Active symptom control with or without chemotherapy in the treatment of patients with malignant pleural mesothelioma (MS01): a multicentre randomised trial

*Martin F Muers, Richard J Stephens, Patricia Fisher, Liz Darlison, Christopher M B Higgs, Erica Lowry, Andrew G Nicholson, Mary O'Brien, Michael Peake, Robin Rudd, Michael Snee, Jeremy Steele, David J Girling, Matthew Nankivell, Cheryl Pugh, Mahesh K B Parmar, on behalf of the MS01 Trial Management Group**

Summary

Background Malignant pleural mesothelioma is almost always fatal, and few treatment options are available. Although active symptom control (ASC) has been recommended for the management of this disease, no consensus exists for the role of chemotherapy. We investigated whether the addition of chemotherapy to ASC improved survival and quality of life.

Methods 409 patients with malignant pleural mesothelioma, from 76 centres in the UK and two in Australia, were randomly assigned to ASC alone (treatment could include steroids, analgesic drugs, bronchodilators, palliative radiotherapy [n=136]); to ASC plus MVP (four cycles of mitomycin 6 mg/m², vinblastine 6 mg/m², and cisplatin 50 mg/m² every 3 weeks [n=137]); or to ASC plus vinorelbine (one injection of vinorelbine 30 mg/m² every week for 12 weeks [n=136]). Randomisation was done by minimisation, with stratification for WHO performance status, histology, and centre. Follow-up was every 3 weeks to 21 weeks after randomisation, and every 8 weeks thereafter. Because of slow accrual, the two chemotherapy groups were combined and compared with ASC alone for the primary outcome of overall survival. Analysis was by intention to treat. This study is registered, number ISRCTN54469112.

Findings At the time of analysis, 393 (96%) patients had died (ASC 132 [97%], ASC plus MVP 132 [96%], ASC plus vinorelbine 129 [95%]). Compared with ASC alone, we noted a small, non-significant survival benefit for ASC plus chemotherapy (hazard ratio [HR] 0·89 [95% CI 0·72–1·10]; p=0·29). Median survival was 7·6 months in the ASC alone group and 8·5 months in the ASC plus chemotherapy group. Exploratory analyses suggested a survival advantage for ASC plus vinorelbine compared with ASC alone (HR 0·80 [0·63–1·02]; p=0·08), with a median survival of 9·5 months. There was no evidence of a survival benefit with ASC plus MVP (HR 0·99 [0·78–1·27]; p=0·95). We observed no between-group differences in four predefined quality-of-life subscales (physical functioning, pain, dyspnoea, and global health status) at any of the assessments in the first 6 months.

Interpretation The addition of chemotherapy to ASC offers no significant benefits in terms of overall survival or quality of life. However, exploratory analyses suggested that vinorelbine merits further investigation.

Funding Cancer Research UK and the Medical Research Council (UK).

Lancet 2008; 371: 1685–94

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*Members listed at end of paper

Leeds General Infirmary, Leeds, UK (M F Muers FRCP); **MRC Clinical Trials Unit, London, UK** (R J Stephens, D J Girling FRCP, M Nankivell MSc, C Pugh BSc Hons, Prof M K B Parmar DPhil); **Weston Park Hospital, Sheffield, UK** (P Fisher FRCR); **University Hospitals of Leicester, Leicester, UK** (L Darlison BSc Hons, M Peake FRCP); **Dorothy House Hospice, Bath, UK** (C M B Higgs MD); **Papworth Hospital, Papworth Everard, UK** (E Lowry BA); **The Royal Brompton Hospital, London, UK** (Prof A G Nicholson DM); **The Royal Marsden Hospital, London, UK** (M O'Brien MD); **St Bartholomew's Hospital, London, UK** (R Rudd MD, J Steele MD); **and Cookridge Hospital, Leeds, UK** (M Snee DM)

Correspondence to:
Richard Stephens, MRC Clinical Trials Unit, 222 Euston Road, London NW1 2DA, UK
rs@ctu.mrc.ac.uk

Introduction

Malignant pleural mesothelioma is almost always fatal, and the worldwide incidence continues to rise. In the UK, the mortality rate increased 12-fold between 1968 and 2001; nearly 2000 deaths were recorded in 2005, and estimates predict that this number will increase to a peak of about 2200 by the year 2013.[1] By 2001, 25 000 deaths had already resulted from mesothelioma in the UK and at least another 65 000 are expected by 2050.[1] Similar figures are seen in other western European countries, with an estimated 250 000 mesothelioma deaths by 2035.[2] The incidence of mesothelioma is directly related to the production and use of asbestos, and whereas the incidence peak is approaching in the USA and western Europe, in future decades the epidemic will shift towards countries that still produce or use large quantities of asbestos—eg, Russia, China, Canada, Kazakhstan, Brazil, Zimbabwe, India, and Thailand.[3]

When this present trial was designed in the late 1990s, no generally accepted standard treatment for mesothelioma existed. The British Thoracic Society (BTS) statement for the management of mesothelioma[4] recommended active symptom control (ASC), which should involve regular specialist follow-up; structured assessment of physical, psychological, and social problems; and appropriate treatment, including palliative radiotherapy and steroids. There was no consensus regarding the role of chemotherapy for this disease, largely because of the scarcity of randomised trials. Several small, non-randomised studies of various single-drug and multidrug regimens had been undertaken, and Ryan and colleagues' review of such studies including 15 or more patients[5] concluded that various single agents had shown temporary, partial response rates of around 20%; furthermore, there was no evidence that drug combinations were better than

single agents. Ryan and colleagues[5] also commented that, because of the diffuse nature of this tumour, response was difficult to measure, and choosing regimens on the basis of response rates might not be the best surrogate for survival benefit.

Since most patients with malignant pleural mesothelioma present with many symptoms, relief or control of these symptoms is a key factor and therefore a worthwhile criterion for selection of treatment. However, at the time that this trial was designed, good published data derived from quality-of-life questionnaires completed by the patient were only available for two regimens: the three-drug combination of mitomycin, vinblastine, and cisplatin (MVP); and single-agent vinorelbine. Middleton and colleagues[6] treated 39 patients with six cycles of MVP (mitomycin 8 mg/m², vinblastine 6 mg/m², and cisplatin 50 mg/m²), with all drugs given on day 1 of a 21-day cycle (mitomycin was omitted from cycles three and five). The regimen was well tolerated, and 62% patients reported an overall improvement in their symptoms (including 79% reporting reduced pain and 67% reduced cough). Steele and colleagues[7] treated 29 patients with single-agent vinorelbine 30 mg/m² every 7 days until disease progression, and assessed quality of life with the Rotterdam Symptom Checklist.[8] The regimen was well tolerated, and although 62% of patients had grade 3 or 4 neutropenia, only one had neutropenic sepsis. 48% of patients reported improved respiratory symptoms and 76% improved psychological functioning.

