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Adjuvant bevacizumab in patients with melanoma at high risk of recurrence (AVAST-M): preplanned interim results from a multicentre, open-label, randomised controlled phase 3 study

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Summary

Background Bevacizumab, a monoclonal antibody that targets VEGF, has shown restricted activity in patients with advanced melanoma. We aimed to assess the role of bevacizumab as adjuvant treatment for patients with resected melanoma at high risk of recurrence. We report results from the preplanned interim analysis.

Methods We did a multicentre, open-label, randomised controlled phase 3 trial at 48 centres in the UK between July 18, 2007, and March 29, 2012. Patients aged 16 years or older with American Joint Committee on Cancer stage (AJCC) stage IIB, IIC, and III cutaneous melanoma were randomly allocated (1:1), via a central, computer-based minimisation procedure, to receive intravenous bevacizumab 7·5 mg/kg, every 3 weeks for 1 year, or to observation. Randomisation was stratified by Breslow thickness of the primary tumour, N stage according to AJCC staging criteria, ulceration of the primary tumour, and patient sex. The primary endpoint was overall survival; secondary endpoints included disease-free interval, distant-metastases interval and quality of life. Analysis was by intention-to-treat. This trial is registered as an International Standardised Randomised Controlled Trial, number ISRCTN81261306.

Findings 1343 patients were randomised to either the bevacizumab group (n=671) or the observation group (n=672). Median follow-up was 25 months (IQR 16–37) in the bevacizumab group and 25 months (17–37) in the observation group. At the time of interim analysis, 286 (21%) of 1343 enrolled patients had died: 140 (21%) of 671 patients in the bevacizumab group, and 146 (22%) of 672 patients in the observation group. 134 (96%) of patients in the bevacizumab group died because of melanoma versus 139 (95%) in the observation group. We noted no significant difference in overall survival between treatment groups (hazard ratio [HR] 0·97, 95% CI 0·78–1·22; p=0·76); this finding persisted after adjustment for stratification variables (HR 1·03; 95% CI 0·81–1·29; p=0·83). Median duration of treatment with bevacizumab was 51 weeks (IQR 21–52) and dose intensity was 86% (41–96), showing good tolerability. 180 grade 3 or 4 adverse events were recorded in 101 (15%) of 671 patients in the bevacizumab group, and 36 (5%) of 672 patients in the observation group. Bevacizumab resulted in a higher incidence of grade 3 hypertension than did observation (41 [6%] *vs* one [<1%]). There was an improvement in disease-free interval for patients in the bevacizumab group compared with those in the observation group (HR 0·83, 95% CI 0·70–0·98, p=0·03), but no significant difference between groups for distant-metastasis-free interval (HR 0·88, 95% CI 0·73–1·06, p=0·18). No significant differences were noted between treatment groups in the standardised area under the curve for any of the quality-of-life scales over 36 months. Three adverse drug reactions were regarded as both serious and unexpected: one patient had optic neuritis after the first bevacizumab infusion, a second patient had persistent erectile dysfunction, and a third patient died of a haemopericardium after receiving two bevacizumab infusions and was later identified to have had significant predisposing cardiovascular risk factors.

Interpretation Bevacizumab has promising tolerability. Longer follow-up is needed to identify an effect on the primary endpoint of overall survival at 5 years.

Funding Cancer Research UK.

Introduction

Melanoma is a chemoresistant cancer. Fewer than 50% of patients with resected locoregional melanoma survive to 5 years.[1] Adjuvant trials assessing interferon alfa have shown that the drug delays melanoma recurrence, but has only a small overall survival benefit.[2] The low survival benefit and high treatment-related toxic effects associated with interferon alfa mean that no internationally agreed standard adjuvant treatment is available for patients with high-risk melanoma.

Targeting the proangiogenic VEGF with the monoclonal antibody bevacizumab provides modest survival gains for patients with some types of advanced cancer.[3] Proangiogenic factors play a key part in neovascularisation of invading and metastasising cancer; therefore, VEGF blockade after locoregional surgery might prevent spread of disease.[4,5] VEGF concentration measured in either the tissue or serum of patients with melanoma correlate with disease stage and tumour burden, and might be prognostic.[6–10] Findings from clinical trials of small-molecule inhibitors with selectivity for VEGFR in patients with advanced melanoma have been disappointing;[11–13] however, bevacizumab activity was more promising.[14,15] We therefore did this study of adjuvant bevacizumab versus observation after resection of melanoma to establish whether angiogenesis inhibition would offer clinical benefit in patients at high risk of recurrence.

Methods

Study design and patients

We did this open-label, randomised controlled phase 3 trial between July 18, 2007, and March 29, 2012, at 48 centres in the UK (appendix). Eligible patients were at least 16 years old, with histological confirmation of completely resected American Joint Committee on Cancer stage IIB (T3bN0M0 and T4aN0M0), IIC (T4bN0M0), or III (TxN1–3M0) cutaneous melanoma. Sentinel lymph-node biopsy was recommended but not mandatory; complete lymphadenectomy was done if the sentinel node was positive. Inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1; a life expectancy of 6 months or more; and adequate haematological, liver, and renal function. Exclusion criteria were evidence of distant or non-regional lymph-node metastases (established by CT or MRI scanning of the body and head within 8 weeks of randomisation), incomplete resection of melanoma, or adjuvant radiotherapy that was ongoing at randomisation. Treatment assignment could not take place within 4 weeks of surgery or in the presence of unhealed wounds, but had to be within 12 weeks of a patient's latest surgery for melanoma. Previous chemotherapy, immunotherapy, or hormonal therapy for melanoma was not allowed within 12 weeks of randomisation. Patients had to be free from drug administration for 28 days either side of any procedure. Patients were also excluded if they had uncontrolled hypertension, or a history or evidence of any disorder that might increase risk of bleeding.

All patients gave written informed consent. We obtained regulatory approval, and ethics approval from a multicentre research ethics committee. Because this interim analysis was preplanned, and in view of the absence of an international standard adjuvant therapy for melanoma, the independent data monitoring committee supported publication of these results in advance of the final analysis anticipated in 2017.

