
To determine the overall survival of patients treated with bevacizumab, compared with standard observation after resection of high risk melanoma.

Secondary Objectives:
To compare the two arms of the study in terms of the following parameters:
- Disease free interval
- Distant metastasis-free interval
- Safety and toxicity
- Quality of life (QoL)

Protection of trial subjects:

The study was approved by a Research Ethics Committee and received authorisation from the Medicine and Healthcare Product Regulatory Authority. Patients received verbal and written information prior to consenting to the trial, and had time to consider their participation and had an opportunity to ask questions. Consenting patients had a series of screening tests to ensure they were suitable for the study and it was safe to proceed. Only the participant's direct care team had access to their recruited participants personal/identifiable information during the trial. On registration to the trial the participants were allocated a unique trial identification number which was used on all data forms and samples sent to the Sponsor, alongside their date of birth and initials. Any participant related information shared by the Sponsor (e.g. for the purposes of analysing translational endpoints) was anonymised, with only reference to the participant's trial identification number being included. This allowed their personal data to remain anonymous.

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	04 July 2007
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: 1343
Worldwide total number of subjects	1343
EEA total number of subjects	0

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)	1014
From 65 to 84 years	324
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The AVAST-M trial planned to recruit 1320 patients (660 patients in each arm), with minimum 5 years follow up. Long term follow-up data for survival and disease recurrence would be collected up to 10 years where possible, or until death. Recruitment commenced on 04/07/2017 and closed on 31/03/2012. In total 1343 patients were randomised.

Pre-assignment

Screening details:

A total of 3394 patients were assessed for eligibility, 694 patients did not give informed consent. 1343 patients were sucessfully screened for eligibility and randomised. Target recruitment of 1320 patients was reached on 23/02/2012. Recruitment remained open to enable those who had already signed consent to enter the study.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

The treatment period continued for up to a total of 17 bevacizumab treatments or 1 calendar year, which ever occured sooner, or until recurrence of disease, or patient/clinician withdrawal for any other reason. After completion of the treatment period patients were followed-up every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

If patients were withdrawn early from bevacizumab treatment (for reasons other than first distant recurrence) they, where possible, continued to have the scheduled study visits and investigations until first distant recurrence.

In the event of first distant recurrence, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	L01FG01
Other name	Avastin
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab (Avastin) was administered by intravenous (i.v.) infusion in accordance with the instructions in the Summary of Product Characteristics, at a dose of 7.5mg/kg on day 1 of the study treatment period. Bevacizumab treatment did not commence within 28 days of major surgery and until all the surgical wounds had fully healed.

Bevacizumab infusions were administered every 3 weeks (+/- 7 calendar days of the scheduled treatment day). Treatment was given for 1 calendar year (max 17 infusions over 1 year) or until disease recurred.

Dose was based on actual weight at baseline visit, unless more than 10% body wieght change from baseline occurred. In this case dosage was recalculated. It was also acceptable to recalculate the bevacizumab dose every cycle using patients' actual weight.

Rounding of the dose was optional and if the investigator decided to round the dose it could only be

rounded to the nearest ml. The recommended infusion duration was 30 (+/- 10) minutes.

Arm title	Observation

Arm description:

Patients received no interventions on this arm. Patients were followed-up at 6 weeks, 3 months, then every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

In the event of first distant recurrence or withdrawal from study, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Treatment	Observation
Started	671	672
Completed	588	600
Not completed	83	72
Consent withdrawn by subject	12	7
Lost to follow-up	71	65

Baseline characteristics

Reporting groups

Reporting group title	Treatment

Reporting group description:

The treatment period continued for up to a total of 17 bevacizumab treatments or 1 calendar year, which ever occured sooner, or until recurrence of disease, or patient/clinician withdrawal for any other reason. After completion of the treatment period patients were followed-up every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

If patients were withdrawn early from bevacizumab treatment (for reasons other than first distant recurrence) they, where possible, continued to have the scheduled study visits and investigations until first distant recurrence.

