Gemcitabine with or without ramucirumab as second-line treatment for malignant pleural mesothelioma (RAMES): a randomised, double-blind, placebo-controlled, phase 2 trial

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For the Italian translation of the abstract see Online for appendix 1

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Summary

Background There is a preclinical rationale for inhibiting angiogenesis in mesothelioma. We aimed to assess the efficacy and safety of the anti-VEGFR-2 antibody ramucirumab combined with gemcitabine in patients with pretreated malignant pleural mesothelioma.

Methods RAMES was a multicentre, randomised, double-blind, placebo-controlled, phase 2 trial done at 26 hospitals in Italy. Eligible patients were aged 18 years or older, had Eastern Cooperative Oncology Group performance status 0–2, and histologically proven malignant pleural mesothelioma progressing during or after first-line treatment with pemetrexed plus platinum. Patients were randomly assigned (1:1) to receive intravenous gemcitabine 1000 mg/m² on days 1 and 8 every 3 weeks plus either intravenous placebo (gemcitabine plus placebo group) or ramucirumab 10 mg/kg (gemcitabine plus ramucirumab group) on day 1 every 3 weeks, until tumour progression or unacceptable toxicity. Central randomisation was done according to a minimisation algorithm method, associated with a random element using the following stratification factors: ECOG performance status, age, histology, and first-line time-to-progression. The primary endpoint was overall survival, measured from the date of randomisation to the date of death from any cause. Efficacy analyses were assessed in all patients who had been correctly randomised and received their allocated treatment, and safety analyses were assessed in all patients who received at least one dose of their assigned treatment. This trial is registered with ClinicalTrials.gov, NCT03560973, and with EudraCT, 2016-001132-36.

Findings Between Dec 22, 2016, and July 30, 2018, of 165 patients enrolled 161 were correctly assigned and received either gemcitabine plus placebo (n=81) or gemcitabine plus ramucirumab (n=80). At database lock (March 8, 2020), with a median follow-up of 21·9 months (IQR 17·7–28·5), overall survival was longer in the ramucirumab group (HR 0·71, 70% CI 0·59–0·85; p=0·028). Median overall survival was 13·8 months (70% CI 12·7–14·4) in the gemcitabine plus ramucirumab group and 7·5 months (6·9–8·9) in the gemcitabine plus placebo group. Grade 3–4 treatment-related adverse events were reported in 35 (44%) of 80 patients in the gemcitabine plus ramucirumab group and 24 (30%) of 81 in the gemcitabine plus placebo group. The most common treatment-related grade 3–4 adverse events were neutropenia (16 [20%] for gemcitabine plus ramucirumab *vs* ten [12%] for gemcitabine plus placebo) and hypertension (five [6%] *vs* none). Treatment-related serious adverse events were reported in five (6%) in the gemcitabine plus ramucirumab group and in four (5%) patients in the gemcitabine plus placebo group; the most common was thromboembolism (three [4%] for gemcitabine plus ramucirumab *vs* two [2%] for gemcitabine plus placebo). There were no treatment-related deaths.

Interpretation Ramucirumab plus gemcitabine significantly improved overall survival after first-line standard chemotherapy, with a favourable safety profile. This combination could be a new option in this setting.

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Introduction

Malignant pleural mesothelioma is a rare tumour with increasing incidence globally and a dismal prognosis, with less than 10% of patients alive at 5 years. Few patients are candidates for multimodal therapy that includes radical surgery, and most receive anticancer drug therapy only. Platinum and pemetrexed chemotherapy has been the standard of care for unresectable disease since 2004.[1] In the CheckMate 743 trial,[2] combined first-line treatment with nivolumab and ipilimumab showed a significant survival benefit versus standard chemotherapy in patients with unresectable malignant pleural mesothelioma. Although knowledge of the biology of the disease has improved in the past two decades, there are no approved therapies for patients who progress during or after first-line treatment.[3]

Single-agent chemotherapy with vinorelbine and gemcitabine,[4] pemetrexed rechallenge,[5] or other novel

Research in context

Evidence before this study

We searched PubMed for studies published between Jan 1, 2005, and Jan 31, 2021, using the following search terms: "mesothelioma" AND "second line" OR "pre-treated", "mesothelioma" AND "antiangiogenic" OR "angiogenesis". Additionally, we examined abstracts from the American Society of Clinical Oncology, the International Association for the Study of Lung Cancer, and the European Society of Medical Oncology annual meetings of the same period. We selected articles that assessed treatment options in patients with malignant pleural mesothelioma who progressed during or after standard chemotherapy. Our search returned 40 studies, 24 of which were relevant to this topic. We selected articles published in English. Second-line therapy in patients with malignant pleural mesothelioma remains an unmet need. Single-agent chemotherapy with vinorelbine or gemcitabine, and re-challenge with pemetrexed, are commonly used in clinical practice even if their efficacy is modest. Pembrolizumab, compared with single-agent chemotherapy (gemcitabine or vinorelbine), did not show any survival improvement in patients with mesothelioma progressing during or after platinum-based chemotherapy in the phase 3 randomized PROMISE-meso trial. Conversely nivolumab, compared with placebo, significantly improved both progression-free and overall survival in pre-treated patients in the phase 3 randomised CONFIRM study. Several preclinical studies support angiogenesis as a therapeutic target in mesothelioma. However, clinical data are discordant. Nintedanib, cediranib, NGR-hTNF, and other tyrosine kinase inhibitors have not shown a clinically meaningful advantage in any line of treatment, whereas the addition of bevacizumab to standard chemotherapy in untreated patients increased median survival by nearly 2 months in the randomised, phase 3 MAPS trial.