Randomisation and masking

Eligible patients were randomly assigned centrally in a 1:1 ratio using a computer-based minimisation algorithm, to receive either adjuvant bevacizumab or standard observation. Randomisation was stratified by Breslow thickness of the primary tumour, N stage according to AJCC staging criteria,[1] ulceration of the primary tumour (absent, present, or unknown), and patient sex. This was an open-labelled trial and therefore participants, investigators, and trial staff were not masked to group allocation.

Procedures

For patients randomly assigned to bevacizumab, 7·5 mg/kg was given via 30 min intravenous infusion once every 3 weeks for 1 calendar year (maximum 17 infusions), or until disease recurred. No dose reductions were permitted, but patients could have a maximum of two drug holidays (at their request), each of no more than 6 weeks. If a patient required any further dose interruptions, treatment was discontinued.

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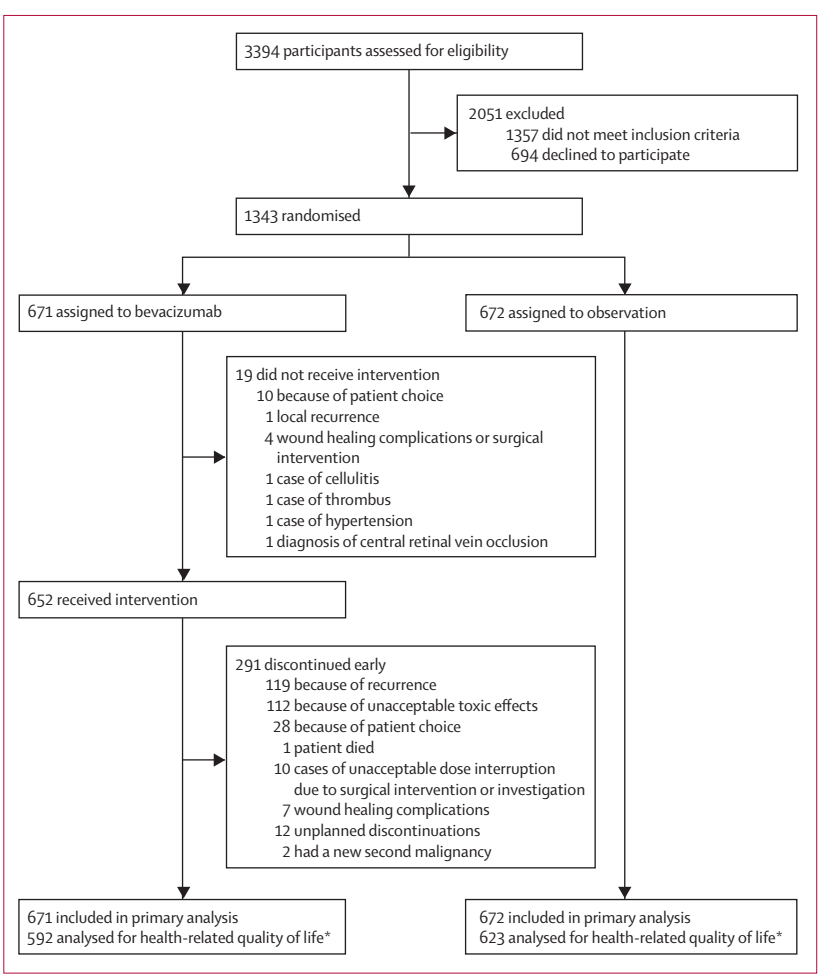

***Figure 1*: Trial profile**
HR=hazard ratio. *Patients were included in the longitudinal quality-of-life analysis if they had completed at least two questionnaires.

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See Online for appendix

Patients in both arms were assessed every 3 months for 2 years; then every 6 months for 3 years; and annually thereafter until 10 years from randomisation, death, or withdrawal for any other reason. Research nurses contacted patients at 6 month intervals between annual clinic visits to enable survival information to be updated. Medical history, physical examination, full blood count, clotting, clinical chemistry, and protein urinalysis were assessed at baseline and every study visit. Chest radiography was done at 3 and 6 months after randomisation; then every 6 months up to 3 years, thereafter annually up to 5 years. Patients completed the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire (EORTC QLQ-C30, version 3.0) every 3 months for 2 years, then at 2·5, 3, 4, and 5 years. Adverse events reported during the first year by patients in the observation group and for 28 days after the last bevacizumab infusion for those in the bevacizumab group were recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Locoregional and distant recurrence were managed as per local hospital practice. Treatment upon disease progression was determined by local investigator decision for both patient groups. Treatment options included surgery; systemic therapy; radiotherapy, dependent on type of recurrence; and patient choice.

We ascertained *BRAF* mutation status in archived tumour tissue with a cobas4800 (Roche Diagnostics, West Sussex, UK) test or by pyrosequencing. *NRAS* mutation status was identified in *BRAF* wild-type tumours by pyrosequencing. *NRAS* status was not established for *BRAF* mutant tumours, because *NRAS* and *BRAF* mutations are generally mutually exclusive.

	Bevacizumab (n=671)	Observation (n=672)
Sex		
Male	377 (56%)	376 (56%)
Female	294 (44%)	296 (44%)
Median age (years)	56 (18–87)	55 (19–88)
Median BMI (kg/m²)	27·7 (15·8–68·6)	27·5 (15·7–50·2)
Breslow thickness of primary tumour (mm)		
<2·0	199 (30%)	200 (30%)
>2–4	203 (30%)	204 (30%)
>4	221 (33%)	216 (32%)
Unknown	48 (7%)	52 (8%)
Ulceration of primary tumour		
Yes	258 (39%)	257 (38%)
No	311 (46%)	321 (48%)
Unknown	102 (15%)	94 (14%)
N classification		
N0+Nx	187 (28%)	181 (27%)
N1a+N2a	142 (21%)	139 (21%)
Other N classes	342 (51%)	352 (52%)
ECOG performance status		
0	602 (90%)	592 (88%)
1	67 (10%)	80 (12%)
Unknown	2 (<1%)	0
AJCC stage*		
IIB	103 (15%)	109 (16%)
IIC	84 (13%)	72 (11%)
IIIA	104 (15%)	95 (14%)
IIIB	242 (36%)	253 (38%)
IIIC	138 (21%)	143 (21%)
Sentinel lymph-node biopsy done		
Yes	218 (32%)	222 (33%)
No	450 (67%)	446 (66%)
Unknown	3 (1%)	4 (1%)
BRAF status established	299 (45%)	346 (51%)
Wild type	173/299 (58%)	181/346 (52%)
V600 mutant	126/299 (42%)	165/346 (48%)
NRAS status established in only patients with *BRAF* wild-type	120 (69%)	119 (66%)
Wild type	67/120 (56%)	66/119 (55%)
Q61 mutant	53/120 (44%)	53/119 (45%)

Data are n (%) median (range), or n/N (%), unless otherwise indicated. BMI=body-mass index. ECOG=Eastern Cooperative Oncology Group. AJCC=American Joint Committee on Cancer Stage. *82 (22%) of the 368 patients with stage IIB and IIC tumours had sentinel lymph-node biopsy, and were therefore pathologically lymph-node negative.