In the event of first distant recurrence, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

Reporting group title	Observation

Reporting group description:

Patients received no interventions on this arm. Patients were followed-up at 6 weeks, 3 months, then every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

In the event of first distant recurrence or withdrawal from study, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

Reporting group values	Treatment	Observation	Total
Number of subjects	671	672	1343
Age categorical Units: Subjects			
Adults (18-64 years)	513	501	1014
From 65-84 years	157	167	324
85 years and over	1	4	5
Age continuous Units: years			
median	56	55	
full range (min-max)	18 to 87	19 to 88	-
Gender categorical Units: Subjects			
Female	294	296	590
Male	377	376	753
Breslow thickness of primary tumour Units: Subjects			
≤2.0mm	198	201	399
>2.0mm - 4.0mm	203	202	405
>4.0mm	221	217	438
Unknown	49	52	101
Ulceration of primary tumour Units: Subjects			
Present	262	256	518

Absent	310	323	633
Unknown	99	93	192
N classification Units: Subjects			
N0	169	160	329
N1a	100	96	196
N1b	119	119	238
N2a	41	39	80
N2b	65	67	132
N2c	61	68	129
N3	98	106	204
NA	18	17	35
ECOG performance status Units: Subjects			
ECOG 0	602	593	1195
ECOG 1	67	79	146
Missing	2	0	2
Stage of melanoma Units: Subjects			
IIB	103	106	209
IIC	84	71	155
IIIA	103	92	195
IIIB	240	255	495
IIIC	141	148	289
Site of primary tumour Units: Subjects			
Head and Neck	74	83	157
Upper Limb	112	97	209
Lower Limb	219	230	449
Trunk	233	228	461
Unknown	28	32	60
Other	5	2	7
Regional lymph node involvement at any time Units: Subjects			
Yes - Detected by SLNB	171	164	335
Yes - Detected clinically	249	264	513
Yes - Unknown detection method	0	1	1
No	222	214	436
Not Assessed	28	27	55
Missing	1	2	3
Previous adjuvant treatment for melanoma Units: Subjects			
Yes- Radiotherapy	9	14	23
Yes - Chemotherapy	0	1	1
Yes - Hormonal therapy	0	0	0
Yes - Interferon	3	2	5
Yes - Vaccine	1	3	4
Yes - Other immunotherapy	2	1	3
No	639	636	1275
Missing	17	13	30

Yes - Radiotherapy and Chemotherapy	0	1	1
Yes - Radiotherapy and Other immunotherapy	0	1	1
BMI			
BMI at baseline was available for 662 subjects on the Treatment Arm and 641 subjects on the Observation Arm; Total n = 1303			
Units: kilogram(s)/square metre			
median	27.7	27.5	
inter-quartile range (Q1-Q3)	24.6 to 31.2	24.7 to 30.6	-

End points

End points reporting groups

Reporting group title	Treatment

Reporting group description:

The treatment period continued for up to a total of 17 bevacizumab treatments or 1 calendar year, which ever occured sooner, or until recurrence of disease, or patient/clinician withdrawal for any other reason. After completion of the treatment period patients were followed-up every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

If patients were withdrawn early from bevacizumab treatment (for reasons other than first distant recurrence) they, where possible, continued to have the scheduled study visits and investigations until first distant recurrence.

In the event of first distant recurrence, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

Reporting group title	Observation

Reporting group description:

Patients received no interventions on this arm. Patients were followed-up at 6 weeks, 3 months, then every 3 months until 2 years, then 6 monthly until 5 years and then annually until up to 10 years from randomisation (where possible).

In the event of first distant recurrence or withdrawal from study, follow up as per above schedule ceased and patients were monitored and managed as indicated locally. Annual follow up (survival and disease recurrence) continued until 10 years from randomisation (where possible), death, loss to follow up or withdrawal of consent.

Primary: Overall survival

End point title	Overall survival

End point description:

Overall survival time is the time between the date of randomisation and death, whatever the cause. Patients discontinuing the study, or lost to follow-up, and still alive were censored at the last known date alive.

End point type	Primary

End point timeframe:

On study

End point values	Treatment	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	671	672		
Units: number of deaths	280	294		

Statistical analyses

Statistical analysis title	Overall Survival

Statistical analysis description:

A Cox proportional hazard model was used to compare overall survival across trial arms and obtain hazard ratios and associated 95% CIs.

Comparison groups	Treatment v Observation
Number of subjects included in analysis	1343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.55
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.12

Secondary: Disease free interval

End point title	Disease free interval

End point description:

Disease-free interval (DFI) is defined as the time between the date of randomisation and the date of tumour progression which occurs at any site of the body (inclusive of both distant and locoregional recurrence), or date of death due to melanoma, whichever occurs first.