Added value of this study

The RAMES study showed a clinically meaningful improvement of overall survival in the gemcitabine plus ramucirumab group, with a median value in the intention-to-treat population prolonged by more than 6 months versus the gemcitabine plus placebo group; similarly, 1-year overall survival was longer in the gemcitabine plus ramucirumab group. The survival advantage was seen in the ramucirumab group regardless of histological subtype and time-to-progression after first-line treatment. Our findings showed that the combination of gemcitabine with ramucirumab can induce a high rate of disease control, despite a response rate comparable to gemcitabine alone, consistent with the mechanism of action of antiangiogenic drugs. Adding ramucirumab to gemcitabine was associated with a mild safety profile, with a low rate of severe toxicities, including some specific class-related adverse events. To our knowledge, the RAMES trial is the first randomised study to show significant improvement in overall survival with an antiangiogenic agent in the second-line treatment of malignant pleural mesothelioma.

Implications of all the available evidence

There is a substantial unmet need for new therapies in pretreated malignant pleural mesothelioma. The results of the RAMES study show that the addition of ramucirumab to gemcitabine can provide a notable improvement in overall survival versus gemcitabine alone, suggesting that this combination could be a novel, well tolerated, and active treatment option in patients with malignant pleural mesothelioma who have progressed on first-line chemotherapy with pemetrexed and platinum.

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compounds (such as trabectedin[6] and lurbinectedin[7]) have shown poor activity. Targeted therapies have generated interest but, until now, several compounds against promising targets have shown poor anticancer activity.[8] Two large placebo-controlled phase 3 trials did not show any survival improvement with vorinostat[9] and NGR-hTNF.[10] Although preliminary uncontrolled trials of immune checkpoint inhibitors suggested encouraging activity, a randomised phase 3 study of pembrolizumab versus single-agent chemotherapy with vinorelbine or gemcitabine showed no survival improvement.[11] However, the phase 3 placebo-controlled CONFIRM study reported a significant improvement of progression-free survival and overall survival with nivolumab in a heavily pretreated population.[12]

The key role of angiogenesis in the pathogenesis of mesothelioma has been shown in several preclinical and translational studies. VEGF and its receptors are overexpressed in serum and tumour tissues of patients with mesothelioma, and higher concentrations are associated with poorer prognoses.[13] Various VEGFR tyrosine kinase inhibitors and monoclonal antibodies against VEGF has been studied in both untreated and pretreated patients.[14] Studies evaluating antiangiogenic drugs, such as bevacizumab and nintedanib, added to cisplatin and pemetrexed reported no or marginal survival improvement with an increased toxicity profile.[15,16] Several single-group studies of VEGFR inhibitors in pretreated patients have shown disappointing results (with a response rate of <15%), as well as maintenance treatment with thalidomide after first-line chemotherapy.[17]

Ramucirumab (also known as IMC-1121B or LY3009806), is a fully humanised monoclonal antibody selectively directed against the extracellular domain of VEGFR-2, which inhibits the VEGF receptor with a much greater affinity than its natural ligands.[18] As a single drug or in combination with different chemotherapy agents, ramucirumab has been approved for second-line treatment of gastric adenocarcinoma, colorectal cancer, non-small-cell lung cancer, and hepatocellular carcinoma. Ramucirumab has shown a manageable toxicity profile across all studies.[19]

No standard treatment option is available for the second-line treatment of patients with malignant pleural mesothelioma who have previously been treated with pemetrexed plus platinum. Nevertheless, gemcitabine is widely used in clinical practice in such scenarios.[4] In the phase 2, randomised RAMES trial, we aimed to provide an initial assessment of the efficacy and safety of combined gemcitabine and ramucirumab as second-line treatment in patients with advanced malignant pleural mesothelioma who had progressed on a pemetrexed plus platinum regimen.

Methods

Study design and participants

RAMES (RAmucirumab MESothelioma treatment) was a multicentre, randomised, double-blind, placebo-controlled, randomised, phase 2 trial done at 26 hospitals in Italy that explored the efficacy and safety of the addition of ramucirumab to gemcitabine as second-line treatment in patients with advanced malignant pleural mesothelioma (appendix 2 p 1).

See Online for appendix 2

Eligible patients (aged ≥18 years) had a histologically confirmed diagnosis of malignant pleural mesothelioma, documented disease progression during or after first-line chemotherapy with pemetrexed plus a platinum compound (either cisplatin or carboplatin), measurable or evaluable lesions according to Response Evaluation Criteria in Solid Tumurs (RECIST) version 1.1,[20] and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. An adequate bone marrow reserve was required, with an absolute neutrophil count of at least $1·5×10^9$ cells per L, platelets of at least $100×10^9$ cells per L and haemoglobin of at least 9 g/dL. Creatinine clearance, calculated by the Cockcroft and Gault formula, had to be at least 50 mL/min, bilirubin 1·5-times the upper limit of normal or lower, and alanine aminotransferase and aspartate aminotransferase 2·5-times the upper limit of normal or lower. A baseline urine dipstick with proteinuria (<2+) was required; patients with high proteinuria (≥2+) had to undergo 24-h urine collection and have 1 g or less of protein per 24 h. Patients previously treated with more than one line of therapy; previously treated with agents targeting the VEGF signalling pathway; with uncontrolled hypertension; with a serious non-healing wound or ulcer; with evidence of bleeding diathesis or coagulopathy; or who had a major surgical procedure, open biopsy, or significant traumatic injury within 28 days before the start of study treatment were not eligible for the trial. Patients were also excluded if they were currently on treatment with anticoagulants, high-dose aspirin (>325 mg per day), or other medications known to predispose individuals to gastrointestinal ulceration.

