Bevacizumab for newly diagnosed pleural mesothelioma in the Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS): a randomised, controlled, open-label, phase 3 trial

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Summary

Background Malignant pleural mesothelioma is an aggressive cancer with poor prognosis, linked to occupational asbestos exposure. Vascular endothelial growth factor is a key mitogen for malignant pleural mesothelioma cells, therefore targeting of vascular endothelial growth factor might prove effective. We aimed to assess the effect on survival of bevacizumab when added to the present standard of care, cisplatin plus pemetrexed, as first-line treatment of advanced malignant pleural mesothelioma.

Methods In this randomised, controlled, open-label, phase 3 trial, we recruited patients aged 18–75 years with unresectable malignant pleural mesothelioma who had not received previous chemotherapy, had an Eastern Cooperative Oncology Group performance status of 0–2, had no substantial cardiovascular comorbidity, were not amenable to curative surgery, had at least one evaluable (pleural effusion) or measurable (pleural tumour solid thickening) lesion with CT, and a life expectancy of >12 weeks from 73 hospitals in France. Exclusion criteria were presence of central nervous system metastases, use of antiaggregant treatments (aspirin ≥325 mg per day, clopidogrel, ticlopidine, or dipyridamole), anti-vitamin K drugs at a curative dose, treatment with low-molecular-weight heparin at a curative dose, and treatment with non-steroidal anti-inflammatory drugs. We randomly allocated patients (1:1; minimisation method used [random factor of 0·8]; patients stratified by histology [epithelioid *vs* sarcomatoid or mixed histology subtypes], performance status score [0–1 *vs* 2], study centre, or smoking status [never smokers *vs* smokers]) to receive intravenously 500 mg/m² pemetrexed plus 75 mg/m² cisplatin with (PCB) or without (PC) 15 mg/kg bevacizumab in 21 day cycles for up to six cycles, until progression or toxic effects. The primary outcome was overall survival (OS) in the intention-to treat population. Treatment was open label. This IFCT-GFPC-0701 trial is registered with ClinicalTrials.gov, number NCT00651456.

Findings From Feb 13, 2008, to Jan 5, 2014, we randomly assigned 448 patients to treatment (223 [50%] to PCB and 225 [50%] to PC). OS was significantly longer with PCB (median 18·8 months [95% CI 15·9–22·6]) than with PC (16·1 months [14·0–17·9]; hazard ratio 0·77 [0·62–0·95]; p=0·0167). Overall, 158 (71%) of 222 patients given PCB and 139 (62%) of 224 patients given PC had grade 3–4 adverse events. We noted more grade 3 or higher hypertension (51 [23%] of 222 *vs* 0) and thrombotic events (13 [6%] of 222 *vs* 2 [1%] of 224) with PCB than with PC.

Interpretation Addition of bevacizumab to pemetrexed plus cisplatin significantly improved OS in malignant pleural mesothelioma at the cost of expected manageable toxic effects, therefore it should be considered as a suitable treatment for the disease.

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Introduction

Malignant pleural mesothelioma is a rare but aggressive cancer, mainly caused by exposure to asbestos.[1] The disease has a poor prognosis, with sarcomatoid or mixed (sarcomatoid and epithelioid) histologies, Eastern Cooperative Oncology Group (ECOG) performance status of 1 or higher, and male sex usually reported as poor prognostic factors.[2] It is generally refractory to local treatment when diagnosed and usually progresses, resulting in a median overall survival (OS) of 12–36 months for localised disease and 8–14 months for advanced disease.[3]

The present standard of care for first-line systemic treatment is cisplatin plus pemetrexed, based on a median OS of 12·1 months (13·3 months in patients receiving vitamins B12 and B9) compared with 12·7 months for cisplatin alone and a median progression-free survival (PFS) of 5·7 months compared with 3·9 months.[4] Findings from a phase 2 study also showed a median OS of 12·7 months and a median PFS of 6·5 months with pemetrexed plus carboplatin for advanced malignant pleural mesothelioma.[5]

Vascular endothelial growth factor (VEGF) signalling plays a crucial part in mesothelioma cell physiopathology.[6,7] Antiangiogenic treatments targeting VEGF were therefore a rational approach to be tested in malignant pleural mesothelioma. Several antiangiogenic drugs have already

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Research in context

Evidence before this study

We searched MEDLINE for full-text articles published from Jan 1, 2000, to Dec 31, 2014, in English or French, reporting phase 3, randomised, clinical trials and phase 2 studies relevant to our study. We used the terms "mesothelioma", "bevacizumab", "angiogenic inhibitors", and "chemotherapy". We found that the standard of care for medical treatment of mesothelioma is pemetrexed plus cisplatin on the basis of a phase 3 study done in 2003 reporting a 12·1 month overall survival (OS) that exceeds 13 months in patients receiving vitamins B9 and B12. Angiogenic inhibitors as monotherapies were reported with modest efficacy because of the role of vascular endothelial growth factor in mesothelioma biology. Investigators of three phase 2 studies reported interesting results with the triple association of the angiogenic drug bevacizumab and a platinum-based doublet with either gemcitabine or pemetrexed. However, no phase 3 data had been reported for addition of bevacizumab to the present standard of care (pemetrexed and cisplatin).

Added value of this study

A pemetrexed-based chemotherapy doublet was recommended as a treatment option for malignant pleural mesothelioma by the 2007 National Institute for Health and Care Excellence guidance that was in place at the beginning of our study for patients with WHO performance statuses of 0 or 1 deemed to have advanced disease and for whom surgical intervention was deemed inappropriate. Findings from our study of bevacizumab plus pemetrexed and cisplatin compared with pemetrexed and cisplatin alone showed a significantly improved median OS and progression-free survival with addition of bevacizumab. Mesothelioma traditionally has a poor prognosis; however, in our study, patient subgroups that have previously shown poor prognosis benefited as much as other subgroups from addition of bevacizumab, including those with an ECOG performance status of 2, a haemoglobin concentration of ≤140 g/L, thrombocytosis, a leucocyte count of $8{\cdot}3 \times 10^9$/L or higher, or sarcomatoid or mixed histology. Therefore, these data show an alternative to present options that have not been improved on since the pivotal study by Vogelzang and colleagues of pemetrexed plus cisplatin more than 10 years ago.