Following encouraging results from a feasibility study to assess whether patients would consent to be randomised into a trial with ASC alone as one of the groups,[9] our three-group randomised trial sought to compare ASC alone with ASC plus MVP and ASC plus vinorelbine in terms of survival, symptom control, toxic effects, quality of life, tumour response, and progression.

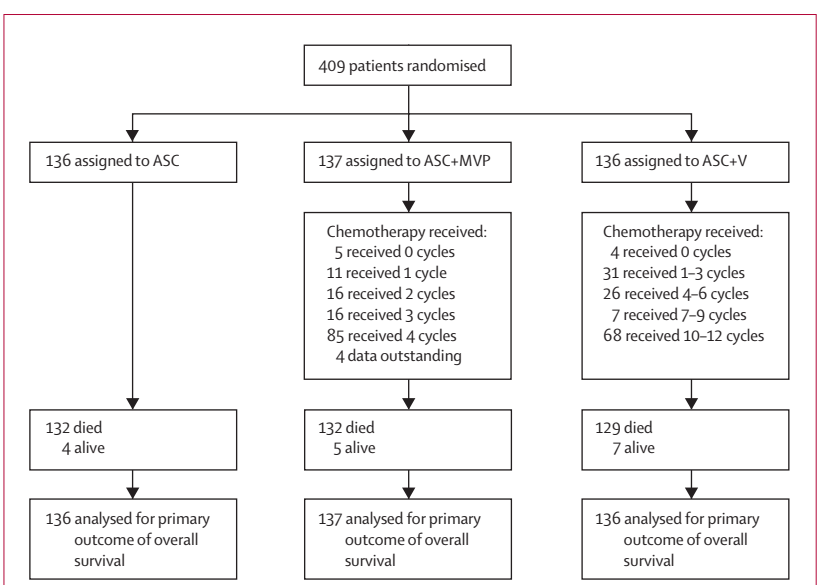

Figure 1: **Trial profile**
After 3 years accrual, the trial design was changed to a two-group comparison by combining the two chemotherapy groups. The three-way randomisation was retained to allow some exploratory analyses of the two different chemotherapy groups. ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine.

Methods

Patients and study design

In this multicentre randomised controlled trial, patients with recently diagnosed malignant pleural mesothelioma were enrolled from 76 centres in the UK and two in Australia between Sept 17, 2001, and July 31, 2006. Eligible patients could have had a previous surgical resection for mesothelioma (provided that a CT scan showed residual stable or progressive disease) or local radiotherapy to an exploratory thoracotomy wound site, but no previous chemotherapy. Patients had to be fit for chemotherapy (WHO performance status 0–2, with normal blood counts, creatinine clearance >50 mL per min, and any symptomatic pleural effusion brought under control), and have no other disease or previous malignancy that was likely to interfere with the protocol treatments or comparisons.

All patients provided written informed consent and the local ethics committee approved the protocol. An independently led trial steering committee was appointed to oversee its execution, and an independent data monitoring committee reviewed the interim data at regular, usually yearly, meetings. No formal stopping rules were used.

Procedures

An independent reference histopathologist (AGN) was available to be consulted about any diagnostic or histopathological queries, and from September 2003, tumour samples were sent to him to check the accuracy of diagnosis. Blood samples were also gathered and sent to a central repository.

Treatment centres telephoned the MRC Clinical Trials Unit (London, UK) who randomly allocated patients using a minimisation process, with stratification for WHO performance status, histology, and centre, to receive ASC alone, ASC plus MVP, or ASC plus vinorelbine. The essential elements of ASC were defined as regular follow-up in a specialist clinic; structured physical, psychological, and social assessments at every clinic visit; rapid involvement of additional specialists; and parallel nursing support. Patients could receive, as required, steroids, analgesic drugs, appetite stimulants, bronchodilators, or palliative radiotherapy.

Patients in the ASC plus MVP group were prescribed four cycles of MVP (mitomycin 6 mg/m², vinblastine 6 mg/m² [max 10 mg], and cisplatin 50 mg/m²) all given on day 1 of a 21-day cycle, in addition to ASC. The protocol recommendation was that patients should receive antiemetic drugs and dexamethasone. Patients in the

	ASC (N=136)	ASC+MVP (N=137)	ASC+V (N=136)
Median age (years [range])	65 (47–85)	65 (46–82)	65 (49–83)
Men	125 (92%)	124 (91%)	122 (90%)
Histology			
Epithelial	99 (74%)	100 (74%)	98 (73%)
Biphasic/mixed	11 (8%)	13 (10%)	17 (13%)
Other	24 (18%)	22 (16%)	19 (14%)
Not reported	2	2	2
WHO performance status			
0	31 (23%)	32 (23%)	30 (22%)
1	87 (64%)	86 (63%)	86 (63%)
2	18 (13%)	19 (14%)	20 (15%)
IMIG stage			
I/II	24 (21%)	32 (28%)	27 (23%)
III	37 (33%)	30 (26%)	39 (34%)
IV	51 (46%)	54 (47%)	50 (43%)
Not reported	24	21	20
Analgesic drugs			
None	27 (21%)	37 (27%)	34 (25%)
Non-opiates	46 (35%)	44 (32%)	44 (32%)
Moderate opiates	38 (29%)	32 (24%)	37 (27%)
Strong opiates	19 (15%)	23 (17%)	21 (15%)
Not reported	6	1	0
Median time from diagnosis to randomisation (days [IQR])	58 (35–80)	61 (36–85)	63 (43–87)

Data are number (%) unless otherwise specified. ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine. IMIG=International Mesothelioma Interest Group.