The study was approved by the Italian Medicines Agency and ethics committees at each participating centre. The recommendations of the International Council for Harmonization Good Clinical Practice guidelines for clinical trials and of the Declaration of Helsinki were followed. Written informed consent was obtained from each patient before enrolment. The study protocol is available in appendix 2.

Randomisation and masking

Patients were randomly assigned (1:1) to receive intravenous gemcitabine in combination with either placebo (gemcitabine plus placebo group) or with intravenous ramucirumab (gemcitabine plus ramucirumab group). Randomisation was done by a centralised web-based procedure, with a minimisation algorithm associated with a random element using the following stratification factors: ECOG performance status (0–1 *vs* 2), age (≤70 years *vs* >70 years), histology (epithelioid *vs* non-epithelioid), and first-line time-to-progression (<6 months *vs* ≥6 months). The random allocation sequence was built with random permuted blocks of different size, and was generated according to the Moses and Oakford algorithm at the Clinical Trials Coordinating Centre, Istituto Toscano Tumori (Florence, Italy). Patients, treating physicians, and those assessing outcomes were unaware of study treatment assignment. Placebo and ramucirumab were sealed in serially numbered containers; their formulation, dose, label, packaging, and storage condition were identical.

Procedures

Patients received intravenous gemcitabine 1000 mg/m² on days 1 and 8 every 3 weeks, combined with either intravenous ramucirumab 10 mg/kg or matching placebo on day 1 of a 3-week cycle, until progressive disease, unacceptable toxicity, or withdrawal of consent to treatment occurred. Ramucirumab could be delayed or reduced if a patient had an adverse event of special interest or grade 3 adverse events that met all of the following conditions: the adverse event was reversible and non-life-threatening; the adverse event was not an adverse event of special interest; the adverse event was considered to be at least possibly related to ramucirumab; and the adverse event resolved to grade 1 or to the patient's pretreatment baseline level within 28 days. Adverse events of special interests were infusion-related reactions, hypertension, proteinuria, arterial or venous thromboembolic events, bleeding or haemorrhage, gastrointestinal perforation, congestive heart failure, wound healing complications, fistula, liver failure or liver injury, and reversible posterior leukoencephalopathy syndrome. Any patient who required a ramucirumab dose reduction continued to receive a reduced dose until discontinuation from ramucirumab or discontinuation from the study. Any patient who had two ramucirumab dose reductions and another event that would cause a third dose reduction was permanently discontinued from ramucirumab but remained on the study. Considering adverse events of special interest, ramucirumab was also permanently discontinued in the event of gastrointestinal perforation,

reversible posterior leukoencephalopathy syndrome, fistula, liver failure or liver injury, very high proteinuria (>3 g per 24 h), nephrotic syndrome, grade 3–4 arterial or venous thromboembolic events, grade 3–4 bleeding or haemorrhage, grade 3–4 congestive heart failure, and grade 4 uncontrolled hypertension or hypertensive encephalopathy. Gemcitabine was delayed or reduced by 25% if patients had grade 4 haematological toxicity (for more than 3 days) or grade 3 gemcitabine-related non-haematological toxicity that was clinically significant (as determined by the investigator). Gemcitabine was permanently discontinued if patients had grade 4 non-haematological toxicity that was related to gemcitabine. Any patient who required a gemcitabine dose reduction continued to receive a reduced dose. Any patient who had two gemcitabine dose reductions and another toxicity event that would cause a third dose reduction was permanently discontinued from gemcitabine but remained on the study.

Baseline assessment included a complete medical history, physical examination, and laboratory tests for white blood cell counts, neutrophils, platelets, haemoglobin, serum creatinine, alanine aminotransferase, aspartate aminotransferase, total bilirubin, coagulation profile, and urinalysis. These tests were done at baseline and at each treatment infusion. A chest and abdomen CT scan was done at baseline and repeated every three cycles until the end of treatment. Radiological response was evaluated according to RECIST (version 1.1).[20] No independent central radiological and pathological review was planned. Treatment toxicity was evaluated continuously throughout the study and during follow-up according to version 4.0 of the National Cancer Institute's Common Terminology Criteria for Adverse Events. After completion of the study treatment, patients were followed up for survival until death or date of last contact if still alive. No post-study treatment was planned.

Diagnostic tumour tissue samples from each patient underwent molecular profile analysis.[21] Whole-blood samples were obtained for cell-free DNA evaluation before the start of chemotherapy, after the first radiological re-evaluation (after three therapy cycles), and at the end of treatment. We assessed quality of life using the European Organization for Research and Treatment of Cancer questionnaire C30 at baseline and at day 1 of each treatment cycle.

Outcomes

The primary endpoint was overall survival, measured from the date of randomisation to the date of death from any cause. Observation time of patients alive or lost to followup at the end of the study was censored at the day of the last study visit.