Table 1: **Baseline characteristics**

Outcomes

The primary endpoint of the trial was overall survival, which we defined as the time from date of randomisation until date of death from any cause, or censored at the last known date alive. Secondary endpoints were disease-free interval, distant-metastasis-free interval, safety and toxic effects, and health-related quality of life. Tertiary endpoints were assessment of biological predictive and prognostic markers. Disease-free interval was defined as the time from the date of randomisation until the date of first tumour recurrence (including distant and locoregional recurrence), or date of death due to melanoma. Distant-metastasis-free interval was defined as the time from the date of randomisation until the date of first distant recurrent disease, or date of death due to melanoma.

Statistical analysis

Patients who withdrew consent for further follow-up were included in the analysis, but censored at the time of withdrawal. The expected rates of 1 year and 5 year overall survival in the standard observation group were roughly 85% and 40%, respectively. A sample size of 1320 patients (660 patients per group) was needed to detect an absolute increase in 5 year overall survival from 40% to 48%, with 85% power and a 5% significance level, which equates to a hazard ratio (HR) of 0·80. An interim analysis was planned after all patients had finished the treatment and

been in the study for at least 1 year, the results of which are reported here.

Survival curves were constructed with the Kaplan-Meier method and compared with a log-rank χ^2 test. A Cox proportional hazard model was used to obtain HRs and associated 95% CIs. HRs were calculated for prognostic subgroups and a HR plot constructed.[16] Multivariable Cox-regression models were used to adjust the treatment effect for stratification variables, to assess the independent predictors of overall survival and disease-free interval, and to assess treatment interaction with the tumour mutation status and whether hypertension, fitted as a time-dependent covariate, affected disease-free interval. We did a sensitivity analysis excluding ineligible patients.

We scored quality-of-life data on a scale from 0 to 100 according to the algorithm described in the EORTC QLQ-C30 scoring manual.[17] High scores imply an improvement in function or quality of life, but more severe symptoms. Quality-of-life data were analysed by standardised area-under-the-curve analysis[18] and compared across trial groups with Wilcoxon rank-sum tests.

Reported p values are two-sided. All analyses were done by intention to treat with the SAS statistical package (version 9.3). This trial is registered as an International Standardised Randomised Controlled Trial, number ISRCTN 81261306.

Role of the funding source

The sponsor and funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. AM had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

1343 patients were randomly assigned to either the bevacizumab group (n=671) or the observation group (n=672; figure 1). Patients' baseline characteristics were similar between groups (table 1). 975 (73%) patients had resected AJCC stage III melanoma, 515 (38%) patients had an ulcerated primary tumour, and 440 (32%) patients underwent sentinel lymph-node biopsy. 368 (27%) patients had no known nodal involvement (N0 and Nx), 281 (21%) had microscopic lymph-node involvement (N1a and N2a), and 694 (52%) had macroscopic lymph-node involvement. We subsequently identified 11 (1%) of enrolled patients as ineligible; three in the bevacizumab group and eight in the observation group: five had metastatic disease, five had incomplete surgery, and one had stage IIA melanoma. These patients were included in all analyses on an intention-to-treat-basis. 44 (3%) of 1343 enrolled patients were lost to follow-up or withdrew consent during the study. Six patients withdrew consent for further follow-up (five [1%] in the bevacizumab group and one [<1%] in the observation group) and 38 patients were lost to follow-up (23 [3%] *vs* 15 [2%]).

19 (3%) of the 671 patients in the bevacizumab group did not start treatment and 291 (43%) discontinued treatment early (figure 1). The median time from surgery to start of bevacizumab was 11 weeks (IQR 4–14). The median number of infusions of bevacizumab was 16 (IQR 7–17) and median duration of treatment was 51 weeks (IQR 21–52). Median dose intensity for the 652 patients who started treatment was 86% (IQR 41–96). 361 (54%) patients completed the planned treatment (either all 17 infusions or 1 year of treatment; figure 1). The main reasons for patients failing to complete the full course of bevacizumab were recurrence or toxic effects. Severity was graded as 3 or 4 in 34 (30%) of the 112 cases of unacceptable toxic effects. The most common toxic