Table 1: **Baseline patient characteristics**

	ASC (N=136)	ASC+MVP (N=137)	ASC+V (N=136)
As reported by clinicians			
Lethargy	26/132 (20%)	37/135 (27%)	32/134 (24%)
Chest pain	36/132 (27%)	29/135 (21%)	28/133 (21%)
Sweating	22/132 (17%)	16/135 (12%)	19/133 (14%)
Anorexia	18/132 (14%)	20/135 (15%)	17/134 (13%)
Cough	15/132 (11%)	19/135 (14%)	17/133 (13%)
Constipation	17/132 (13%)	18/135 (13%)	13/134 (10%)
Other pain	14/130 (11%)	11/134 (8%)	20/132 (15%)
MRC grade 4+ breathlessness*	44/128 (34%)	41/131 (31%)	38/133 (29%)
As reported by patients with the QOL questionnaire			
Shortness of breath	49/126 (39%)	46/126 (37%)	42/124 (34%)
Tiredness	45/126 (36%)	37/125 (30%)	37/122 (30%)
General pain	43/127 (34%)	35/127 (28%)	32/124 (26%)
Worried	37/126 (29%)	22/127 (17%)	23/123 (19%)
Chest pain	31/125 (25%)	28/127 (22%)	21/124 (17%)
Cough	28/126 (22%)	26/128 (20%)	23/125 (18%)
Sweating	23/106 (22%)	19/114 (17%)	24/110 (22%)
Constipation	29/127 (23%)	26/127 (20%)	18/124 (15%)

ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine. QOL=quality of life. *Scored as follows: MRC grade: 1=climbs hills or stairs without dyspnoea; 2=walks any distance on the flat without dyspnoea; 3=walks over 100 m without dyspnoea; 4=dyspnoea on walking 100 m or less; 5=dyspnoea on mild exertion—eg, undressing; 6=dyspnoea at rest.

Table 2: **Moderate or severe symptoms at baseline**

ASC plus vinorelbine group were prescribed one injection of vinorelbine (Laboratoires Pierre Fabre, Catres, Toulouse, France) every week for 12 weeks (30 mg/m² [max 60 mg]) in addition to ASC, with a 2-week gap between injections six and seven.

The recommendation was that chemotherapy should start as soon as possible after randomisation. Detailed dose modifications for each regimen were listed in the protocol, but generally, patients only received chemotherapy if they had an adequate blood count (total white blood cell count >3000 cells per µL, neutrophils >1500 cells per µL, and platelets >100 000 cells per µL) and if there was no clinical evidence of infection. For patients allocated to ASC plus MVP, the criteria also included no renal toxic effects, severe constipation, or ototoxicity. In the management of haematological toxic effects (and hepatic toxic effects in the ASC plus vinorelbine group), the protocol recommendation was that chemotherapy be delayed for 1 week, and the patient then be reassessed. Clinicians were free to provide non-protocol treatment at any stage if it was felt to be in the patient's best interest, although such patients remained in the trial for follow-up and analysis.

Local research staff completed reports to cover the baseline assessment (before randomisation), pathology, chemotherapy (if allocated), and follow-up (every 3 weeks to 21 weeks after randomisation, and then every 8 weeks thereafter). Reports included details of treatment, blood counts and other relevant tests, tumour response, performance status, and details of symptoms or adverse events. We formally assessed tumour response by CT scan at 15 weeks using RECIST (Response Evaluation Criteria in Solid Tumors) criteria[10] modified (as suggested by Byrne and co-workers[11]) because of the diffuse nature of mesothelioma, measuring the thickness of circumferential pleural tumour at three or more separate levels on transverse sections.

We asked patients to complete the EORTC (European Organization for Research and Treatment of Cancer) core quality-of-life questionnaire (QLQ-C30)[12] and the lung cancer module (LC13)[13] at baseline and at every subsequent assessment. Since one of the main aims of treatment was the control of common presenting symptoms (particularly chest pain, breathlessness, malaise, and sweating), and since the EORTC questionnaires did not include an item on sweating, this additional question was added.

Statistical analysis

The primary outcome measure was overall survival; secondary outcome measures were symptom control,

toxic effects, quality of life, tumour response, and progression.

With an estimated median survival in the control group (ASC alone) of 9 months, the trial was designed to detect an improvement of 3 months (ie, to 12 months) in the ASC plus MVP and ASC plus vinorelbine groups. A total of 840 patients (280 in each group) was needed to detect this difference, with 512 events (deaths) in both comparisons (ASC *vs* ASC plus MVP, and ASC *vs* ASC plus vinorelbine) with 5% significance and 90% power. This number of patients was also considered sufficient to reliably detect differences of half a standard deviation between ASC and the two chemotherapy groups in terms of symptom control and quality of life, with 90% power. We aimed to accrue patients within 4 years.

	N	Improved	Controlled	Prevented	Palliated*	p value†
Lethargy						
ASC	110	4 (4%)	33 (35%)	18 (19%)	55 (50%)	
ASC+MVP	122	11 (9%)	22 (18%)	22 (18%)	55 (45%)	0·54
ASC+V	119	8 (7%)	17 (14%)	18 (15%)	43 (36%)	0·047
Chest pain						
ASC	111	8 (7%)	23 (21%)	23 (21%)	54 (49%)	
ASC+MVP	122	13 (11%)	37 (30%)	35 (29%)	85 (70%)	0·0017
ASC+V	117	12 (10%)	29 (25%)	32 (27%)	73 (62%)	0·051
Sweating						
ASC	111	5 (5%)	21 (19%)	46 (41%)	72 (65%)	
ASC+MVP	122	11 (9%)	21 (17%)	66 (54%)	98 (80%)	0·012
ASC+V	117	7 (6%)	16 (14%)	59 (50%)	82 (70%)	0·48
Anorexia						
ASC	111	8 (7%)	16 (14%)	48 (43%)	72 (65%)	
ASC+MVP	122	7 (6%)	18 (15%)	61 (50%)	86 (70%)	0·44
ASC+V	117	8 (7%)	14 (12%)	55 (47%)	77 (66%)	0·99
Cough						
ASC	111	11 (10%)	27 (24%)	30 (27%)	68 (61%)	
ASC+MVP	121	14 (12%)	35 (29%)	37 (31%)	86 (71%)	0·15
ASC+V	117	10 (9%)	33 (28%)	38 (32%)	81 (69%)	0·26
Constipation						
ASC	111	7 (6%)	11 (10%)	56 (50%)	74 (67%)	
ASC+MVP	122	11 (9%)	10 (8%)	61 (50%)	82 (67%)	0·96
ASC+V	119	6 (5%)	23 (19%)	62 (52%)	91 (76%)	0·13
Other pain						
ASC	110	4 (4%)	20 (18%)	41 (37%)	65 (59%)	
ASC+MVP	122	8 (7%)	24 (20%)	54 (44%)	86 (70%)	0·093
ASC+V	118	11 (9%)	21 (18%)	43 (36%)	75 (64%)	0·58
Breathlessness						
ASC	107	9 (8%)	16 (15%)	6 (6%)	31 (29%)	
ASC+MVP	118	11 (9%)	16 (14%)	9 (8%)	36 (31%)	0·92
ASC+V	113	10 (9%)	14 (12%)	9 (8%)	33 (29%)	0·91

ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine. *Patients who had died by 3 months were considered not palliated. †χ^2 test compared with ASC. ‡Improved: moderate or severe at baseline, mild or nil at 3 months; controlled: mild at baseline, mild or nil at 3 months; and prevented: nil at baseline, nil at 3 months.