Secondary endpoints were progression-free survival (defined as the time from randomisation to disease progression or death, whichever happened first), objective response rate, disease control rate, safety, quality of life, and predictive biomarkers. The objective response rate was calculated as the number of patients achieving complete or partial response. The disease control rate was defined as the number of patients achieving a best overall response of complete response, partial response or stable disease. Patients without a tumour response assessment for any reason were considered to be nonresponders. Analyses of biomarkers and quality of life data are ongoing and are not reported here.

Statistical analysis

We planned to enrol 156 patients to observe 114 deaths from any cause; with that number of events, it was estimated that the study would have 80% power to detect a hazard ratio for death of 0·70 at a one-sided significance level of 15%. This hypothesis assumed a cumulative proportion of overall survival equal to 40% at 1 year in the gemcitabine plus placebo group,[22] and an absolute 13% improvement at 1 year in the gemcitabine plus ramucirumab group. All efficacy analyses were assessed in the modified intention-to-treat population (ie, all patients who had been correctly randomised and received allocated treatment). Patients who were randomised in error or did not receive any component of study treatment were excluded from this population. Patients were grouped according to the randomised treatment assignment.

We calculated the median period of follow-up for the entire study cohort according to the reverse Kaplan-Meier method. We estimated distributions of time-to-event variables with the use of the Kaplan-Meier product-limit method. We used the unstratified log-rank test as the primary analysis for comparison of treatment groups and used Cox proportional-hazards modelling as supportive analysis. The proportional hazards assumption for treatment group was tested to analyse the degree of correlation between the scaled Schoenfeld residuals and time, and was rejected in the presence of a p value of 0·15 or lower. All statistical tests were one-sided, and p values of 0·15 or lower were considered to indicate statistical significance. For prespecified subgroup analyses of overall survival, we used a two-sided interaction test with a significance level equal to 0·10 to determine the consistency of the treatment effect according to key baseline characteristics (age ≤70 years *vs* >70 years, ECOG performance status 0 *vs* 1–2, histology epithelioid *vs* non-epithelioid, first-line time-to-progression <6 months *vs* ≥6 months). We present crude estimates of the hazard ratios (HRs) and associated 70% (or 90% CIs for subgroup analyses). If the proportional hazards assumption was not met, the 2-year restricted mean survival time for each treatment group and the between-group contrast were also reported as post-hoc analysis, with their 70% CIs. The one-sided p value threshold for the restricted mean survival time analysis was set at 0·15. We analysed progression-free survival with the same statistical techniques described for the primary efficacy variable. We calculated 95% CIs for overall response rate and 70% CIs

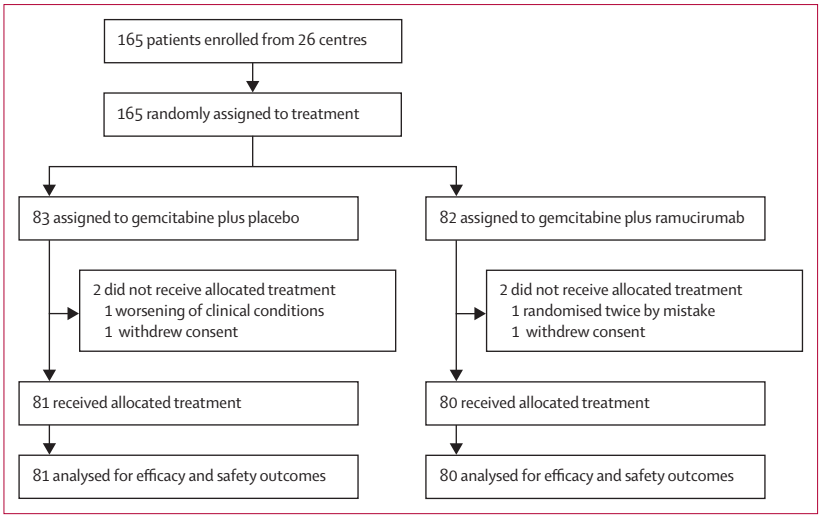

Figure 1: **Trial profile**

	Gemcitabine plus ramucirumab (n=80)	Gemcitabine plus placebo (n=81)
Median age, years (range)	69 (45–81)	69 (44–79)
Age, years		
≤70	49 (61%)	46 (57%)
>70	31 (39%)	35 (43%)
Sex		
Male	59 (74%)	60 (74%)
Female	21 (26%)	21 (26%)
ECOG performance status		
0	50 (63%)	46 (57%)
1	29 (36%)	34 (42%)
2	1 (1%)	1 (1%)
Histotype		
Epithelioid	68 (85%)	70 (86%)
Non-epithelioid	12 (15%)	11 (14%)
First-line time-to-progression, months		
<6	47 (59%)	48 (59%)
≥6	33 (41%)	33 (41%)

Data are n (%) unless otherwise specified. ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline characteristics**

for disease control rate. We did a post-hoc analysis of duration of response, measured from the first date of response until the date of disease progression; 70% CIs were calculated.

We assessed safety in all patients who received at least one dose of their assigned treatment. To determine whether there were sufficient safety concerns to justify the termination of study treatment or enrolment, an interim analysis of safety was planned after about 80 patients completed 6 weeks of therapy or discontinued treatment due to other reasons, whichever came first. An internal data monitoring committee reviewed adverse event profiles, adverse events of special interest, dose modifications, reasons for patient discontinuations, and other safety data. There were no prespecified rules for stopping the trial due to safety concerns.