End point type	Secondary

End point timeframe:

On study, until disease progression or death due to melanoma

End point values	Treatment	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	671	672		
Units: Events	346	386		

Statistical analyses

Statistical analysis title	Disease free interval

Statistical analysis description:

A Cox proportional hazard model was used to compare disease free interval across trial arms and obtain hazard ratios and associated 95% CIs.

Comparison groups	Observation v Treatment

Number of subjects included in analysis	1343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	0.97

Secondary: Distant metastasis-free interval

End point title	Distant metastasis-free interval

End point description:

Distant metastasis-free interval (DMFI) is defined as the time between the date of randomisation and the date of recurrent disease occurring at distant sites (excluding locoregional disease amenable to surgical resection), or date of death due to melanoma, whichever occurs first.

End point type	Secondary

End point timeframe:

On study until distant progression, or death due to melanoma

End point values	Treatment	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	671	672		
Units: Events	301	327		

Statistical analyses

Statistical analysis title	Distant metastatic free interval

Statistical analysis description:

A Cox proportional hazard model was used to compare distant metastatic free interval across trial arms and obtain hazard ratios and associated 95% CIs.

Comparison groups	Treatment v Observation
Number of subjects included in analysis	1343
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.04

Secondary: Quality of life (QoL)

End point title	Quality of life (QoL)

End point description:

Global health scale assessed through the EORTC QLQC30 patient-completed questionnaire at time points: 3 monthly until 2 years, then at 2.5 years, 3 years, 4 years and 5 years

End point type	Secondary

End point timeframe:

On Study until 5 years from randomisation

End point values	Treatment	Observation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	600	626		
Units: Standardised area under a curve				
median (inter-quartile range (Q1-Q3))	81.7 (69.8 to 90.7)	81.9 (68.6 to 91.7)		

Statistical analyses

Statistical analysis title	Global health scale

Statistical analysis description:

The global heath scale of the EORTC-QLQ-C30 QoL questionnaire data were analysed by standardised area under the curve (AUC) and compared across trial arms using Wilcoxon rank sum tests

Comparison groups	Treatment v Observation
Number of subjects included in analysis	1226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.52
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment arm: All adverse events which occurred from randomisation until 28 days after the final dose of study drug
Observation arm: All adverse events which occurred from randomisation until year 1 or distant recurrence, whichever occurred first

Adverse event reporting additional description:

The national cancer institute common terminology criteria for adverse events (CTCAE) version 3.0 were used in this study. All toxic events were graded according to NCI CTCAE V3.0.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Treatment
Reporting group description: -	
Reporting group title	Observation

Reporting group description: -

Serious adverse events	Treatment	Observation	
Total subjects affected by serious adverse events			
subjects affected / exposed	140 / 671 (20.86%)	49 / 672 (7.29%)	
number of deaths (all causes)	280	294	
number of deaths resulting from adverse events	8	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary Malignancy			
subjects affected / exposed	2 / 671 (0.30%)	6 / 672 (0.89%)	
occurrences causally related to treatment / all	0 / 2	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Hypertension			
subjects affected / exposed	40 / 671 (5.96%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	44 / 49	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hematoma			

subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal flow			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis/thrombus/embolism			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy of partner			
subjects affected / exposed	2 / 671 (0.30%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ectopic pregnancy			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 671 (0.45%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	4 / 671 (0.60%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	

Fever			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	7 / 671 (1.04%)	3 / 672 (0.45%)	
occurrences causally related to treatment / all	3 / 7	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rigors/chills			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma			
subjects affected / exposed	1 / 671 (0.15%)	3 / 672 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sweating			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erectile dysfunction			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hemorrhage vaginal			
subjects affected / exposed	2 / 671 (0.30%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irregular menses			
subjects affected / exposed	3 / 671 (0.45%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 671 (0.45%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest tightness			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Voice changes			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusion			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Depression			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hemoglobin			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Intraop Injury - Other (Specify)			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac General - Other (Specify)			
subjects affected / exposed	4 / 671 (0.60%)	2 / 672 (0.30%)	
occurrences causally related to treatment / all	3 / 4	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac ischemia/infarction			
subjects affected / exposed	4 / 671 (0.60%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	4 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac pain			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asystole			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular systolic dysfunction			

subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal episode			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
CNS hemorrhage			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CNS ischemia			
subjects affected / exposed	3 / 671 (0.45%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	7 / 671 (1.04%)	2 / 672 (0.30%)	
occurrences causally related to treatment / all	4 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory neuropathy			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	2 / 671 (0.30%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Syncope (fainting)			
subjects affected / exposed	2 / 671 (0.30%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ear and labyrinth disorders			
External ear pain			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoacusis			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blurred vision			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Optic neuritis			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 671 (0.75%)	2 / 672 (0.30%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	1 / 671 (0.15%)	3 / 672 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal - Other (Specify, __)			
subjects affected / exposed	1 / 671 (0.15%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhage rectum			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal hemorrhage			
subjects affected / exposed	2 / 671 (0.30%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucositis			
subjects affected / exposed	2 / 671 (0.30%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	2 / 671 (0.30%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured appendix			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (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	2 / 671 (0.30%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Gallbladder pain			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage of liver			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver Cirrhosis			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatology/Skin - Other (Specify, __)			
subjects affected / exposed	1 / 671 (0.15%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	2 / 671 (0.30%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ulceration			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 671 (0.30%)	3 / 672 (0.45%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chest wall pain			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint pain			
subjects affected / exposed	4 / 671 (0.60%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal/Soft Tissue - Other (Specify, __)	Additional description: Granulomatous Erosion		
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			

subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pain in extremity			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infections and infestations			
Abdominal infection			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	8 / 671 (1.19%)	7 / 672 (1.04%)	
occurrences causally related to treatment / all	1 / 9	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection - Other			
subjects affected / exposed	6 / 671 (0.89%)	2 / 672 (0.30%)	
occurrences causally related to treatment / all	3 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic infection			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
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 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	3 / 671 (0.45%)	5 / 672 (0.74%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
ALT			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
AST			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GGT			
subjects affected / exposed	3 / 671 (0.45%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypercalcemia			
subjects affected / exposed	0 / 671 (0.00%)	1 / 672 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatremia			

subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphatemia			
subjects affected / exposed	1 / 671 (0.15%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders Other (Specify, __)	Additional description: Increased LDH		
subjects affected / exposed	2 / 671 (0.30%)	0 / 672 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Treatment	Observation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	624 / 671 (93.00%)	414 / 672 (61.61%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	232 / 671 (34.58%)	52 / 672 (7.74%)	
occurrences (all)	346	57	
Nervous system disorders			
Dizziness			
subjects affected / exposed	39 / 671 (5.81%)	15 / 672 (2.23%)	
occurrences (all)	45	15	
Headache			
subjects affected / exposed	162 / 671 (24.14%)	30 / 672 (4.46%)	
occurrences (all)	262	34	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	242 / 671 (36.07%)	60 / 672 (8.93%)	
occurrences (all)	352	61	
Pain			

subjects affected / exposed	146 / 671 (21.76%)	67 / 672 (9.97%)	
occurrences (all)	208	77	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	43 / 671 (6.41%)	18 / 672 (2.68%)	
occurrences (all)	45	19	
Diarrhea			
subjects affected / exposed	90 / 671 (13.41%)	27 / 672 (4.02%)	
occurrences (all)	129	30	
Nausea			
subjects affected / exposed	100 / 671 (14.90%)	22 / 672 (3.27%)	
occurrences (all)	141	25	
Vomiting			
subjects affected / exposed	47 / 671 (7.00%)	7 / 672 (1.04%)	
occurrences (all)	59	7	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	54 / 671 (8.05%)	28 / 672 (4.17%)	
occurrences (all)	60	28	
Epistaxis			
subjects affected / exposed	116 / 671 (17.29%)	1 / 672 (0.15%)	
occurrences (all)	147	1	
Voice changes			
subjects affected / exposed	34 / 671 (5.07%)	0 / 672 (0.00%)	
occurrences (all)	39	0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	63 / 671 (9.39%)	14 / 672 (2.08%)	
occurrences (all)	81	14	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	56 / 671 (8.35%)	28 / 672 (4.17%)	
occurrences (all)	60	29	
Joint pain			
subjects affected / exposed	50 / 671 (7.45%)	16 / 672 (2.38%)	
occurrences (all)	64	19	