Implications of all the available evidence

Addition of bevacizumab to the present standard of care cisplatin and pemetrexed significantly increased OS and progression-free survival in mesothelioma, with manageable toxic effects. We believe that this result has important implications for future first-line treatment of mesothelioma because the pemetrexed plus cisplatin plus bevacizumab regimen should be considered as a new treatment option for patients with newly diagnosed mesothelioma who are eligible to receive bevacizumab and who are not candidates for curative-intent surgery.

been assessed as single drugs, with modest activity.[8–11] Addition of bevacizumab to gemcitabine plus cisplatin for treatment of malignant pleural mesothelioma was assessed in a randomised, placebo-controlled, phase 2 study by Kindler and colleagues,[12] who reported a median PFS of 6·9 months with bevacizumab versus 6·0 months in the placebo group. However, median OS was 15·6 months for the triplet combination versus 14·7 months for gemcitabine plus cisplatin, which was not significantly different, possibly related to a large proportion of patients receiving second-line pemetrexed-based treatment in both groups.[12] An alternative explanation could be an underpowered design due to the long survival in the control group as compared with the 4 month PFS, which was used to calculate sample size and power. Whether VEGF plasma concentrations could serve as prognostic biomarkers or predict bevacizumab efficacy in malignant pleural mesothelioma remains controversial owing to the absence of data from phase 3 trials.

The phase 2/3 Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS) was initiated to assess the effect on survival of bevacizumab when added to the present standard of care, cisplatin plus pemetrexed, as first-line treatment of advanced malignant pleural mesothelioma. The primary phase 2 outcome was disease control rate at 6 months in the PCB group, established by an expert panel masked to the randomisation arm using modified Response Evaluation Criteria in Solid Tumors,[13,14] with safety as a secondary outcome. This phase 2 part met its statistical outcome, reporting 27 patients with 6 month disease control of the first 47 patients included (57%) in the experimental group, without any unexpected toxicity signals.[15] The phase 3 part of the study was then initiated in 2010. Here, we report the results of the phase 3 part of MAPS as the continuation of the positive results of the phase 2 part.

Methods

Study design and participants

In this multicentre, randomised, controlled, open-label, phase 3 trial, we recruited patients aged 18–75 years from 73 hospitals in France. We recruited patients with histologically proven malignant pleural mesothelioma with pleural biopsies (thoracoscopy was recommended) who had not received previous chemotherapy, had an ECOG performance status of 0–2, had no substantial cardiovascular comorbidity, were not amenable to curative surgery (according to a multidisciplinary tumour board, including a mesothelioma-experienced surgeon), had at least one evaluable (pleural effusion) or measurable (pleural tumour solid thickening) lesion with CT, and had a life expectancy of longer than 12 weeks. Prophylactic radiation treatment of all tracts (3×7 Gy) before chemotherapy and within 28 days after pleural biopsy

was mandatory.[16,17] Adequate haematological, liver, and renal function (creatinine clearance of ≥60 mL/min), a coagulation international normalised ratio of less than or equal to 1·5, and a prothrombin time of less than or equal to 1·5 times the upper limit of normal within 7 days before enrolment were also needed.

Exclusion criteria were presence of central nervous system metastases, use of antiaggregant treatments (aspirin ≥325 mg per day, clopidogrel, ticlopidine, or dipyridamole), anti-vitamin K drugs at a curative dose, treatment with low-molecular-weight heparin at a curative dose (anticoagulants at a preventive dose were allowed), and treatment with non-steroidal anti-inflammatory drugs. We also excluded patients with uncontrolled hypertension, haemoptysis, or major surgery (including thoracotomy) within 28 days before enrolment, and those with a history of inherited bleeding, diathesis, or coagulopathy, recent myocardial infarction or cerebrovascular accident (<6 months before date of diagnosis), uncontrolled ischaemic cardiopathy (unstable angina), congestive heart failure, severe uncontrolled cardiac arrhythmia or history of abdominal fistula, or gastrointestinal perforation within 6 months of enrolment.

The research protocol was approved by the North West 3 Ethics Committee for Person Protection (Comité de Protection des Personnes), and the study was done according to the Declaration of Helsinki of 1964 and Good Clinical Practice guidelines. Patients gave written informed consent to participate.

Randomisation and masking

We used an interactive web response system to generate random allocation of treatment in a non-masked fashion. We randomly assigned patients enrolled by investigators (1:1) to the two treatment groups. Randomisation was centrally performed by computer. We used a minimisation method (random factor of 0·8) and stratified patients by histology (epithelioid *vs* sarcomatoid or mixed histology subtypes), performance status score (0–1 *vs* 2), study centre, and smoking status (never smokers *vs* smokers). We included smoking status to increase concealment of the minimisation process.

Procedures

Patients received intravenously 500 mg/m² pemetrexed (day 1) plus 75 mg/m² cisplatin (PC; day 1) or PC plus 15 mg/kg bevacizumab (PCB; day 1) in 21 day cycles for up to six cycles. We gave vitamin B12 with a 1000 µg intramuscular injection every three cycles and oral vitamin B9 (folate) daily (400 µg per day) in both groups during the whole duration of pemetrexed-based chemotherapy, beginning 7 days before the first cycle and ending 3 weeks after the last pemetrexed-based cycle. The PCB group allowed maintenance bevacizumab after the six cycles until disease progression or toxic effects. In case of grade 2 or higher cisplatin-induced renal toxic effects, we allowed a switch to a carboplatin area under the curve of five. Growth factor support was not recommended as primary prophylaxis against neutropenia in the first cycle, but was authorised as secondary prophylaxis if grade 3–4 neutropenia developed. Second-line treatment could be used at the discretion of the investigators, but crossover and use of second-line bevacizumab in patients in the PC group was not allowed.