No adjustment for multiple comparisons was made. We used SAS software (version 9.2) for all statistical analyses. This study is registered with ClinicalTrials.gov, NCT03560973, and with EudraCT, 2016-001132-36.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 22, 2016, and July 30, 2018, 165 patients were randomly assigned to study treatment; 83 to gemcitabine plus placebo and 82 to gemcitabine plus ramucirumab; figure 1. Four patients were excluded from the analysis: two patients assigned to the gemcitabine plus placebo group who received no treatment and two patients assigned to the gemcitabine plus ramucirumab group, one of whom was randomised twice by mistake and another who withdrew consent immediately after randomisation (before treatment began). The remaining 161 patients were included in the analysis as the modified intention-to-treat population (81 in the gemcitabine plus placebo group, 80 in the gemcitabine plus ramucirumab group).

Baseline demographic and clinical characteristics of patients are shown in table 1. Overall, median age was 69 years (range 44–81), 119 (74%) patients were male, 138 (86%) had epithelioid histology, and 95 (59%) had a first-line time-to-progression of less than 6 months. All participants were White. At database lock (March 8, 2020), five (6%) of 81 patients in the gemcitabine plus placebo group and six (8%) of 80 patients in the gemcitabine plus ramucirumab group were still on treatment. The median number of cycles was 3·5 (range 1–31) for placebo and 7·5 (1–28) for ramucirumab. The main reasons for treatment discontinuation were radiological disease progression in 45 (56%) of 81 patients in the gemcitabine plus placebo group and in 39 (49%) of 80 in the gemcitabine plus ramucirumab group, and worsening of clinical condition (ECOG performance status >2) in 14 (17%) of 81 patients in the gemcitabine plus placebo group and in 11 (14%) of 80 in the gemcitabine plus ramucirumab group. Dose reductions of either components of the treatment regimen were required in eight (10%) of 81 patients in the gemcitabine plus placebo group and in 25 (31%) of 80 in the gemcitabine plus ramucirumab group. Discontinuations attributed to study drug toxicity occurred in four (5%) of 81 patients in the gemcitabine plus placebo group (grade 3 thromboembolism in three patients and grade 2 creatinine increased in one patient), and in nine (11%) of 80 patients in the gemcitabine plus ramucirumab group (grade 1–2 thromboembolism in

three patients; grade 3 thromboembolism, grade 4 thromboembolism, grade 3 febrile neutropenia, grade 3 hypertension, grade 2 atrial fibrillation, and grade 3 peripheral oedema in one patient each).

Median follow-up was 21·9 months (IQR 17·7–28·5). Median overall survival was 7·5 months (70% CI 6·9–8·9) in the gemcitabine plus placebo group and 13·8 months (12·7–14·4) in the gemcitabine plus ramucirumab group (HR 0·71, 70% CI 0·59–0·85; unstratified log-rank test p=0·028). Overall survival rates at 6 months and 12 months were 63·9% (70% CI 57·9–69·2) and 33·9% (28·3–39·5) in the gemcitabine plus placebo group and 76·0% (70·6–80·5) and 56·5% (50·4–62·1) in the gemcitabine plus ramucirumab group, respectively (figure 2A). The number of events for overall survival were 64 in the gemcitabine plus placebo group and 59 in the gemcitabine plus ramucirumab group.

Median progression-free survival was 3·3 months (70% CI 3·0–3·9) in the gemcitabine plus placebo group and 6·4 months (5·5–7·6) in the gemcitabine plus ramucirumab group (HR 0·79, 0·66–0·94; un-stratified log-rank test p=0·082; figure 2B). As the proportional hazards assumption for treatment group did not hold for the progression-free survival analysis (appendix 2 p 2), 2-year restricted mean survival time was calculated post hoc. 2-year restricted mean survival time was 6·6 months (70% CI 5·8–7·4) in the gemcitabine plus placebo group and 8·3 months (7·5–9·1) in the gemcitabine plus ramucirumab group (restricted means survival time ratio 1·26, 70% CI 1·08–1·47; p=0·12). The number of events for progression-free survival were 72 in the gemcitabine plus placebo group and 71 in the gemcitabine plus ramucirumab group.

Prespecified subgroup analyses of overall survival data according to randomisation strata are shown in figure 3.

The objective response rates according to RECIST version 1.1 are reported in table 2. No complete response was seen. Eight (10%) of 81 patients in the gemcitabine plus placebo group and five (6%) of 80 in the gemcitabine plus ramucirumab group had a partial response; 34 (42%) patients in the gemcitabine plus placebo group and 53 (66%) in the gemcitabine plus ramucirumab group had stable disease. Disease control was achieved in 42 (52%; 70% CI 46–58) of 81 patients in the gemcitabine plus placebo group and in 58 (73%; 66–78) of 80 in the gemcitabine plus ramucirumab group. 30 (37%) of 81 patients in the gemcitabine plus placebo group and 15 (19%) of 80 in the gemcitabine plus ramucirumab group had disease progression during treatment. In a post-hoc analysis, the median duration of response was 5·4 months (70% CI 2·1–17·0) in the gemcitabine plus placebo group and 8·4 months (4·2–11·5) in the gemcitabine plus ramucirumab group.