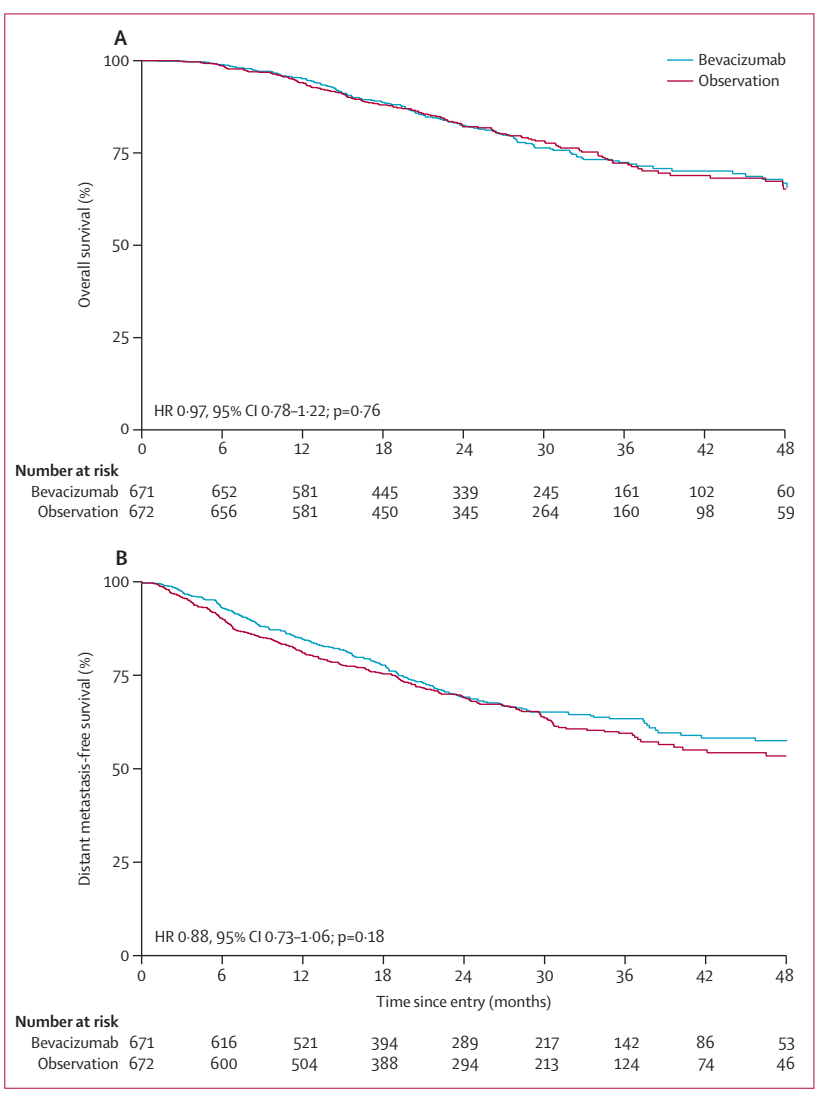

***Figure 2*: Overall survival (A) and distant metastasis-free interval (B), analysis unadjusted for stratification factors**
HR=hazard ratio.

effect causing treatment discontinuation was hypertension in 36 (5%) patients. Only 261 (3%) of 8126 bevacizumab infusions were delayed for more than 7 days. The main reasons for delay were for planned drug holidays or toxic effects (data not shown).

286 (21%) of 1343 enrolled patients had died at the time of the interim analysis (140 [21%] of 671 patients in the bevacizumab group and 146 [22%] of 672 patients in the observation group). 134 (96%) of patients in the bevacizumab group died because of melanoma versus 139 (95%) in the observation group. The median follow-up was 25 months (IQR 17–37). Median overall survival had not yet been reached. We noted no significant difference in overall survival between treatment groups (figure 2); this finding persisted after adjustment for stratification variables (HR 1·03; 95% CI 0·81–1·29; p=0·83). Overall survival at 1 year was 95% (95% CI 93–97) for patients in the bevacizumab group and 94% (92–96) for those in the observation group. Multivariable analysis identified disease stage, ECOG performance status, and primary melanoma ulceration as independent predictors of overall survival (table 2). The treatment effect remained non-significant for overall survival after adjustment for the three prognostic variables (HR 1·02, 95% 0·81–1·28; p=0·89).

	n (%; N=1343)	Number of events (%)	Hazard ratio (95% CI)	p value
Overall survival				
Disease stage				<0·0001
II	368 (27%)	45 (12%)	1·00	..
III (N1a and N2a)	281 (21%)	39 (14%)	1·42 (0·91–2·21)	..
III (other N)	694 (52%)	202 (29%)	3·05 (2·16–4·32)	..
ECOG performance status				<0·0001
0	1194 (89%)	235 (20%)	0·54 (0·39–0·73)	..
1	147 (11%)	50 (34%)	1·00	..
Ulceration				0·02
Yes	515 (38%)	109 (21%)	1·00	..
No	632 (47%)	121 (19%)	0·68 (0·52–0·89)	..
Unknown	196 (15%)	56 (29%)	0·75 (0·53–1·06)	..
Disease-free interval				
Disease stage				<0·0001
II	368 (27%)	118 (32%)	1·00	..
III (N1a and N2a)	281 (21%)	76 (27%)	1·12 (0·82–1·52)	..
III (other N)	694 (52%)	370 (53%)	2·78 (2·20–3·51)	..
Breslow thickness (mm)				<0·0001
≤2·0	399 (30%)	160 (40%)	1·00	..
>2–4	407 (30%)	165 (41%)	1·25 (1·01–1·57)	..
>4	437 (33%)	200 (46%)	1·74 (1·38–2·20)	..
Unknown	100 (7%)	39 (39%)	0·84 (0·59–1·19)	..
Trial group				0·03
Treatment	671 (50%)	264 (39%)	0·83 (0·70–0·98)	..
Observation	672 (50%)	300 (45%)	1·00	..
ECOG performance status				0·04
0	1194 (89%)	490 (41%)	1·30 (1·02–1·67)	..
1	147 (11%)	73 (50%)	1·00	..

ECOG=Eastern Cooperative Oncology Group.

***Table 2*: Results from the multivariate analyses for overall survival and disease-free interval**

We recorded an improvement in disease-free interval for patients in the bevacizumab group compared with those in the observation group (figure 3). At 1 year, 77% (95% CI 73–80) of patients given bevacizumab were disease free, as were 70% (66–73) for those who underwent observation. The treatment effect for disease-free interval remained irrespective of the stratification variables (figure 4). Multivariable analysis identified disease stage, Breslow thickness of the primary melanoma, trial group, and ECOG performance status as independent predictors of disease-free interval (table 2). There was a suggestion of an improved distant-metastasis-free interval with bevacizumab, but it was not significant (figure 2). Types of recurrence and the treatment methods used for recurrence were similar between treatment groups (table 3). 184 (65%) of the 283 local recurrences and 68 (16%) of the 430 distant recurrences were treated with surgery alone. Results from the analysis of disease-free interval were unchanged in a sensitivity analysis excluding the ineligible patients.

BRAF status was available for 645 (48%) patients (table 1). A *BRAF V600* mutation was detected in 291 (45%) of the 645 assessed patients (table 1). Sufficient material remained to undertake NRAS testing in 239 (68%) of 354 patients with *BRAF* wild-type; 106 (44%) of these patients had a mutation at codon 61. No codon 12 or 13 mutations were detected. The interaction between treatment and *BRAF* status was not significant (p=0·10); however, in patients with *BRAF* mutant tumours, we noted an improvement in the disease-free interval in those given bevacizumab (figure 3). Disease-free interval did not differ significantly between treatment groups in the wild-type *BRAF* population (figure 3).