Table 3: **Symptom palliation at 3 months‡**

Analysis was by intention to treat. Duration of survival was calculated from the date of randomisation to the date of death from any cause, with survivors being censored at the date that they were last known to be alive. We calculated progression-free survival from the date of randomisation to the date of first progression, recurrence, or death, whichever was soonest. Patients alive and progression free were censored at the date that they were last known to be alive and free of progression. We used hazard ratios to compare overall survival. Comparisons of symptom control, performance status, use of analgesic drugs, quality of life, toxic effects, and response were tested with the Kruskal-Wallis or Mann-Whitney test. We used the χ^2 test to test for interactions involving binary and categorical variables, and the test for interaction for continuous data. All p values are two sided.

Changes to the trial design

Accrual to this trial began in September 2001, although the 34 patients who had been randomly assigned between all three groups in the feasibility trial were also included. However, by January 2004, only 232 patients had been entered, and it was clear that the target number of patients was not going to be reached in a timely manner. The trial design was therefore changed to a two-group comparison by combining the two chemotherapy groups, although the three-way randomisation was retained to allow some exploratory analyses of the two different chemotherapy groups. The two-group design needed a total of 420 patients (140 ASC, 280 ASC plus chemotherapy) and 380 events (deaths) to reliably detect an improvement from 9 months median survival with ASC alone to 12 months with ASC plus chemotherapy (5% significance level, 76% power). Since accrual decreased through 2005, a closure date of July 31, 2006, was set.

This study is registered, number ISRCTN54469112.

Role of the funding source

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

Results

Figure 1 shows the trial profile. The number of patients who were screened for eligibility was not recorded. 409 patients were enrolled, and only two patients (who moved abroad) have been lost to follow-up. 136 patients were assigned to ASC, 137 to ASC plus MVP, and 136 to ASC plus vinorelbine. The three treatment groups were well matched for all characteristics at baseline (table 1). The median age of patients was 65 years (range 46–85), 371 (91%) were men, and 352 (86%) had a WHO

performance status of 0 or 1. 297 (74%) of 403 patients were considered by the local histopathologist to have epithelial histology. The median time from diagnosis to randomisation was 60 days (IQR 37–85) and most patients had disease of International Mesothelioma Interest Group stage III[14] (106 [31%] of 344) or stage IV (155 [45%] of 344). Additionally, 107 (27%) of 402 were already on moderate opiates and 63 (16%) of 402 on strong opiates. Patients presented with several symptoms (table 2), and 123 (31%) of 392 had dyspnoea walking 100 m or less. Data from the quality-of-life questionnaires completed by the patient reflected symptoms reported by clinicians, with the commonest moderate or severe symptoms relating to shortness of breath, tiredness, and pain (table 2). Consequently, patients reported poor physical functioning (eg, 181/375 [48%] having difficulties taking a long walk), limited leisure and social activities, and reduced overall quality of life.

Of the 193 patients who were randomly assigned after instigation of collection of samples for histological review, 135 consented to donate their tumour samples; however, three patients had only cytology preparations and 27 samples were unobtainable. Thus 105 cases with anonymised histology reports and slides or blocks were sent for review, of which 103 were confirmed as mesothelioma. In two cases, immunochemistry failed to identify a phenotype for definitive diagnosis, but samples contained epithelial or biphasic malignancy that was consistent with mesothelioma and were classified as such after clinical-pathological review.

85 (64%) of 133 patients received the prescribed four cycles of MVP. A further 16 (12%) received three cycles, 16 (12%) two cycles, and 11 (8%) one cycle. Only five (4%) patients who were allocated to ASC plus MVP did not receive any protocol chemotherapy (one patient refused, two progressed, one died before starting, and one was given carboplatin, rather than cisplatin, because of tinnitus). The information about the treatment received for the remaining four patients is outstanding. Of the 128 patients who received MVP, 47 (37%) had some delays (>28 days between cycles) and 67 (52%) had a dose modification (>10% dose change).

Of the 136 patients who were prescribed one injection of vinorelbine every week for 12 weeks, 68 (50%) received between ten and 12 injections, seven (5%) between seven and nine injections, 26 (19%) between four and six injections, and 31 (23%) between one and three injections. Only four (3%) received no protocol chemotherapy (two refused, two died before starting). Of the 132 patients who started vinorelbine, 104 (79%) had a delay (>10 days between injections) and 48 (36%) a modification (>10% dose change). The main problem was neutropenia (26/63 [41%] patients having grade 3+ neutropenia after this specific question was added to the case report forms), although only eight (6%) patients were reported as stopping prematurely because of haematological toxic effects.