Pain in extremity subjects affected / exposed occurrences (all)	41 / 671 (6.11%) 46	36 / 672 (5.36%) 41	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 October 2007	-To include an appendix in the protocol for the treatment of hypertension -To make changes to the conduct of the trial, including inclusion and exclusion criteria -To add additional research bloods -To include a patient card -To update the protocol, patient information sheet and GP letter to reflect recently published information regarding use of bevacizumab in the treatment of melanoma and other cancers. -To update the protocol, patient information sheet and GP letter to reflect recently published information regarding use of interferon as adjuvant treatment of melanoma.
10 July 2008	- To include new patient groups (AJCC stage IIB (T3bNoMo)) - Lengthen time baseline CT/MRI scans and Chest X-ray need to be done prior to randomisation. - To clarify a number of points in the protocol especially regarding what happens to patients if they have recurrence. - To change the CI, to change the PI at some sites and to add new sites.
13 July 2009	Inclusion criteria: – Addition of 12 week timelimit from SLNB to CLND if these are the lastest surgeries for melanoma. – Addition that BP must be ≤ 150 systolic AND ≤ 100 diastolic mmHg. – Addition of the clause 'unless pre-existing abnormality' to the adequate liver function criterion. Exclusion criteria: – Deletion of 'even if previously treated' from evidence of CNS metastases criterion. – Deletion of the uncontrolled hypertension criterion, as BP values added to inclusion criteria. – Deletion of 'or participation in another clinical trial' from treatment with any other investigational agent criterion. – Changing treatment period from 51 weeks to 1 calendar year to make it easier to keep track of when the treatment period ends. – Inclusion of guidance on seromas. – Removal of dose capping for Avastin – Inclusion of a section on pregnancy reporting. – Adding into the study assessments, flowchart & schedule that contact needs to be made with patients for survival info annually from 5.5 yrs. – Other wording clarifications
11 March 2011	New sections have been added to reflect new safety information and study results. A number of points have been clarified to help with the conduct of the trial and several eligibility criteria have been amended. The PIS and ICF have been combined to make a single document. A number of grammatical changes & re-ordering of content have been made. Information has been added to reflect new study results and safety information. Addition of a sentence to say guidelines on the management of hypertension are available from the coordination team if required.

03 November 2016	Request to close the study to the MHRA for regulatory purposes in March 2017 to correspond with 5 year follow-up analysis. This amendment was declined by MHRA
22 May 2017	Update to reference safety information, addition of new undesirable effects
28 August 2017	As the 5 year final analysis has now been performed, patient clinic visits and trial interventions will cease following 5 years post randomisation. Survival and recurrence data only will continue to be collected until 10 years post randomisation up to 2022. Patients on the AVAST-M trial have consented to be followed up for up to 10 years after randomisation. This includes collecting survival and recurrence information. Once established, survival and recurrence data will be collected centrally until 2022 on an annual basis by remote data collection from the appropriate Government Department of Health national registry (i.e. Public Health England (National Cancer Registration and Analysis Service or Office for National Statistics). Long term follow-up data for survival and disease recurrence may be collected using NHS Spine by the local research team. Reference Safety Information identified for Investigational Medicinal Product in protocol as requested by the MHRA.
28 February 2018	Patients in Scotland and Wales (n=75) will not participate in remote data collection due to the financial aspects of applying to each different Government registry. All patients in the AVAST-M trial have already completed 5 years of follow-up after randomisation. The 5 year follow-up data has provided us with sufficient information to enable the main trial objectives for this stage in the trial to be answered. The 5 year analysis has now been performed and patient clinic visits and trial investigations have ceased (as per amendment 41). Survival and recurrence data only is being collected until up to 10 years post randomisation up to 2022 for patients in England only. Patients on the AVAST-M trial have consented to be followed up for up to 10 years after randomisation, therefore we will not be re-consenting patients to the trial as a result of this amendment A new Trial Participant letter for patients in Scotland and Wales which has been included as part of this substantial amendment outlining changes to follow-up arrangements for the AVAST-M trial for patients in Scotland and Wales.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/24745696

http://www.ncbi.nlm.nih.gov/pubmed/30010756