An interim analysis of safety was done by an internal study committee after 80 patients completed 6 weeks of study treatment (May 11, 2018), and no safety concerns were found to justify the early termination of the accrual.

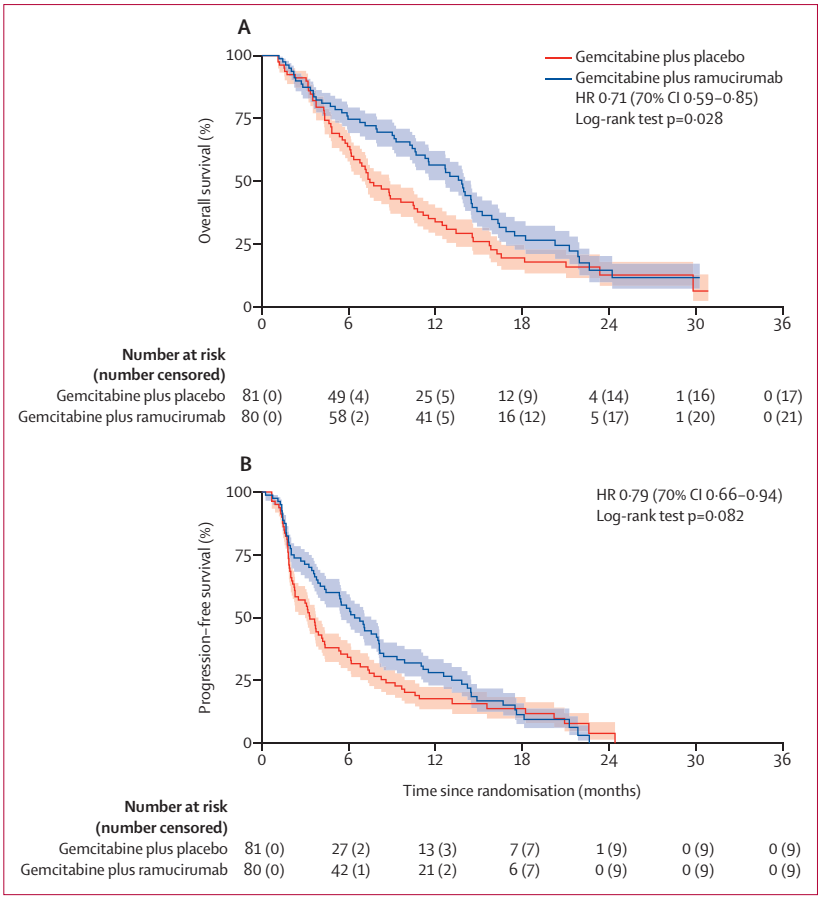

Figure 2: **Overall survival (A) and progression-free survival (B)**
Shaded areas represent 70% CIs. HR=hazard ratio.

Grade 3–4 treatment-related adverse events were reported in 35 (44%) of 80 patients treated in the gemcitabine plus ramucirumab group and 24 (30%) of 81 treated in the gemcitabine plus placebo group. The most common treatment-related grade 3–4 adverse events were neutropenia (16 [20%] of 80 patients in the gemcitabine plus ramucirumab group *vs* ten [12%] of 81 patients in the gemcitabine plus placebo group), hypertension (five [6%] *vs* none), and fatigue (four [5%] *vs* three [4%]; table 3). Treatment-related serious adverse events were reported in five (6%) of 80 patients in the gemcitabine plus ramucirumab group and in four (5%) of 81 patients in the gemcitabine plus placebo group. Thromboembolism was seen in three (4%) of 80 patients in the gemcitabine plus ramucirumab group versus two (2%) of 81 patients in the gemcitabine plus placebo group; aspartate or alanine aminotransferase increase and fatigue were seen each in one (1%) of 80 patients in the gemcitabine plus ramucirumab group, and anaemia and non-specific increase of cardiac enzymes were reported each in one (1%) of 81 patients in the gemcitabine plus placebo group. No severe (grade 3–4)bleeding or haemorrhage events were reported in either treatment group. There