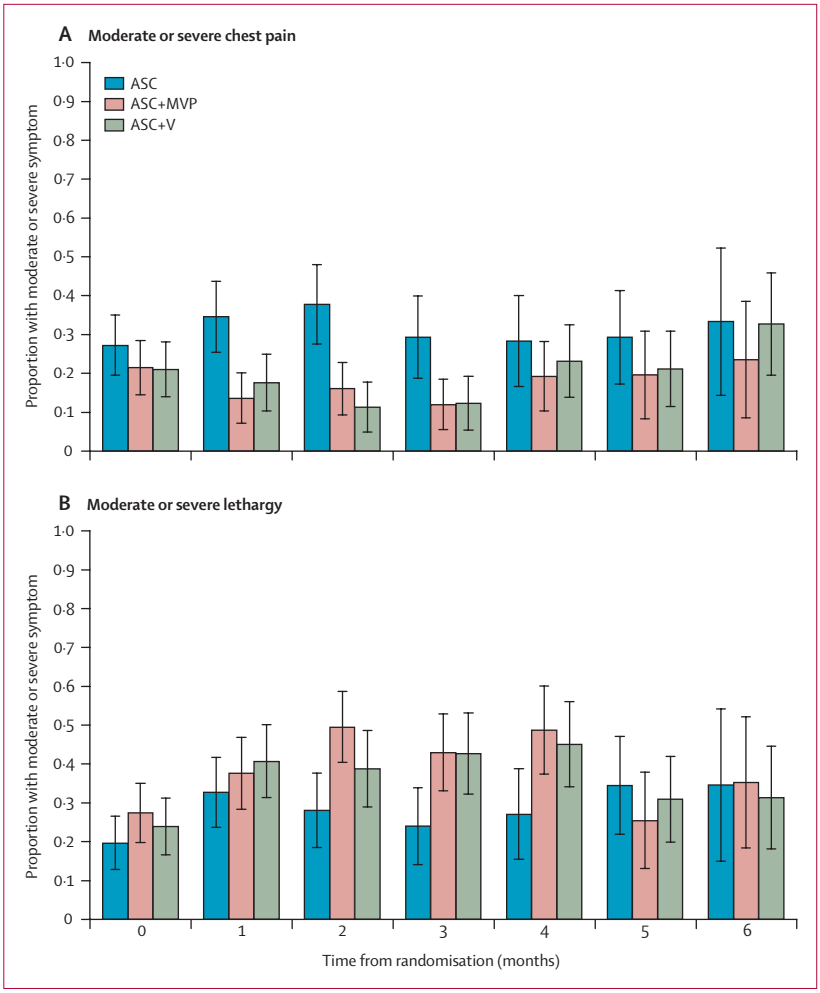

Figure 2: **Clinicians assessment of symptoms and side-effects**
(A) Proportion of patients with moderate or severe chest pain. (B) Proportion of patients with moderate or severe lethargy. Error bars indicate 95% CIs. ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine.

Only 140 patients (84 ASC plus MVP, 56 ASC plus vinorelbine) had a formal tumour assessment after the course of chemotherapy, of whom only eight (10%) in the ASC plus MVP group and nine (16%) in the ASC plus vinorelbine group had a response to protocol chemotherapy. A further 52 (62%) patients in the ASC plus MVP group and 33 (59%) in the ASC plus vinorelbine group had stable disease. Because of the difficulty of assessing response in this disease, clinicians were also asked at 15 weeks after randomisation whether, in their opinion, the tumour had improved, stayed the same, or worsened. We assessed a total of 369 patients (118 ASC, 124 ASC plus MVP, and 127 ASC plus vinorelbine) in this way and 91 patients (16 [14%] ASC, 36 [29%] ASC plus MVP, and 39 [31%] ASC plus vinorelbine) were reported to have improved at this time. 87 (74%) patients in the ASC group, 80 (65%) in the ASC plus MVP group, and 78 (61%) in the ASC plus vinorelbine group were reported as stable.

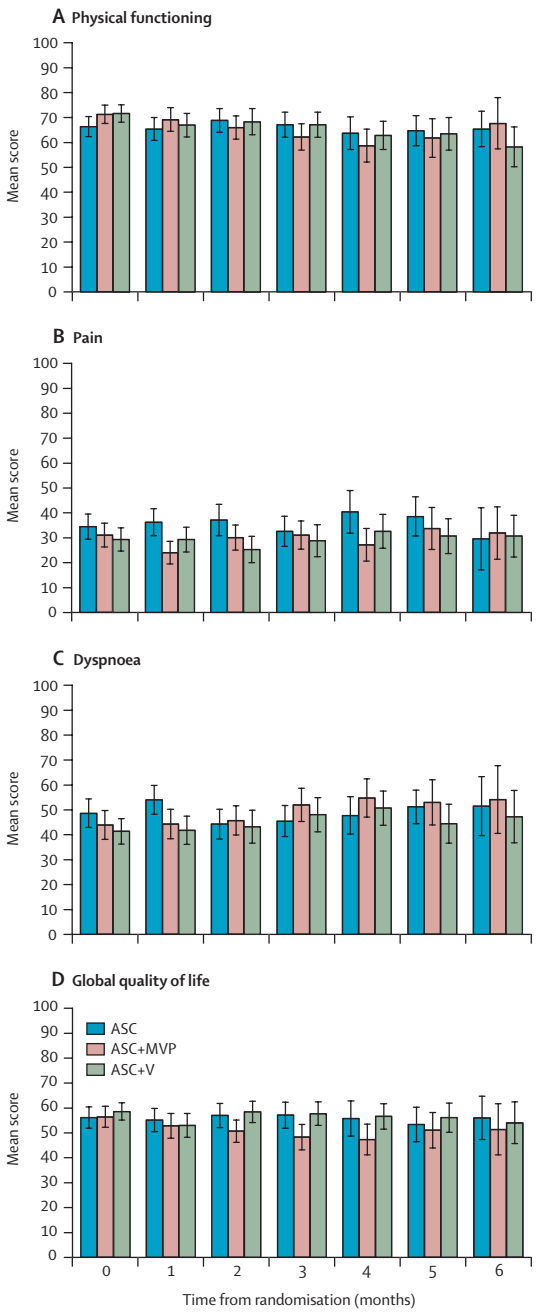

Figure 3: **Mean standardised scores for the four predefined quality-of-life endpoints**

(A) Physical functioning; (B) pain; (C) dyspnoea; and (D) global quality of life. Error bars indicate 95% CIs. ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine.

Clinicians reported the occurrence and severity of 16 key symptoms at every assessment (table 3). One definition of palliation is that moderate or severe symptoms at baseline should be improved, mild symptoms should be controlled, and other symptoms prevented from occurring.[15] With these criteria, we undertook exploratory analyses to compare changes from baseline to 3 months of the eight commonest symptoms reported at baseline (table 3).

The only symptoms for which there seemed to be evidence of palliation were noted with the MVP regimen for chest pain (ASC plus MVP *vs* ASC, p=0·0017) and sweating (ASC plus MVP *vs* ASC, p=0·012) (table 3). Nevertheless, as expected, patients had chemotherapy side-effects, although the only comparisons showing evidence of increased side-effects were alopecia (ASC plus MVP [six of 117] *vs* ASC [none of 95], p=0·025; ASC plus vinorelbine [six of 108] *vs* ASC [none of 95], p=0·020), lethargy (ASC plus vinorelbine [49/109] *vs* ASC [28/95], p=0·023), and haematological toxic effects, which were only collected in the latter half of the trial (ASC plus MVP [eight of 60] *vs* ASC [none of 50], p=0·007; ASC plus vinorelbine [18/50] *vs* ASC [none of 50], p<0·0001). However, when we repeated these analyses at 6 months we recorded no significant differences between treatments. Patterns of symptoms and side-effects can be seen by plotting the proportion of patients with moderate or severe symptoms over time, and figure 2 shows histograms for chest pain and lethargy.