180 grade 3 or 4 adverse events were recorded in 101 (15%) of 671 patients in the bevacizumab group and 36 (5%) of 672 patients in the observation group. 216 (32%) patients had hypertension in the bevacizumab group (table 4), but the disorder was generally manageable; we recorded grade 3 or 4 hypertension in 41 (6%) patients (table 4). Hypertension did not significantly affect disease-free interval (HR 0·85, 95% CI 0·67–1·09; p=0·20) after adjustment for trial group.

Three adverse drug reactions were regarded as both serious and unexpected. One patient developed optic neuritis after the first bevacizumab infusion, which resulted in 90% loss of vision in one eye. A second patient had persistent erectile dysfunction, but continued to receive treatment. A third patient died of a haemopericardium after receiving two bevacizumab infusions, and was later identified to have had significant predisposing cardiovascular risk factors.

8846 (87%) of 10 151 quality-of-life forms were returned. 1215 (90%) of 1343 patients returned at least two forms

and were included in the analyses: 592 (88%) of 671 patients in the bevacizumab group and 623 (93%) of 672 patients in the observation group. Baseline quality-of-life scores were similar in both groups (data not shown). After Bonferroni adjustment for multiple testing, no significant differences were noted between treatment groups in the standardised area under the curve for any of the quality-of-life scales over 36 months (table 5).

Discussion

Our findings show an improvement in disease-free interval with bevacizumab in patients with resected melanoma at high risk of recurrence as compared with observation alone. Median disease-free interval and overall survival have not yet been reached. The curves for disease-free interval remain separate at this interim analysis. Follow-up of patients and timing of clinic visits were similar between treatment groups. Clearly, it will be important to ascertain whether this treatment effect ultimately translates into a benefit in overall survival at final analysis, which is follow-up driven and planned for when all patients have been on study for a minimum of 5 years, at which time 736 events are anticipated. The conditional power for futility of the primary outcome of overall survival at this interim analysis was 35%.

To our knowledge, AVAST-M is one of the largest adjuvant melanoma trials and the largest bevacizumab monotherapy study ever undertaken (panel). By contrast with most published adjuvant melanoma trials, we chose overall survival as the primary endpoint in AVAST-M. Patients and regulatory agencies increasingly value relapse-free survival as a primary endpoint in this setting, which is justified now that systemic therapies have been shown to improve overall survival in advanced disease.[19–21] However, when we started AVAST-M bevacizumab was a new drug with significant toxic effects (albeit reported mainly in combination with cytotoxic chemotherapy), and so we felt that a benefit in overall survival would need to be shown to change clinical practice. We chose disease-free interval and distant-metastasis-free interval as secondary endpoints to identify the effect of bevacizumab on disease recurrence. However, disease-free interval in this trial could be indiciative of relapse-free survival, because only seven additional deaths from other causes without recurrence would have been included in an analysis of relapse-free survival; these inclusions would not have changed the results from those reported for disease-free interval.

The most frequently used adjuvant melanoma treatment worldwide is interferon alfa. The role of adjuvant interferon is controversial and, despite being used in both the USA and Europe, it is not an international standard of care. Moreover, in many countries adjuvant therapy for resected melanoma is not routinely offered at all. The controversy regarding use of interferon surrounds the interpretation of its clinical