We did baseline disease assessment with chest CT scanning, brain MRI or CT scanning, and abdominal ultrasound or CT scanning. In the case of thoracoscopy, we did a baseline CT scan at least 3 weeks after the procedure. We did CT scans every three cycles, with response assessed by modified Response Evaluation Criteria in Solid Tumors.[13,14] We assessed quality of life (QoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QoL questionnaire C30 (QLQ-C30) version 3 and Lung Cancer Symptom Score (LCSS)-Meso[18] at baseline, treatment initiation, and then every 9 weeks. For each scale or item in QLQ-C30 and LCSS-Meso, we applied a linear transformation to standardise the raw score to a range from 0 to 100, with 100 representing best possible function or QoL for functional scales and highest burden of symptoms for symptom scales and symptom items. A ten point change in an item or domain is

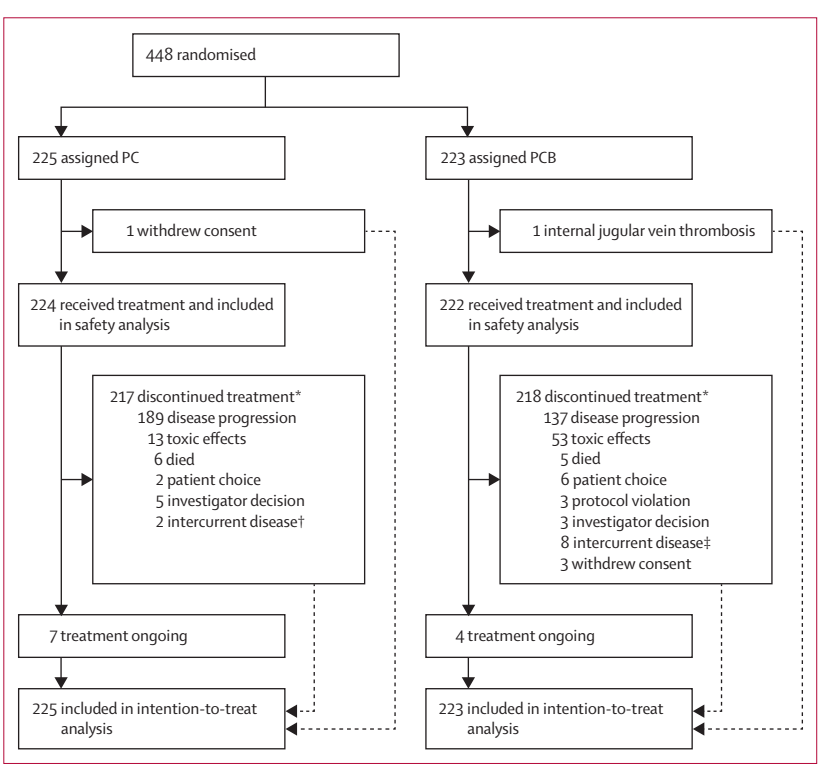

Figure 1: **Trial profile**
Data not available for number of patients assessed for eligiblity. PC=pemetrexed plus cisplatin. PCB=pemetrexed plus cisplatin plus bevacizumab. *We followed patients up until death. †One patient had diabetes. The other had amaurosis. ‡One patient had a pancreatic lesion needing invasive explorations. One needed a hip surgery for hip arthrosis and pain. One needed a gallbladder resection for lithiasis. Two had sigmoiditis needing exploration. Two patients had a second cancer diagnosed (extrathoracic). One had cardiac insufficiency that was deemed at the time of occurrence not related to bevacizumab by the investigator, but the funder now thinks it could be related because cardiac insufficiency has been described as a new specific bevacizumab-related toxic effect.

perceived to be clinically meaningful.[19] For QLQ-C30 scores, we qualified QoL as improved when we noted a ten point increase or greater for functioning scales and a ten point reduction or greater for symptom domains or items between baseline and 9 week assessments. We deemed QoL stable for variations of less than ten points for functioning scales and symptom domains and items and worsened for ten point or greater decreases for functioning scales and ten point or greater increases for symptom domains or items. To compute treatment exposure, we calculated the ratio of the dose intensity measured as a proportion of the theoretical dose intensity.

Outcomes

The extended phase 3 primary outcome was OS (defined as the time from randomisation to death from any cause). Secondary outcomes were PFS (time from randomisation to documented disease progression or death, whichever occurred first), QoL, and safety.

See Online for appendix

	PCB (n=223)	PC (n=225)	Total (n=448)
Sex			
Male	168 (75%)	170 (76%)	338 (75%)
Female	55 (25%)	55 (24%)	110 (25%)
Median age (years)	65·7 (61·5–70·0)	65·6 (60·8–70·3)	65·7 (61·3–70·2)
Histology			
Epithelioid	179 (80%)	182 (81%)	361 (81%)
Sarcomatoid or mixed	44 (20%)	43 (19%)	87 (19%)
ECOG performance status			
0–1	216 (97%)	217 (96%)	433 (97%)
2	7 (3%)	8 (4%)	15 (3%)
Smoking status			
Smoker	125 (56%)	129 (57%)	254 (57%)
Never smoker	98 (44%)	96 (43%)	194 (43%)
Weight loss			
Mean (%)	5·4% (2·9)	5·4% (3·1)	5·4% (3·0)
Median (%)	5·5% (2·9–7·4)	5·1% (3·3–7·1)	5·1% (3·1–7·3)
n	151 (68%)	168 (75%)	319 (71%)
Leucocyte count			
<8·3 × 10^9/L	132 (59%)	124 (55%)*	256 (57%)*
≥8·3 × 10^9/L	91 (41%)	100 (45%)*	191 (43%)*
Haemoglobin concentration			
>140 g/L	74 (33%)	65 (29%)	139 (31%)
≤140 g/L	149 (67%)	160 (71%)	309 (69%)
Platelet count			
<400 × 10^9/L	172 (77%)	164 (73%)*	336 (75%)*
≥400 × 10^9/L	51 (23%)	60 (27%)*	111 (25%)*
Thoracoscopy			
Yes	193 (87%)	189 (84%)	382 (85%)
No	30 (13%)	36 (16%)	66 (15%)
Patient with pleural effusion relapsing after thoracoscopy	26 (12%)	17 (8%)	43 (10%)

Data are n (%), median (IQR), or mean (SD). PCB=pemetrexed plus cisplatin plus bevacizumab. PC=pemetrexed plus cisplatin. ECOG=Eastern Cooperative Oncology Group. *Data missing for one patient.

Table 1: **Baseline characteristics**

We assessed adverse events (AEs) according to the National Cancer Institute Common Terminology Criteria version 3.0. For patients receiving bevacizumab, we investigated specific AEs every 3 weeks, including arterial hypertension and proteinuria. We studied the prognostic or predictive effect of baseline serum VEGF concentrations, assessed by ELISA using commercially available ELISA kits (R&D Systems, Minneapolis, MN, USA), as preplanned exploratory objectives.