The number of patients completing the EORTC questionnaires (as a proportion of the number alive at the various timepoints) fell from 381 (93%) at baseline (ASC 127 [93%] of 136, ASC plus MVP 129 [94%] of 137, ASC plus vinorelbine 125 [92%] of 136), to 280 (75%) at 3 months (ASC 88 [74%] of 119, ASC plus MVP 100 [78%] of 129, ASC plus vinorelbine 92 [73%] of 126) and 175 (58%) at 6 months (ASC 56 [62%] of 90, ASC plus MVP 46 [46%] of 101, ASC plus vinorelbine 73 [67%] of 109). Reduced levels of completion (usually due to questionnaires not being handed out or patients being too unwell to complete them) make analyses difficult, since whether data are missing at random (and thus could be imputed) or not (and thus could bias the comparison) is unclear. Equally, many statistical comparisons (eg, testing between every treatment at each timepoint) can produce false positive results, and could lead to misinterpretation. Consequently, simple descriptive plots showing patterns over time and absolute changes can usually be most informative. The EORTC QLQ-C30 can be de-aggregated into five functional and nine symptom scales, as well as a score for global heath status. Figure 3 shows histograms of the mean standardised scores for the four predefined quality-of-life endpoints (physical functioning, pain, dyspnoea, and global health status), indicating little change in any of these subscales over time or between treatments. The addition of chemotherapy therefore seemed to have no major overall positive or negative effect on quality of life.

Most patients (218 [53%]) received no extra anticancer treatment. Much the same numbers of patients in the

three groups received additional chemotherapy (ASC 21 [15%], ASC plus MVP 23 [17%], and ASC plus vinorelbine 14 [10%]), although only 15 patients (ASC seven, ASC plus MVP six, ASC plus vinorelbine two) received pemetrexed. More patients assigned to ASC alone than to chemotherapy groups received radiotherapy (ASC 37 [27%], ASC plus MVP 21 [15%], ASC plus vinorelbine 26 [19%]) and measures to control pleural effusion (ASC 20 [15%], ASC plus MVP 12 [9%], ASC plus vinorelbine 11 [8%]). During the course of the trial, 263 patients (ASC 97 [71%], ASC plus MVP 78 [57%], ASC plus vinorelbine 88 [65%]) needed increased doses of analgesic drugs.

At the time of analysis, 393 (96%) patients had died (ASC 132 [97%], ASC plus MVP 132 [96%], ASC plus vinorelbine 129 [95%]), and the median follow-up of the 16 survivors was 36·4 months (IQR 13·2–50·2). Five patients (three ASC plus MVP, two ASC plus vinorelbine) were still alive more than 4 years after randomisation. The cause of death was reported to be mesothelioma in 365 patients (ASC 127 [96%], ASC plus MVP 122 [92%], ASC plus vinorelbine 116 [90%]). One patient in the ASC plus vinorelbine group was considered to have had a treatment-related death, although treatment was regarded as a contributory factor in a further three patients in the ASC plus MVP group and nine in the ASC plus vinorelbine group.

Figure 4 shows the overall survival for ASC plus chemotherapy versus ASC alone. We noted a small but non-significant benefit for patients in the ASC plus chemotherapy group (hazard ratio [HR] 0·89 [95% CI 0·72–1·10]; p=0·29). In the ASC alone group, the estimated median survival was 7·6 months and and 29% of patients were alive at 1 year. Application of the HR to these figures resulted in a median survival of 8·5 months and 1-year survival of 32% for the ASC plus chemotherapy group. In exploratory analyses (figure 4), patients in the ASC plus vinorelbine group had a longer overall survival than did those in the ASC alone group (HR 0·80 [0·63–1·02]; p=0·08), which was equivalent to a 2-month absolute increase in median survival (from 7·6 months with ASC to 9·5 months with ASC plus vinorelbine), although we noted no evidence of a benefit with ASC plus MVP (HR 0·99 [0·78–1·27]; p=0·95). A comparison of the two chemotherapy groups directly gave an HR of 0·77 (95% CI 0·61–0·99; p=0·04), suggesting a benefit of vinorelbine compared with MVP.

141 patients (ASC 49 [36%], ASC plus MVP 46 [34%], ASC plus vinorelbine 46 [34%]) were reported as having progressive disease and 402 as having either progressed or died (ASC 134 [99%], ASC plus MVP 136 [99%], ASC plus vinorelbine 132 [97%]). Overall, we noted a small but non-significant benefit for chemotherapy in progression-free survival (HR 0·91 [95% CI 0·74–1·12]; p=0·39), giving a median progression-free survival of 5·1 months for ASC and 5·6 months for ASC plus chemotherapy, and 1-year progression-free survival of 22% and 25%, respectively. We observed no evidence of a benefit in progression-free survival for patients in the ASC plus MVP group (HR 1·01 [0·79–1·28]; p=0·96), but we noted a non-significant benefit with ASC plus vinorelbine (HR 0·82 [0·65–1·05]; p=0·114; figure 5). Application of the HR to the ASC values gives a median progression-free survival of 5·1 months and a 1-year progression-free survival of 22% for ASC plus MVP, and 6·2 months and 28%, respectively, for ASC plus vinorelbine.

To explore whether there was any evidence that subgroups of patients (defined by the baseline characteristics in table 1) benefited more or less from chemotherapy, univariate predictive analyses were undertaken (table 4). We saw no clear evidence that any subgroup of patients benefited more or less from chemotherapy.