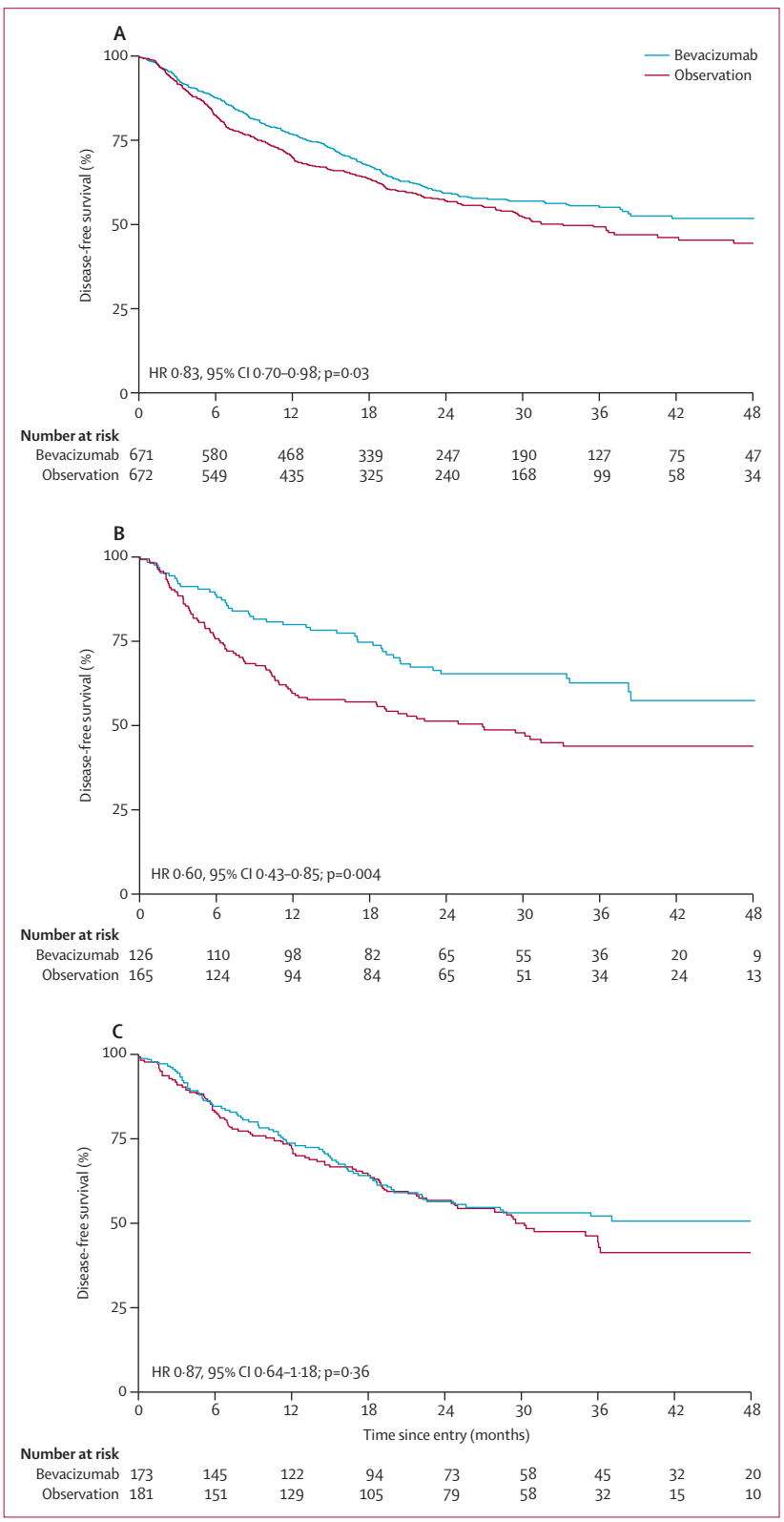

***Figure 3*: Disease-free interval for all patients (A), for patients with a BRAF mutation (B), and for those with BRAF wild type (C)**
HR=hazard ratio.

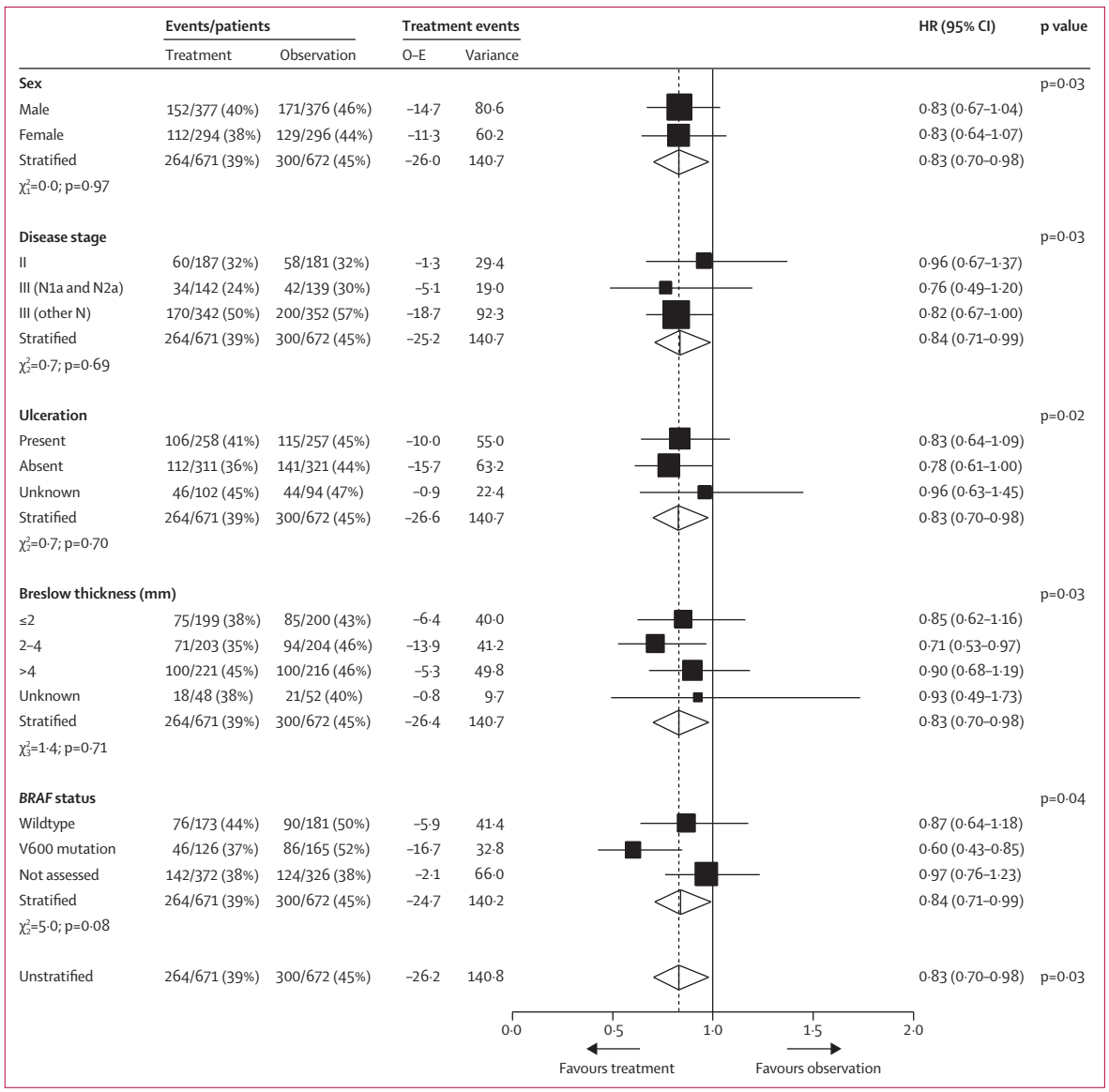

***Figure 4*: Hazard ratio plot of the treatment effect by prognostic factors for disease-free interval**
O–E=observed–expected events. HR=hazard ratio.

significance attributable to marginal survival benefits alongside potential for harm due to drug side-effects. Trials assessing different doses and formulations of interferon alfa have not identified the optimum adjuvant regimen for patients with melanoma,[2] while this treatment is recognised to be associated with substantial toxic effects, including liver dysfunction, fatigue, and depression.[22,23] Other immunotherapeutic strategies, including several vaccines, have been rigorously tested in patients with melanoma, with disappointing results overall.[24] This outcome is exemplified by the results of the DERMA randomised trial, in which a MAGE A3 vaccine did not improve relapse-free survival (its first co-primary endpoint) in patients with resected stage III melanoma expressing the MAGE A3 antigen.[25] Our results suggest that the extent of patient benefit offered with bevacizumab might be similar to that with interferon alfa for the endpoint of relapse-free survival (HR for interferon alfa 0·82, 95% CI 0·77–0·87), but the overall survival benefit (0·89, 0·82–0·96) on ifterferon alfa was not noted with bevacizumab.[2]

At this interim analysis, few patients had received immunotherapy or targeted therapy at relapse, and the most common intervention was surgery. This finding is consistent with the high rate of locoregional recurrence as a result of the fairly low use of sentinel node biopsy and the inclusion of high risk primary tumours, together with the scarcity of active systemic therapy options

available until more recently. The effect of subsequent treatments at relapse on overall survival is likely to be small at this time point, but will be of greater importance in the future. Even so, the delay in melanoma recurrence noted with adjuvant bevacizumab in this trial might be clinically relevant.