Statistical analysis

We included all randomised patients in the intention-to-treat population in which we did the efficacy analyses. We included patients who received at least one cycle of study treatment in the safety population (safety analysis). The phase 3 part needed 445 patients (including those from the phase 2 part) and 385 deaths over 48 months, with a 24 month follow-up (80% power; two-sided α=0·05; appendix). Patients enrolled in the phase 2 part contributed in the phase 3 part without inflating the α risk because of the hierarchical nature of the phase 2 and 3 hypotheses, also known as closed tests.[20] We based this sample size on a primary outcome of median OS increasing from roughly 13 months to 17·3 months—ie, a 33% improvement—with addition of bevacizumab (hazard ratio [HR] 0·75). We plotted PFS and OS with Kaplan-Meier curves and compared them with Cox models. We censored follow-up on Jan 15, 2015. We estimated HRs and 95% CIs from a Cox model, adjusting for minimisation variables as appropriate.[21] We tested the proportional hazards assumption by including an interaction term between the randomised treatment indicator and log-transformed follow-up time. We did planned subgroup analyses for the primary outcome by testing the interaction term between the treatment group and known risk factors in a Cox model adjusting for minimisation variables. We used SAS software version 9.4 for statistical analyses; all p values and CIs were two sided.

We planned an interim analysis for phase 3 after 193 deaths, with p<0·003 as the predefined stopping boundary and a final p<0·047 according to the O'Brien-Fleming method.[22] On Dec 10, 2014, estimating that release of the MAPS results could be ethically important for clinicians and patients, the independent data monitoring committee (IDMC) requested a further interim analysis when 342 events (89%) had occurred. We adapted the sequential design accounting for the first preplanned analysis (after 223 deaths; nominal α=0·003), the present unplanned analysis (after 342 deaths; nominal α=0·029), and the final analysis (needing 397 deaths; nominal α=0·041). This additional interim analysis was available for the IDMC meeting on Feb 3, 2015, which recommended that the results should be publicly released because they met the prespecified statistical criteria. The IDMC recommended early trial termination for superiority on the basis of this second requested interim analysis.

We tested the prognostic effect of serum VEGF concentration using a Cox model adjusting for treatment group, minimisation variables, and known risk factors previously used in EORTC score (sex, histology, performance status, and leucocytes).[23] We used bootstrap resampling to assess model stability. We assessed the predictive effect of VEGF by testing the interaction term between treatment group and VEGF in a Cox model adjusting for minimisation variables.

This IFCT-GFPC-0701 trial is registered with ClinicalTrials.gov, number NCT00651456.

Role of the funding source

Bevacizumab was provided by Roche (France). Intergroupe Francophone de Cancérologie Thoracique (IFCT) collected and interpreted data. IFCT investigators and staff had a role in study design and data analysis. IFCT had no role in 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 the publication.

Results

Between Feb 13, 2008, and Jan 5, 2014, we randomly assigned 448 patients to PCB (223 [50%]) or PC (225 [50%]), with 222 (>99%) receiving PCB and 224 (>99%) receiving PC (figure 1). Baseline characteristics were balanced between groups (table 1). The dose actually delivered compared with the theoretical dose for cisplatin was 91·8% for the PCB group versus 93·2% for the PC group, 95·6% versus 97·0% for pemetrexed, and 98·6% versus not applicable for bevacizumab. The proportion of patients who received six cycles of platinum-based triplets or doublets was 74·9% in the PCB group versus 76·0% in the PC group (difference of –1·1%). Median follow-up was 39·4 months (25·5–54·8), with no difference between the two groups.

The primary outcome of OS was significantly extended with PCB (median OS 18·8 months [95% CI 15·9–22·6]; 164 [74%] of 223 died) versus PC (16·1 months [14·0–17·9]; 178 [79%] of 225 died; adjusted HR 0·77 [0·62–0·95]; p=0·0167; figure 2). Multivariate subgroup analysis of OS is also shown on figure 2. In the preplanned subgroup analyses, the effect on OS of the bevacizumab-containing regimen compared with standard chemotherapy was homogeneous, with no significant interaction when the analyses were stratified by important prognostic factors, such as sex, age, performance status, histology subtype, haemoglobin concentration, or leucocyte count.

The major cause of death in both treatment groups was cancer: 168 (94%) of the 178 patients who died, died from cancer in the PC group compared with 153 (93%) of