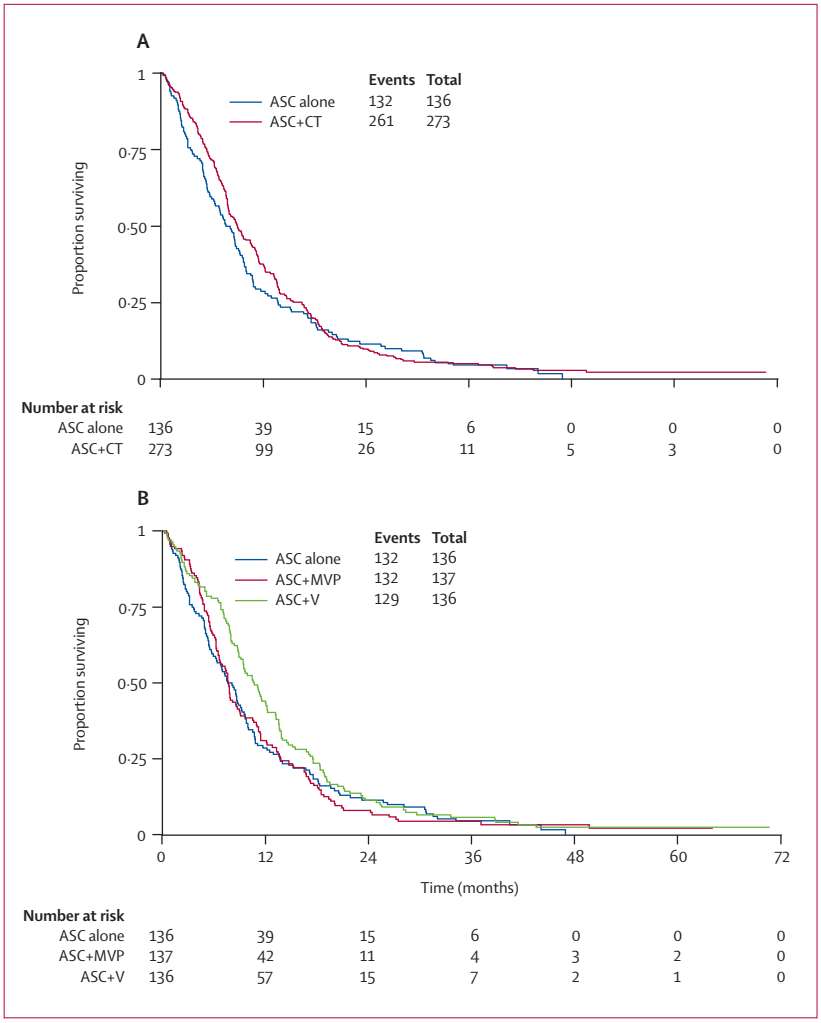

Figure 4: **Overall survival**
(A) Two-group comparison: ASC *vs* ASC plus chemotherapy. (B) Three-group comparison: ASC *vs* ASC plus MVP *vs* ASC plus vinorelbine. ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine. CT=chemotherapy.

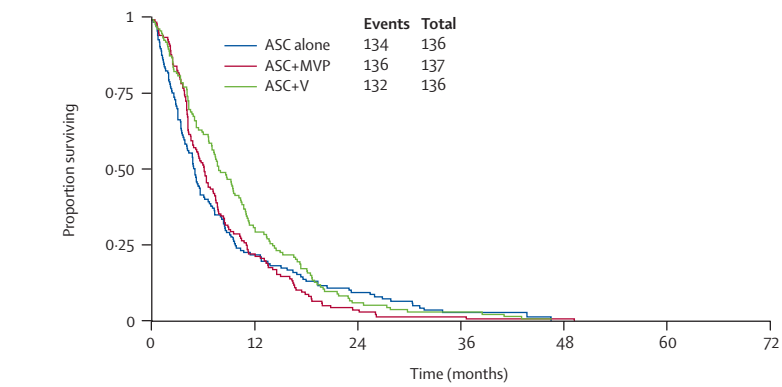

Figure 5: **Progression-free survival**
ASC=active symptom control. MVP=mitomycin, vinblastine, and cisplatin. V=vinorelbine.

	Type of analysis	p value	
		ASC *vs* ASC+CT	ASC *vs* ASC+V
Age	Continuous	0·18	0·21
Sex	Category (men, women)	0·10	0·22
Histology	Category (epithelial, other)	0·087	0·10
WHO PS	Trend (PS0, PS1, PS2)	0·83	0·43
IMIG stage	Trend (I/II, III, IV)	0·15	0·18
Analgesic drugs	Trend (none, non-opiates, moderate opiates, strong opiates)	0·083	0·062
Time from diagnosis to randomisation	Continuous	0·29	0·59

ASC=active symptom control. CT=chemotherapy. V=vinorelbine. PS=performance status. IMIG=International Mesothelioma Interest Group.

Table 4: **Predictive factors (exploration of interactions between treatment and baseline patients' characteristics)**

Discussion

In this large randomised controlled trial in mesothelioma, we identified no significant survival benefit from the addition of chemotherapy to ASC, and no evidence of a difference in quality of life. However, exploratory analyses suggest that vinorelbine needs further investigation. Clinicians and patients can now make better informed decisions about advantages and disadvantages of chemotherapy and can discuss the balance of possible survival gain against the inconvenience and toxic effects of treatment, which is especially important in view of the increasing median age of patients presenting with malignant mesothelioma.

This study was launched with the aim of accruing 840 patients with malignant mesothelioma in a three-group trial to assess the value of both MVP and vinorelbine compared with ASC alone, on the basis of phase II data showing good symptom control with these two chemotherapy regimens. Trials that incorporate an ASC group are difficult to recruit to, and despite a feasibility study suggesting that about half of the patients would accept such a randomisation,[9] accrual was slower than was required, and the design had to revert to the more generic comparison of ASC versus ASC plus chemotherapy to accommodate a smaller sample size.

There seemed to be two main reasons for the slow accrual. First, the results of a large randomised trial showing a modest survival advantage (2·8 months, HR 0·77, p=0·020) for cisplatin and pemetrexed, compared with cisplatin alone, were presented at the American Society for Clinical Oncology yearly meeting in 2002.[16] Subsequently, many UK patients who were fit for chemotherapy received this combination, or carboplatin and pemetrexed, as part of the expanded access programme that was undertaken by the company making pemetrexed. Approaches to the drug company to include the cisplatin and pemetrexed regimen in our trial were unsuccessful. Second, some patients simply did not want any chemotherapy, as confirmed by a study in Leeds[17] that audited all referred mesothelioma cases between 2002 and 2005; of 54 patients who were fit for, and offered, chemotherapy, 28 (52%) declined it. The results of our trial suggest that some patients receiving ASC alone can do surprisingly well. Patients allocated ASC alone generally had good symptom control and of course avoided the toxic effects related to chemotherapy, resulting in overall quality of life which was very comparable to that of patients receiving chemotherapy.