Bevacizumab monotherapy seems to be well tolerated: grade 3 or 4 adverse events associated with bevacizumab were fewer than those reported with interferon, depending on the dose used, although cross-trial comparisons should be made with caution.[22,23]

There was no obvious safety signal associated with surgical interventions or haemorrhage to account for patients' early discontinuation. The protocol specified dose interruptions around surgical interventions, requiring 28 days free from drug administration either side of any procedure, and preventing drug administration in the presence of any unhealed wound. Drug-associated complications in wound healing seem to be negligible, and only a few patients failed to complete planned treatment due to unacceptable delays in wound healing, suggesting that, in routine clinical practice, withholding treatment in such circumstances need not be so stringent. Fairly high patient withdrawal rates have been reported in both low-dose and high-dose adjuvant interferon alpha trials: 15% in the UK AIM HIGH trial[23] and 37% in the EORTC 18991 trial.[22] However, it is worth noting that, in the EORTC 18991 trial, grade 3 and 4 adverse events were reported in 12% of patients receiving placebo. Withdrawal rates will be affected by the duration of intended treatment, but low-level chronic side-effects in an otherwise fit population might account for patients electing to stop prematurely and this should be considered in future adjuvant trial designs. A placebo-controlled trial might have improved patient willingness to remain on treatment for longer, but the additional cost of a placebo would have been prohibitive in this charity-funded trial.

Multivariate analyses of disease-free interval and overall survival were undertaken to explore whether some subsets of patients were more likely to benefit from therapy than others. Disease stage and Breslow thickness were the most significant predictors of disease-free interval; disease stage and ECOG performance status were the most significant predictors of overall survival. A tenth of patients had an ECOG performance status score of 1 on trial entry; the reason for their poor outcome is not apparent, but will be assessed fully in the final analysis.

AVAST-M includes a prespecified translational study, aimed at identifying predictive and prognostic biomarkers. We retrospectively obtained tumour blocks with which to test *BRAF* mutation status; therefore, the possibility of ascertainment bias cannot be excluded. The 45% *BRAF V600* mutation rate within the assessed population is consistent with data derived from other advanced melanoma populations. Firm conclusions about whether bevacizumab might result in a longer disease-free interval for the subgroup of patients with *BRAF* mutant tumours cannot yet be made, but further analysis including multivariate analyses will be undertaken at the final analysis. The subgroup of patients assessed for *NRAS* mutation was too small to provide reliable results for disease-free interval and overall survival at this stage. Firm conclusions from the *BRAF* subgroup analysis cannot yet be made, but we will do multivariate analyses at the final analysis. Investigation into the biological basis for this initially unexpected finding is ongoing, but it is consistent with emerging evidence of the MAP kinase pathway playing a role in the control of VEGF expression. Studies in a mouse model of

	Bevacizumab (n=671)	Observation (n=672)
Any disease recurrence reported		
No	408/671 (61%)	374/672 (56%)
Yes*	263/671 (39%)	298/672 (44%)
Locoregional recurrence first	125/263 (48%)	150/298 (50%)
Distant recurrence first	138/263 (52%)	148/298 (50%)
Locoregional recurrence		
N (%)	130 (19%)	153 (23%)
Type†		
Local recurrence at primary site	61 (47%)	64 (42%)
In-transit metastases	44 (34%)	44 (29%)
Regional lymph-node metastases‡	55 (42%)	71 (46%)
Treatment†		
None	3 (2%)	7 (5%)
Chemotherapy	7 (6%)	9 (6%)
Immunotherapy or biological therapy	3 (3%)	5 (3%)
Radiotherapy	28 (22%)	23 (15%)
Surgery	110 (85%)	131 (86%)
Other	4 (3%)	5 (3%)
Unknown	2 (2%)	1 (1%)
First distant recurrence		
N (%)	207 (31%)	223 (33%)
Type		
M1a (skin, subcutaneous, or lymph nodes with normal LDH)	27 (13%)	28 (12%)
M1b (lung)	47 (23%)	55 (25%)
M1c (other sites or raised LDH)	133 (64%)	140 (63%)
Treatment†		
None	43 (21%)	33 (15%)
Chemotherapy	70 (34%)	74 (33%)
Immunotherapy or biological therapy	28 (14%)	23 (10%)
Radiotherapy	50 (24%)	47 (21%)
Surgery	49 (24%)	64 (29%)
Other	12 (6%)	28 (13%)
Unknown	9 (4%)	6 (3%)

Data are n/N (%) or n (%), unless otherwise indicated. *An additional three patients (one in the bevacizumab group and two in the observation group) who died of melanoma before details of their recurrence being reported are included in the analyses of disease-free interval. †Patients can have more than one site of locoregional recurrence and treatment for recurrence recorded. ‡20 (16%) of the patients with regional lymph-node recurrence had previously had a sentinel lymph-node biopsy.