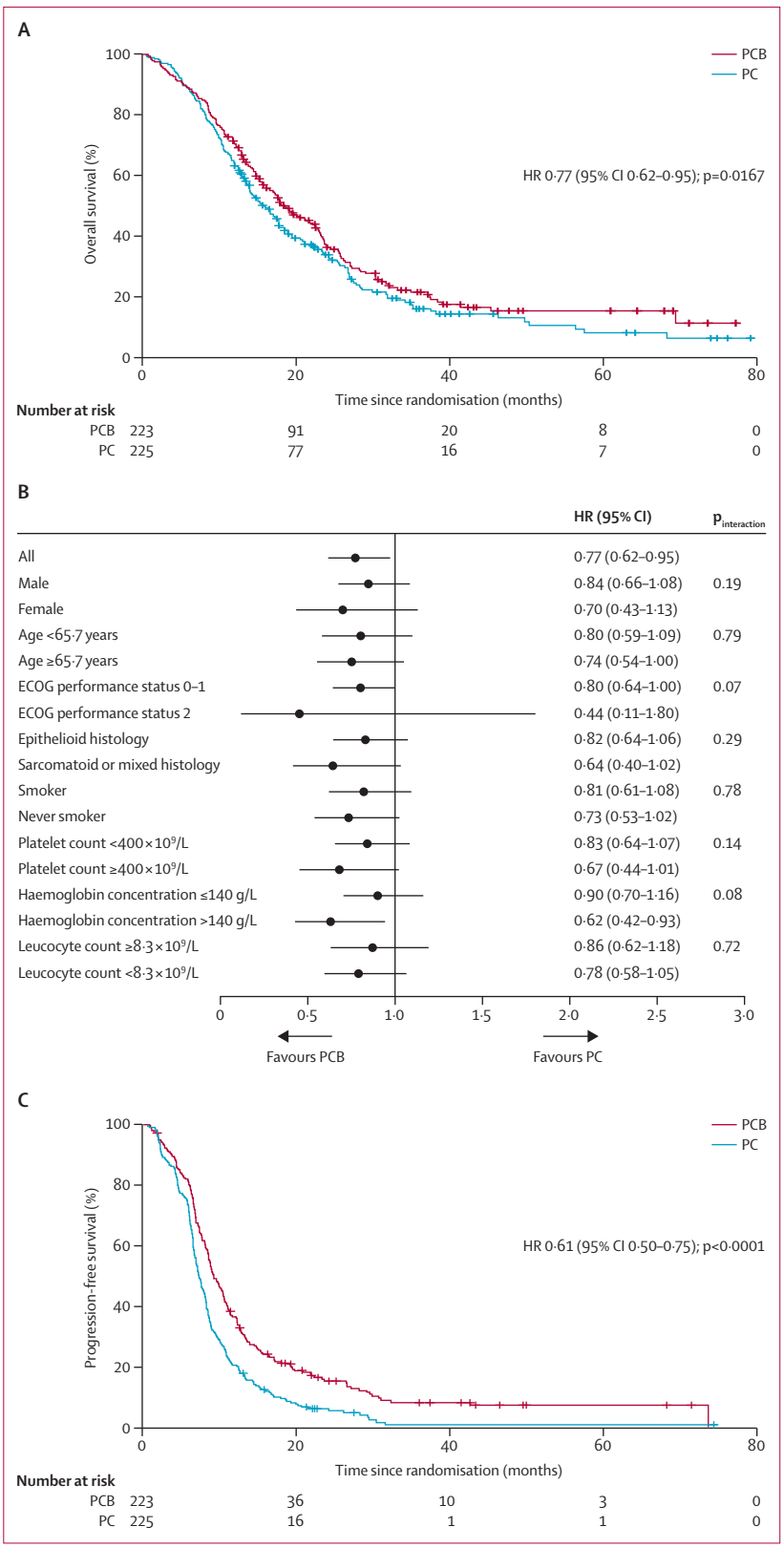

Figure 2: **Efficacy results**

(A) Kaplan-Meier curves of overall survival. (B) Forest plot of interactions for overall survival subgroup analyses. (C) Kaplan-Meier curve of progression-free survival. Crosses denote censored patients. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. PC=pemetrexed plus cisplatin. PCB=pemetrexed plus cisplatin plus bevacizumab.

164 in the PCB group. All-cause mortality within the first 3 months of treatment (early death) was similar in both groups (PC five [2·8%] deaths; PCB eight [4·9%] deaths; difference –2·1% [95% CI –6·8 to 2·2]; p=0·31).

PFS was also significantly improved with PCB (median PFS 9·2 months [8·5–10·5]; 198 [89%] of 223 died) versus PC (7·3 months [6·7–8·0]; 217 [96%] of 225 died; adjusted HR 0·61 [0·50–0·75]; p<0·0001; figure 2). More patients stopped first-line treatment for disease progression in the PC group (189 [87·1%] of 217) than in the PCB group (137 [62·8%] of 218; difference 24·3% [16·3–31·9]; p<0·0001).

Post-study treatment was given significantly less frequently in the PCB group (129 [62·0%] of 208 consisting of further chemotherapies and 11 [5·3%] of 208 further bevacizumab) than in the PC group (152 [72·4%] of 210 consisting of further chemotherapies, but no crossover to bevacizumab; further chemotherapy difference –10·4% [–19·1 to –1·4]; p=0·02; appendix). Pemetrexed rechallenge was used in 79 (35%) patients in the PC group and 65 (29%) in the PCB group, whereas rechallenge with a platinum-containing regimen was used in 81 (36%) in the PC group and 61 (27%) in the PCB group.

At baseline, QoL items measured in QLQ-C30 or LCSS-Meso were balanced. At 9 weeks, 131 (58%) of 225 patients in the PC group and 121 (54%) of 223 in the PCB group completed LCSS-Meso, whereas 151 (67%) of 225 patients in the PC group and 159 (71%) of 223 in the PCB group completed QLQ-C30. More patients in the PCB group had significant improvement in fatigue score as assessed by QLQ-C30, whereas more patients receiving PC tended to improve their constipation score (figure 3). However, treatment groups did not differ according to the other QLQ-C30 items, either for physical or functional symptoms, and global health status improved in more than 20% of patients in both groups. Significantly more patients experienced worsened score in the PC group than in the PCB group at 9 weeks with the LCSS-Meso for interference with the activity level item (PC 68 [52%] of 130; PCB 44 [37%] of 119; p=0·015) and general condition item (PC 63 (48%) of 131; PCB 43 [36%] of 121; p=0·04). Percentages of patients with improvement did not differ for other individual items or global score (appendix). Respiratory-specific symptoms (dyspnoea and cough) improved in both groups (40 [27%] of 150 patients in the PCB group and 47 [30%] of 159 in the PC group for cough, and 64 [43%] of 150 in the PCB group and 63 [39%] of 162 in the PC group for dyspnoea). Similarly, pain improved in both groups, in 48 (33%) of 147 patients in the PCB group and 56 (35%) of 159 in the PC group.

We assayed serum VEGF baseline concentrations in 372 (83%) of 448 patients (190 [85%] of 223 in the PCB group and 182 [81%] of 225 in the PC group), with no demographic differences in patients undergoing VEGF analysis compared with the overall study population (data not shown). Distribution of VEGF serum concentrations and median values in patients in both groups are shown in the appendix. The prognostic analysis based on VEGF assessed as a continuous variable showed that high VEGF concentrations were associated with worse PFS and OS (appendix). In the bootstrap resampling, VEGF significantly correlated with worse PFS in 891 (89%) of 1000 bootstrapped samples and with OS in 979 (98%) of 1000 bootstrapped samples, with an optimism-corrected concordance index of 0·64 for PFS and 0·65 for OS. We noted similar results by dichotomisation at the median value as a cutoff (data not shown). The predictive analysis based on VEGF assessed as a continuous variable showed that the interaction between treatment group and VEGF concentration was not significant for PFS (p=0·60) or OS (p=0·99).

An exploratory subgroup analysis according to baseline serum VEGF concentration dichotomised at the median value showed that patients with VEGF concentrations of less than (adjusted HR 0·56 [95% CI 0·41–0·77]; p=0·0004) or more than (0·59 [0·44–0·80]; p=0·0007) the median value derived similar benefit from bevacizumab in PFS (appendix). Patients with baseline VEGF concentrations lower than the median value derived a 5·2 month longer OS with PCB (median OS 23·7) than with PC (median OS 18·5; adjusted HR 0·73 [0·52–1·03]; p=0·07; appendix), whereas patients with higher baseline VEGF concentrations than the median value treated in the PCB group derived a 2·3 month benefit (PCB 15·7 months; PC 13·4 months; adjusted HR 0·86 [0·63–1·19]; p=0·37; appendix).