However, despite the importance of quality of life, collection of good longitudinal data is a challenge in populations with short survival, and our compliance dropped to less than 60% of patients surviving at 6 months, which is a proportion not uncommon in trials of patients with advanced non-small cell lung cancer.[18] Improving on these levels of compliance needs substantial financial, organisational, and training resources.[19]

Nevertheless, the results of our trial suggest that chemotherapy is feasible and acceptable, although the survival benefit might be small, perhaps increasing median survival by about 1 month. Although more than 400 patients were enrolled, this number was insufficient to make reliable conclusions about the two different chemotherapy regimens used. However, despite patients in the vinorelbine group having more neutropenia and receiving less of their prescribed course of treatment, they seemed to have similar response rates and symptom control to those receiving MVP, but possibly better survival.

Therefore, in a disease with few therapeutic options, vinorelbine certainly deserves further investigation. One disadvantage of this regimen is the weekly schedule, although now that oral vinorelbine is available, and considered to be equivalent to intravenous administration in non-small cell lung cancer,[20] a weekly regimen becomes much more viable than it previously was, and would be an attractive alternative for patients.

Our trial needs to be considered in the context of the two other large randomised trials in this disease. In the Vogelzang trial,[21] 456 patients were randomly assigned to receive cisplatin alone or cisplatin plus pemetrexed. The combination group had a median survival of 12·1 months compared with 9·3 months for patients in the cisplatin-alone group (HR 0·77, p=0·02). Van Meerbeeck and colleagues[22] randomly assigned 250 patients to cisplatin alone or cisplatin plus raltitrexed. The median survival was 11·4 months for the combination group compared with 8·8 months for cisplatin alone (HR 0·76 [95% CI 0·58–1·00], p=0·048).

Thus the three large randomised trials undertaken so far suggest that pemetrexed, raltitrexed, and vinorelbine could have a role in this disease, but they do not clarify the role of platinum. Ellis and colleagues' review[23] suggested that cisplatin had the highest response rate of all single agents, although this rate was only 20% and based on only 108 patients. In the two trials[21,22] in which cisplatin (75–80 mg/m²) was used as the control, the median survival rates were 8·8 months and 9·3 months, compared with 7·6 months for ASC in our trial. This finding might or might not show the efficacy of cisplatin, since there is a great danger in comparing across trials, and this difference could well have been due to different methods of patient selection in the three trials. Nevertheless, the relative failure of the cisplatin-based treatment in our trial (MVP) was unexpected. It could have been because we used only cisplatin 50 mg/m² or stopped after four cycles (rather than continue to progression). One UK centre has recently updated their experience with MVP[24] and reported a similarly disappointing outcome with a fairly low median survival (7 months) despite good symptomatic improvement.

Clarification of the role of platinum in this disease is a priority, since the age of the cohort of patients most at risk of developing mesothelioma in the UK and Europe is increasing inexorably. This cohort is composed of men born between 1945 and 1950,[2] which thus corresponds to a median age at presentation of 55–60 years in 2005, of 70–75 years in 2020, and 80–85 years in 2030. Thus now, and especially in the future, we will need to direct our research at treatments that are applicable and acceptable to an elderly (and over the next few years, a very elderly) group of patients, who might not be suitable for cisplatin-based chemotherapy.

Where do we go from here? Pemetrexed is the only licensed compound for the treatment of mesothelioma in the UK.[23] The results of our trial suggest that vinorelbine might be effective, but non-inferiority trials (which typically include many more patients than the largest superiority trials reported so far) would be virtually impossible to undertake in this disease. One option might be to try to incorporate vinorelbine with cisplatin and pemetrexed (either concurrently or sequentially), but as with most cancers, the emergence of many new agents and targeted treatment might hold most promise.[25]

Contributors

All authors were members of the Trial Management Group, contributed to the discussions and interpretation of the data, and to the writing of the report. All the clinicians (MFM, PF, MO'B, MPe, RR, MS, and JS) entered and followed up a proportion of the patients. MFM was the chief investigator, chair of the Trial Management Group, and contributed to the design of the trial. RS was the lead CTU Investigator and contributed to the analysis of the data. LD and EL advised on the nursing aspects of the trial. CMH advised on the active symptom control aspects of the trial. AGN advised on the pathological aspects of the trial. RR contributed to the design of the trial. DJG was the project leader for the lung cancer trials in the MRC CTU (until 2002), and contributed to the design of the trial and analyses of the data. MN was the trial statistician and was responsible for the data analysis. CP was the trial manager and was responsible for the data management. MPa was the programme leader for the lung cancer trials in the MRC CTU, and contributed to the design of the trial and analysis of data.
Trial Management Group: M F Muers (Chief Investigator), L Darlison, P Fisher, D J Girling, C M B Higgs, E Lowry, A Nicholson, M O'Brien, M Peake, R Rudd, M Snee, J Steele, and R J Stephens.
Other members of the protocol development group: M Britton, M Lind, R Milroy, J Masters, M Nicolson, N Rowell, and I Smith.
Independent data monitoring committee: M H Cullen (Chair), J Slattery, J Tobias, D Sebag-Montefiore, and G Giaccone.
Trial Steering Committee: H Kitchener (Chair), T Maughan, and M T Seymour
Clinicians and research staff who entered patients into this trial are listed in the webappendix.
MRC Clinical Trials Unit: Danielle Andrews, Hannah Brooks, Christina Chung, Adrian Hodson, Ed Kay, Dawn Lobban, Jacque Millett, Robert Owens, Wendi Qian, John Roberts, Robert Sambrook, and Monica Verma.

See **Online** for webappendix

Conflict of interest statement

RS and MS have received honoraria from Pierre Fabre Oncology for lecturing at meetings. MO'B has received honoraria for lecturing at meetings and travel support from Pierre Fabre Oncology. All other authors declare that they have no conflict of interest.

Acknowledgments

The trial was funded by Cancer Research UK and the Medical Research Council, supported by the British Thoracic Society and the June Hancock Mesothelioma Research Fund, and run by the MRC Clinical Trials Unit. Additional support, in the form of discounted drug, and the funding of a Cancerbackup booklet (Understanding the mesothelioma treatment trial [MS01]) was provided by Pierre Fabre Oncology. We would particularly like to thank all the patients who participated in this study.

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