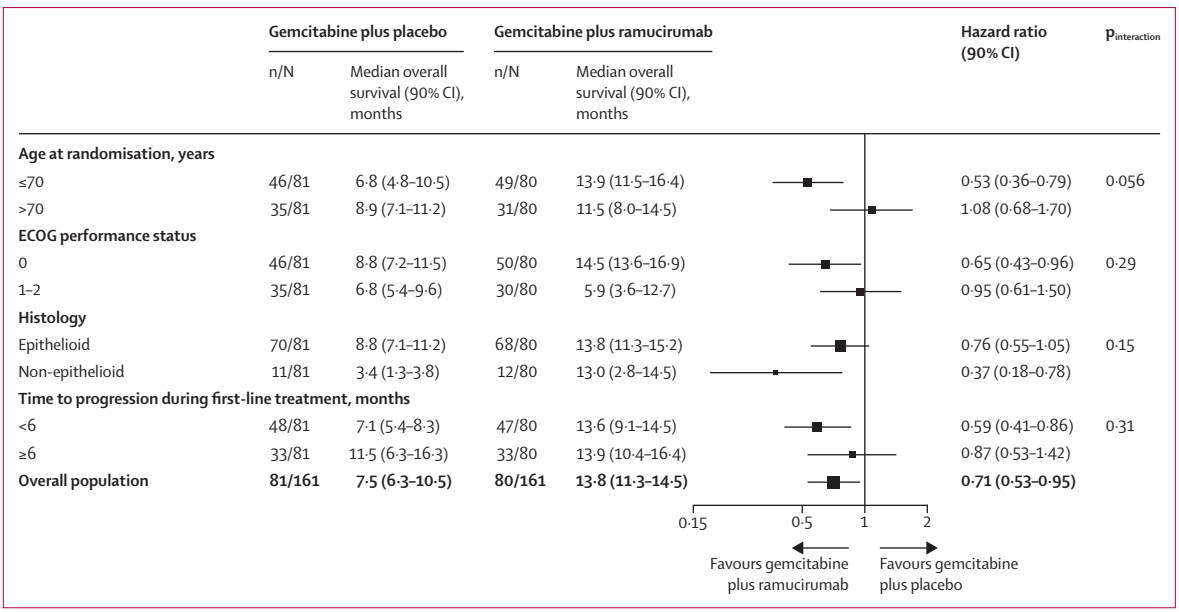

Figure 3: **Overall survival in predefined patient subgroups**
ECOG=Eastern Cooperative Oncology Group.

	Gemcitabine plus ramucirumab (n=80)	Gemcitabine plus placebo (n=81)
Overall response rate	5 (6%; 2–14)*	8 (10%; 4–19)*
Complete response	0	0
Partial response	5 (6%)	8 (10%)
Stable disease	53 (66%)	34 (42%)
Disease control rate	58 (73%; 66–78)†	42 (52%; 46–58)†
Progressive disease	15 (19%)	30 (37%)
Not evaluated	7 (9%)	9 (11%)
Median duration of response, months	8·4 (4·2–11·5)†	5·4 (2·1–17·0)†

Data are n (%; 95% CI or 70% CI) or n (%) in the modified intention-to-treat population (ie, all patients who had been correctly randomised and received their allocated treatment). Patients were grouped according to their randomised treatment assignment. *95% CI. †70% CI.

Table 2: **Tumour response**

were no treatment-related deaths in either study group. All the deaths reported at database lock were the result of disease progression.

Discussion

The RAMES study showed that the addition of ramucirumab to gemcitabine chemotherapy led to an overall survival improvement in patients with pretreated malignant pleural mesothelioma, with a tolerable toxicity profile. The benefit of ramucirumab was independent of histological subtype and outcome of first-line treatment with platinum plus pemetrexed.

Due to the challenges of radiological response assessment in mesothelioma, and according to the recommendation of expert consensus,[23] overall survival was set as the primary endpoint of the RAMES study. The randomised and double-blind design of the trial, and the stratification according to histology, first-line time-to-progression, and ECOG performance status mitigated the possibility of selectively enrolling patients with more indolent disease, a bias that is common in single-group studies in this setting. The addition of ramucirumab to gemcitabine therapy led to an improvement in median overall survival from 7·5 to 13·8 months compared with gemcitabine plus placebo. Moreover, the 6-month and 12-month overall survival rates suggest a long-term benefit, with an increase in 1-year survival in patients treated with gemcitabine plus ramucirumab from 33·9% to 56·5%. The survival advantage was seen in subgroups of patients that usually show poor prognoses, including those with non-epithelioid histology and a time-to-progression of less than 6 months after first-line platinum plus pemetrexed. A similar finding in non-epithelioid patients with the use of antiangiogenic therapy was reported in the phase 3 MAPS trial.[15] A significant benefit with gemcitabine plus ramucirumab was not seen in patients aged 70 years or older nor in patients with ECOG performance status of 1–2. However, these subgroups were small in patient number and the analysis had insufficient statistical power; therefore, results from these subgroup analyses should be interpreted with caution. Disease control rate and progression-free survival were also improved with the combined treatment, despite a low response rate in both groups. This is consistent with the mechanism of action of ramucirumab, which leads to tumour stabilisation rather than regression—as with all antiangiogenics. A few early clinical progressions were seen in both study

groups. No post-study treatment was planned in our trial. Third-line immunotherapy was not available in Italy at the time of the study.

The overall survival gain with the addition of ramucirumab in the RAMES trial was achieved without a marked increase in toxicity. Although all-grade adverse events were reported more frequently in the gemcitabine plus ramucirumab group than in the gemcitabine plus placebo group, grade 3–4 adverse events were similar between the two groups. As expected with a VEGF-targeting agent, higher rates of hypertension and thromboembolic events were reported with ramucirumab; however, these adverse events were generally mild, with only five (6%) of 80 patients reporting a grade 3–4 hypertension and three (4%) of 80 reporting a grade 3–4 thromboembolism.