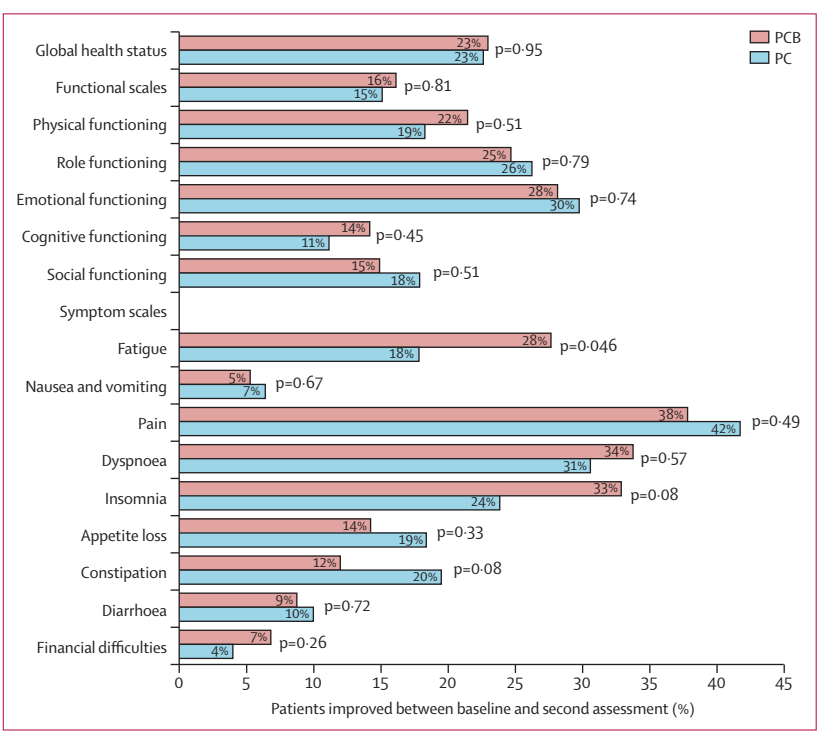

***Figure 3*: Quality of life questionnaire C30 scores**
PC=pemetrexed plus cisplatin. PCB=pemetrexed plus cisplatin plus bevacizumab.

	PCB (n=222)		PC (n=224)		Difference (%)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	173 (77·9%)	98 (44·1%)	177 (79·0%)	100 (44·6%)	–1·1% (–8·7 to 6·5)	–0·5% (–9·6 to 8·6)
Febrile neutropenia	4 (1·8%)	4 (1·8%)	7 (3·1%)	7* (3·1%)	–1·3% (–4·7 to 1·8)	–1·3% (–4·7 to 1·8)
Thrombocytopenia	130 (58·6%)	22 (9·9%)	119 (53·1%)	21 (9·4%)	5·4% (–3·8 to 14·5)	0·5% (–5·1 to 6·1)
Anaemia	163 (73·4%)	16 (7·2%)	187 (83·5%)	30 (13·4%)	–10·1% (–17·6 to –2·4)	–6·2% (–11·9 to –0·5)
Asthenia or fatigue	155 (69·8%)	30 (13·5%)	152 (67·9%)	28 (12·5%)	2·0% (–6·6 to 10·5)	1·0% (–5·3 to 7·3)
Weight loss	22 (9·9%)	0	22 (9·8%)	0	0·1% (–5·6 to 5·7)	0 (–1·7 to 1·7)
Anorexia	75 (33·8%)	5 (2·3%)	75 (33·5%)	9 (4·0%)	0·3% (–8·4 to 9·0)	–1·8% (–5·4 to 1·7)
Constipation	47 (21·2%)	2 (0·9%)	44 (19·6%)	1 (0·4%)	1·5% (–6·0 to 9·0)	0·5% (–1·5 to 2·4)
Diarrhoea	37 (16·7%)	1 (0·5%)	26 (11·6%)	2 (0·9%)	5·1% (–1·4 to 11·6)	–0·4% (–2·0 to 1·1)
Oral mucositis	37 (16·7%)	2 (0·9%)	33 (14·7%)	1 (0·4%)	1·9% (–4·9 to 8·7)	0·5% (–1·5 to 2·4)
Nausea or vomiting	174 (78·4%)	18 (8·1%)	172 (76·8%)	18 (8·0%)	1·6% (–6·1 to 9·3)	0·1% (–5·1 to 5·3)
Creatinine concentration increase	86 (38·7%)	8 (3·6%)	63 (28·1%)	4 (1·8%)	10·6% (1·9 to 19·1)	1·8% (–1·4 to 5·3)
Haemorrhage	91 (41·0%)	2† (0·9%)	16 (7·1%)	0	33·8% (26·3 to 41·0)	0·9% (–5·1 to 5·3)
Sepsis	3 (1·4%)	3‡ (1·4%)	3 (1·3%)	3 (1·3%)	<0·1% (–2·7 to 2·7)	<0·1% (–2·7 to 2·7)
Hepatic enzymes	5 (2·3%)	0	3 (1·3%)	1 (0·4%)	0·9% (–1·9 to 3·9)	–0·4% (–2·5 to 1·3)
Cardiovascular AEs	137 (61·7%)	64 (28·8%)	6 (2·7%)	2 (0·9%)	59·0% (51·8 to 65·3)	27·9% (21·9 to 34·2)
Hypertension	125 (56·3%)	51 (23·0%)	3 (1·3%)	0	55·0% (47·9–61·4)	23·0% (17·6 to 28·9)
Arterial and venous thromboembolic events	16 (7·2%)	13 (5·8%)	3 (1·3%)	2 (0·9%)	5·9% (2·2 to 10·1)	5·0% (1·6 to 8·9)

Data are n (%) or % (95% CI). PCB=pemetrexed plus cisplatin plus bevacizumab. PC=pemetrexed plus cisplatin. AE=adverse event. *Including one grade 5 febrile neutropenia case. †Including one fatal brain haemorrhage. ‡Including two toxic deaths.

Table 2: **Adverse events**

Overall, 158 (71%) of 222 patients in the PCB group had grade 3–4 AEs versus 139 (62%) of 224 in the PC group. We noted haematological AEs (any grade) in 205 (92%) versus 211 (94%), with grade 3–4 haematological AEs noted in 105 (47%) versus 111 (50%), representing most of the grade 3–4 AEs. We noted similar proportions of non-haematological AEs in the PCB and PC groups, including asthenia or fatigue, anorexia, constipation, and nausea or vomiting (table 2). More patients stopped first-line treatment because of toxic effects in the PCB group (53 [24·3%] of 218) than in the PC group (13 [6·0%] of 217; difference 18·3% [95% CI 11·7–24·9; p<0·0001).