***Table* 3: Patterns of disease recurrence**

	Bevacizumab (n=671)			Observation (n=672)		
	1–2	3	4	1–2	3–4	4
Auditory	10 (1%)	1 (<1%)	0	5 (1%)	0	0
Blood or bone marrow	34 (5%)	2 (<1%)	0	24 (4%)	1 (<1%)	0
Hypertension	175 (26%)	41 (6%)	0	40 (6%)	1 (<1%)	0
Other cardiac	19 (3%)	3 (<1%)	2 (1%)	4 (1%)	2 (<1%)	0
Dermatological	188 (28%)	3 (<1%)	0	83 (12%)	5 (1%)	0
Endocrine	24 (4%)	0	0	8 (1%)	1 (<1%)	0
Fatigue	222 (33%)	3 (<1%)	1 (<1%)	58 (9%)	1 (<1%)	0
Other constitutional symptoms	78 (12%)	0	0	32 (5%)	0	0
Diarrhoea	84 (13%)	0	0	22 (3%)	2 (<1%)	0
Other gastrointestinal	249 (37%)	3 (<1%)	0	62 (9%)	3 (<1%)	1 (<1%)
Haemorrhage or bleeding	152 (23%)	1 (<1%)	0	12 (2%)	1 (<1%)	0
Infection	190 (28%)	7 (1%)	0	83 (12%)	5 (1%)	0
Lymphatic	42 (6%)	1 (<1%)	0	45 (7%)	0	0
Metabolic	75 (11%)	12 (2%)	0	31 (5%)	1 (<1%)	0
Musculoskeletal	91 (14%)	1 (<1%)	0	26 (4%)	3 (<1%)	1 (<1%)
Neurological	89 (13%)	7 (1%)	2 (<1%)	58 (9%)	1 (<1%)	0
Ocular	29 (4%)	1 (<1%)	1 (<1%)	5 (1%)	1 (<1%)	0
Headache	150 (22%)	5 (1%)	0	23 (3%)	2 (<1%)	0
Other pain	249 (37%)	12 (2%)	0	140 (21%)	8 (1%)	0
Pulmonary	135 (20%)	1 (<1%)	0	45 (7%)	1 (<1%)	0
Altered menstruation	23 (3%)	3 (<1%)	0	5 (1%)	1 (<1%)	0
Thromboembolic event	1 (<1%)	1 (<1%)	0	0	0	0
Second malignancy	0	2 (<1%)		0	4 (1%)	

Data are n (%). Adverse events are recorded for all patients who had an event of grade 3 or 4 severity and include any other adverse events that were recorded in 10% or more patients. Patients can have more than one type of adverse event. We classified events are classified with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 3.0).

***Table 4*: Overview of adverse events**

	Bevacizumab	Observation	p value*
Function			
Physical functioning	96·1 (86·7–100)	96·7 (88·3–100)	0·16
Role functioning	94·4 (79·2–100)	94·8 (79·2–100)	0·50
Emotional functioning	89·0 (75·9–97·9)	87·5 (74·0–97·2)	0·23
Cognitive functioning	93·8 (81·3–100)	95·8 (83·3–100)	0·009
Social functioning	94·4 (79·2–100)	95·8 (83·3–100)	0·06
Symptom			
Fatigue	13·3 (4·4–26·2)	11·1 (3·2–22·9)	0·02
Nausea and vomiting	0 (0–2·8)	0 (0–2·8)	0·51
Pain	8·3 (0–20·0)	7·5 (0–22·2)	0·68
Dyspnoea	0 (0–9·5)	0 (0–8·3)	0·94
Insomnia	12·5 (0–28·2)	12·5 (0–33·3)	0·75
Appetite loss	0 (0–4·2)	0 (0–5·6)	0·38
Constipation	0 (0–6·7)	0 (0–4·2)	0·04
Diarrhoea	0 (0–5·6)	0 (0–5·6)	0·29
Financial difficulties	0 (0–8·3)	0 (0–4·8)	0·06
Global health			
Quality of life	81·3 (68·1–89·6)	81·9 (68·8–91·1)	0·26

Data are median (IQR), unless otherwise indicated. Scores are on a scale of 0–100, with high values for function scale and low values for symptom scales representing improved quality of life. *Unadjusted. p values less than 0·003 would be significant after adjustment with Bonferroni correction for multiple testing.

***Table 5*: Quality of life standardised area-under-curve analyse**

melanoma and human melanoma tissue have shown that *BRAF* signalling affects VEGF production.[26] In *BRAF* mutant mouse xenografts, *BRAF* inhibition resulted in increased T-cell infiltration of tumours, an effect that was mediated by downregulation of VEGF. If this mechanism applies to melanomas in human beings, it would provide a basis for the selection of patients for bevacizumab therapy, and a rationale for future potential combination regimens.

Three trials testing adjuvant bevacizumab in combination with chemotherapy have been reported in patients with colon[27,28] and breast cancer.[29] All three trials had disease-free survival as the primary endpoint, and none identified any improvement. These negative trials have called into question whether inhibition of micrometastatic disease by bevacizumab is a realistic goal. Angiogenesis inhibitors have immunomodulatory effects[30,31] and (by contrast with epithelial cancers), melanoma is a highly immunogenic tumour. It is possible that any benefit attributable to bevacizumab is due to immunological effects, which can persist beyond the treatment period. Both immunological and angiogenic biomarkers are now being explored with tumour and blood samples collected from most patients recruited to the AVAST-M trial.

Panel: Research in context

Systematic review

An international standard adjuvant therapy for patients at risk of melanoma recurrence has not yet been established. We searched PubMed for clinical trials published in English between Jan 1, 2000 and Feb 1, 2014, assessing systemic therapy specifically in melanoma, with the search terms "melanoma" and "adjuvant". Inhibition of angiogenesis as an adjuvant strategy has not previously been tested in melanoma patients.

Interpretation

To our knowledge, AVAST-M is the first phase 3 trial assessing bevacizumab as adjuvant therapy for melanoma and the largest bevacizumab monotherapy every undertaken. In this preplanned interim analysis no overall survival benefit was noted, bevacizumab improved the disease-free interval, a secondary outcome measure. Prespecified biomarker analysis points to the benefit being in those patients with *BRAF*-mutant melanoma, which is consistent with the MAP kinase pathway regulating VEGF expression. Longer follow-up is needed to identify the effect of bevacizumab on overall survival at 5 years.

Effective treatment to prevent melanoma relapse remains an unmet need. Bevacizumab is not yet established as an effective treatment for melanoma and other drugs are being tested in the adjuvant setting. The results of these trials, alongside the final results of the AVAST-M trial, will have a key role in identifying future adjuvant strategies for this disease.

Contributors

PC was the chief investigator, responsible for the trial design, trial management, data interpretation, and preparation of the manuscript. AM was the trial statistician who analysed the data, created the tables and figures, and contributed to the trial design, trial management, data interpretation, and preparation of the manuscript. JAD contributed to the trial design, trial management, and data interpretation. MRM was responsible for the tumour genotyping and contributed to the trial design, trial management, data interpretation, and revision of the manuscript. PN, MG, ND, SN, CK, MM, SD, EM, SH, RB, AW, JN, MH, SK recruited the highest numbers of patients and were involved in data collection at their sites. GY was involved in data collection and coordination of the trial. PL contributed to the trial design, trial management, data interpretation, and revision of the manuscript. All authors participated in the revision and finalisation of the manuscript.

Declaration of interests

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