Specific bevacizumab-related AE frequencies were significantly higher in the PCB group than in the PC group, including hypertension. Haemorrhages were also increased, but were mainly grade 1–2 epistaxis in the PCB group (PCB 83 [37·4%] of 222; PC 14 [6·3%] of 224; difference 31·1% [95% CI 23·9–38·1]). We noted more blood creatinine concentration increases in the bevacizumab-containing group. Other bevacizumab-related toxic effects included higher proportions of any-grade and grade 3–4 arterial and venous thromboembolic events, with 12 (5·4%) any-grade pulmonary embolism and venous thrombosis in the PCB group and three (1·3%) in the PC group (difference 4·1% [0·7–8·0]), of which six (2·7%) were grade 4 in the PCB group and one (0·4%) was in the PC group (difference 2·3% [–0·25 to 5·4]). We also noted 37 (16·7%) any-grade proteinuria events in the PCB group, with one (0·4%) in the PC group (difference 16·3% [11·4–21·7]), of which seven (3·2%) were grade 3 in the PCB group versus none in the PC group (difference 3·2% [0·8–6·4]). No gastrointestinal perforation occurred. One (<1%) grade 5 brain haemorrhage and two (1%) toxic deaths occurred in the PCB group (both sepsis-related deaths) versus none in the PC group, and one (<1%) grade 5 case of febrile neutropenia and one (<1%) case of intercurrent disease resulted in death in the PC group versus none in the PCB group. AEs that led to treatment cessation are shown in appendix.

Discussion

The present standard of care for first-line treatment of malignant pleural mesothelioma is cisplatin plus pemetrexed.[4] In this large, multicentre, randomised, controlled trial, addition of bevacizumab to cisplatin and pemetrexed significantly improved OS, the primary outcome of this study. As only pleural mesothelioma were included in this trial, these results do not apply to peritoneal mesothelioma. Patient subgroups that have previously shown poor prognosis had similar OS increases to other subgroups from addition of bevacizumab, including those with an ECOG performance status of 2, a haemoglobin concentration of 140 g/L or lower, thrombocytosis, a leucocyte count of $8·3\times10^9$/L or higher, or sarcomatoid or mixed histology. The interaction between treatment group and VEGF serum concentration was also not significant. We also noted a significant improvement for PFS. Of note, we observed this PFS improvement despite the higher proportion of patients stopping first-line treatment because of toxic effects in

the bevacizumab group than in the standard chemotherapy group. Median PFS and OS with PCB in this trial were longer than those noted with gemcitabine, cisplatin, and bevacizumab in a small phase 2 study[12] (6·9 months for PFS and 15·6 months for OS), which could be related to the better efficacy of the pemetrexed-based chemotherapy backbone than of gemcitabine.

Use of pemetrexed rechallenge and rechallenge with a platinum-containing regimen in both treatment groups could have extended OS in our trial. Median OS and PFS noted with PC in this study were longer than those seen with PC were in the pivotal study by Vogelzang and colleagues[4] (13·3 months in patients receiving vitamin B12 and 6·1 months in those receiving vitamin B9). This discrepancy might be because most patients had thoracoscopy as the diagnostic procedure, leading to 405 (90%) efficient pleurodesis procedures that could be due either to the thoracoscopy done in the diagnosis phase or to spontaneous resolution. This high proportion of efficient pleurodesis could have thus avoided recurring abundant pleural effusion that could otherwise alter QoL and impair general condition or cytotoxic treatment administration because of progressive respiratory insufficiency. The effect of second-line treatments on OS (eg, pemetrexed rechallenge) could also have improved OS compared with previous studies in which such rechallenge was uncommon.

More patients in the PC group received post-study treatments than those in the PCB group did, who still had a longer OS. We could not exclude either that extension of VEGF inhibition with a bevacizumab maintenance treatment was the main reason for extension of survival. Whether pemetrexed maintenance treatment could have led to such an increase in PFS and OS remains speculative in the absence of dedicated trial testing, such as pemetrexed maintenance in patients with mesothelioma. Another explanation for the difference between this study and the 2003 study by Vogelzang and colleagues[4] could be that extrapleural pneumonectomy was a reference treatment for many clinicians in the USA at that time, whereas it has been virtually abandoned in Europe during the course of this trial. Our fit patients could possibly have received radical curative-intent surgery in 2003, and patients in the study by Vogelzang and colleagues could have been refused surgical aggressive treatment and thus possibly be in worse condition than our patients were. Finally, patient selection criteria for bevacizumab use could have led to a better prognosis study population in our study than in the study by Vogelzang and colleagues because we excluded patients with cardiovascular comorbidities. Thus, the results of our study should only be applied to the same type of patients, without cardiovascular comorbidities, because of the risk of higher AEs than those noted in this study if the bevacizumab contraindications are not strictly respected in a real-life setting.[24] The PCB median PFS and OS results in this study were also longer than were those noted with PCB in a phase 2 single-arm study[25] in advanced malignant pleural mesothelioma (6·9 months for PFS and 14·8 months for OS) and the pemetrexed, carboplatin, and bevacizumab regimen assessed in a single-arm study[26] in advanced malignant pleural mesothelioma (6·9 months for PFS and 15·3 months for OS). However, cross-trial comparisons should be viewed with caution owing to differences in study design, assessment techniques, underpowered phase 2 trials, and patient populations.

AE frequencies were generally similar between the two treatments, although patients in the PCB group had higher rates of any-grade creatinine increases and any-grade and grade 3–4 thromboembolic events than those in the PC group did. We also noted higher rates of both any-grade and grade 3–4 hypertension and haemorrhage with PCB, whereas patients in the PC group had a higher frequency of anaemia (any grade and grades 3–4) than those in the PCB group did. However, these AEs were expected with addition of bevacizumab and were manageable because they were predominantly of grade 1–2 severity. Creatinine concentration increase did not translate into significantly more carboplatin switch in the PCB group, and bevacizumab-related AEs did not translate into either unbalanced exposure to cisplatin and pemetrexed doublet or worsening of QoL. Again, although more patients stopped first-line treatment in the PCB group because of toxic effects than in the PC group, it did not translate into worsening of QoL in the PCB group.

In comparison with AEs previously reported in phase 3 trials using bevacizumab in patients with non-small-cell lung cancer[27] or colorectal cancer,[28,29] we noted no specific toxic effect signal in patients with mesothelioma in this trial, with a noticeable absence of haemoptysis compared with patients with non-small-cell lung cancer.[27] Additionally, we noted no severe gastrointestinal haemorrhage compared with the 3·4% noted in the E3200 phase 3 trial.[29] The epistaxis rate in the PCB group is lower than that previously reported in colorectal cancer.[28,29] The rate of proteinuria compared favourably with the previously noted rates of 21–63% (according to bevacizumab dose) in a 2007 meta-analysis.[30] Conversely, the proportion of grade 3 hypertension is slightly higher than the previous grade 3–4 hypertension proportion reported in breast cancer (15·5%),[31] colorectal cancer (11%),[28] or non-small-cell lung cancer (9%) is,[27] but the median age of 65·7 years in patients with mesothelioma in this trial is somewhat higher than in these other studies (median age of 56 years in breast cancer, 59·5 years in colorectal cancer, and 59 years in non-small-cell lung cancer), which also used lower doses of bevacizumab than in our trial (10 mg/kg in breast cancer, 5 mg/kg in colorectal cancer, and 7·5 mg/kg in non-small-cell lung cancer).

Some potential limitations could be emphasised in the this trial. First, this study was an open-label trial. OS was the primary outcome, not likely to be affected by knowledge of the study group. However, assessment of QoL could have been slightly altered by the absence of masking and should therefore be interpreted with caution. Before

initiation of the MAPS trial, the Intergroupe Francophone de Cancérologie Thoracique investigators had been questioned on their will to participate in a placebo-controlled trial. Most of our investigators judged that giving monthly intravenous placebo infusion in hospital during the maintenance part of the treatment would have been a barrier to inclusions because patients with advanced cancer and low survival expectancy would not have been compliant during this maintenance phase. Secondly, results of interim analyses should be interpreted with caution, in particular when unplanned.[32] However, in this study, the number of events was large (ie, 89% of the expected events), and the second interim analysis was requested by the IDMC independently from the investigators. We cannot exclude either that some patients in this trial would have been referred to a surgeon for a curative-intent surgery in the USA where this surgery is still done by specialised surgical teams. However, radical surgery is not often used in Europe now because of the negative results of the EORTC[33] and MARS[34] trials, findings from which showed that such a surgery failed to improve OS as compared with patients treated medically. Another potential caveat could be the extra costs of bevacizumab that could limit bevacizumab use in this disease in some countries. However, bevacizumab could be publicly available at lower cost shortly because of Avastin (Genentech, South San Francisco, CA, USA) patent expiration.[35] At that time, biosimilars will be available, making the price decrease. Meanwhile, a cost-effectiveness analysis based on the data of this trial will be published separately later.

Finally, the 2·7 month OS improvement could be viewed as slight, but it still accounts for the longest OS ever obtained in a large controlled trial of pleural mesothelioma, a disease in which no progress had been accomplished since the approval of pemetrexed 10 years ago,[4] and yet malignant pleural mesothelioma will account for thousands of deaths of people previously exposed to asbestos worldwide. Moreover, since no efficacious standard second-line treatment has been approved in the disease, any improvement in first-line treatment could actually be viewed as a major advance.

Addition of bevacizumab to cisplatin and pemetrexed significantly increased OS and PFS in malignant pleural mesothelioma with expected and manageable toxic effects This result has important implications for future first-line treatment of the disease because the pemetrexed plus cisplatin plus bevacizumab regimen should be considered as a new treatment option for patients who are eligible to receive bevacizumab and are not candidates for curative-intent surgery.

Contributors

CC, GZ, JMaz, FM, DM-S, J-JP, FR, AS, and QT did the literature search. GZ, FM, J-JP, and FR assembled the figures. CC, GZ, CL, JMar, JMaz, BM, FM, DM-S, J-JP, FR, and AS designed the study. CA-V, VG, GZ, LG, HJ, M-PL, CL, JMar, JMaz, BM, OM, IM, FM, DM-S, FR, AS, RG, and QT collected data. RC, CC, GZ, JMaz, FM, DM-S, J-JP, FR, AS, RG, and QT analysed and interpreted data. All authors contributed to the writing, review, and approval of the final manuscript.

Declaration of interests

GZ participated in advisory boards for Roche, Eli Lilly, Bristol-Myers Squibb, Clovis Oncology, AstraZeneca, Boehringer Ingelheim, and Pfizer, all outside the submitted work, and received a research grant from Roche. OM participated in advisory boards for Roche and Boehringer Ingelheim outside the submitted work. JMaz has received grants from Roche outside the submitted work. RC reports personal fees and non-financial support from Roche, Eli Lilly, and Bristol-Myers Squibb; personal fees from Boehringer Ingelheim and AstraZeneca; and non-financial support from Amgen, all outside the submitted work. AS reports grants from Roche during the conduct of this study. He was an advisory board member for Merck Sharp & Dohme, Bristol-Myers Squibb, Seattle Genetics, Roche, and AstraZeneca; received research grants from Amgen, Teva, and Roche; received travel grants from Boehringer Ingelheim; and had investigators in clinical trials in his department for Celgene, Merck Sharp & Dohme, AstraZeneca, MedImmune, Verastem, Pierre Fabre, Clovis, Roche, GlaxoSmithKline, Atex, Lilly, and BI, all outside the submitted work. VG reports personal fees from Eli Lilly and Roche outside the submitted work. DM-S reports personal fees from Roche, Eli Lilly, Pfizer, Novartis, AstraZeneca, Clovis, Amgen, and Boehringer Ingelheim, all outside the submitted work. LG reports grants, personal fees, and non-financial support from Roche; personal fees and non-financial support from Eli Lilly and AstraZeneca; and personal fees from Bristol-Myers Squibb and Boehringer Ingelheim, all outside the submitted work. CA-V reports personal fees from Roche and Eli Lilly during the conduct of this study and personal fees from Amgen, Boehringer Ingelheim, Sismex-Inostics, AstraZeneca, Bristol-Myers Squibb, Novartis, Pfizer, and Clovis, all outside the submitted work. BM reports grants and personal fees from Roche during the conduct of this study, grants from and being a board member of Lilly, grants and personal fees from Bristol-Myers Squibb and AstraZeneca, and personal fees from Chugai, all outside the submitted work. All other authors declare no competing interests.

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