There is a strong rationale for inhibiting angiogenesis in mesothelioma. Ramucirumab targets the extracellular domain of VEGFR-2 with great affinity; it has, therefore, potential advantages over bevacizumab, which, by targeting VEGF-A, affects VEGFR-1, VEGFR-2, and the non-catalytic coreceptors neuropilin-1 and neuropilin-2. Ramucirumab does not bind to the VEGFR-1 receptor, which might behave like a decoy receptor, providing additional potency to the VEGFR-2 inhibitory effect.[24] In a large retrospective series, VEGFR-2 was strongly expressed on more than 90% of malignant pleural mesothelioma tissue samples.[25] Notably, VEGFR-2 is also expressed on macrophages, which are often abundant in the mesothelioma tumour microenvironment, and are considered responsible for resistance to both chemotherapy and immunotherapy.[26] The VEGFR-2 inhibition in macrophages results in decreased tumour immune infiltration and cytokine and chemokine release, which inhibits tumour growth and proliferation. Indeed, neoangiogenesis and immune suppression are two connected, key hallmarks of the pathogenesis of mesothelioma. Tumour-associated macrophages accumulate in hypoxic regions, and their recruitment and M2 polarisation is promoted by hypoxia-inducible factor-1α.[27] VEGF itself plays a role in cancer immune evasion by reducing lymphocyte adhesion to vessel walls. Vascular-targeting agents can restore an immune-permissive tumour microenvironment by remodelling tumour vasculature, promoting T-cell priming and activation via dendritic cell maturation, and decreasing regulatory T cells and myeloid-derived suppressor cells. Conversely, an increasing number of studies have shown that immunotherapeutic agents might induce changes in the tumour vasculature, thus improving the efficacy of antiangiogenic drugs.[28]

Three other randomised studies in pretreated patients with malignant pleural mesothelioma have been reported, all focusing on the role of immunotherapy: the MAPS-2,[29] the PROMISE-Meso,[11] and the CONFIRM[12] trial. The main patient baseline characteristics of these studies were similar to those in RAMES, except for the higher percentage of participants with an ECOG performance status of 0 in RAMES. This disparity is probably due to RAMES being a purely second-line study, whereas 20–71% of patients were treated in the third or further line of therapy in PROMISE-Meso, MAPS-2, and CONFIRM. Both RAMES and CONFIRM were powered to detect a difference in overall survival between the two groups, whereas the primary endpoints of MAPS-2 and PROMISE-meso were disease control rate at 12 weeks and progression-free survival, respectively. Overall survival with gemcitabine plus ramucirumab in RAMES (13·8 months; 70% CI 12·7–14·4) was longer than that seen in CONFIRM in the nivolumab group (9·2 months; 95% CI 7·5–10·8), but these trials are difficult to compare because patients enrolled in CONFIRM were more heavily pretreated. Median overall survival in the control chemotherapy group of RAMES was shorter than that of the control group of PROMISE-Meso (7·5 *vs* 11·8 months). A potential explanation of this survival difference could be that more than 50% of RAMES patients had a first-line time-to-progression of less than 6 months, which is an established negative prognostic factor for second-line chemotherapy in malignant pleural mesothelioma; these data were not reported for PROMISE-Meso.

Our study had some limitations, mostly due to its phase 2 design, with a relatively small sample size, and low power in subgroup analyses. Moreover, the proportional hazards assumption for progression-free survival was not met, although alternative analyses were done to confirm the secondary endpoint result. Finally, the combination of gemcitabine with ramucirumab was based on a pragmatic choice rather than on previous clinical data.

In summary, the RAMES study showed that the combination of ramucirumab and gemcitabine was an

	Gemcitabine plus ramucirumab (n=80)			Gemcitabine plus placebo (n=81)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Neutropenia	11 (14%)	13 (16%)	3 (4%)	13 (16%)	9 (11%)	1 (1%)
Anaemia	15 (19%)	0	0	21 (26%)	4 (5%)	0
Thrombocytopenia	9 (11%)	2 (3%)	0	7 (9%)	1 (1%)	0
Febrile neutropenia	0	1 (1%)	0	0	0	1 (1%)
Fatigue	43 (54%)	4 (5%)	0	37 (46%)	2 (2%)	1 (1%)
Nausea or vomiting	25 (31%)	1 (1%)	0	13 (16%)	0	0
Hypertension	20 (25%)	5 (6%)	0	4 (5%)	0	0
AST or ALT increase	17 (21%)	2 (3%)	0	4 (5%)	2 (2%)	0
Thromboembolism	10 (13%)	2 (3%)	1 (1%)	5 (6%)	2 (2%)	0
Diarrhoea	11 (14%)	0	0	5 (6%)	0	0
Bleeding	8 (10%)	0	0	0	0	0
Proteinuria	6 (8%)	1 (1%)	0	1 (1%)	1 (1%)	0
Mucositis	13 (16%)	0	0	9 (11%)	0	0
Skin	3 (4%)	0	0	10 (12%)	0	0

Data are n (%). Safety was assessed in all patients who received at least one dose of their assigned study intervention. Grade 1–2 adverse events with an incidence of at least 10% and all grade 3 and 4 adverse events were reported. No grade 5 toxicity occurred. AST=aspartate aminotransferase. ALT=alanine aminotransferase.

Table 3: **Drug-related adverse events**

efficacious and safe regimen in patients with malignant pleural mesothelioma who progressed after standard first-line chemotherapy, and could, therefore, be a new treatment option in this setting. Moreover, the results of the Checkmate 743 study, and of other ongoing trials assessing the addition of chemotherapy and anti-angiogenics to immune checkpoint inhibitors in the first-line setting, will probably change the therapeutic algorithm of unresectable malignant pleural mesothelioma in the near future.[30] In this new scenario, the combination of gemcitabine plus ramucirumab warrants exploration in a further prospective phase 3 trial stratified according to patient clinical and pathological features and previous treatments, including immune checkpoint inhibitors and antiangiogenics.

Contributors

All authors were involved in data collection, and reviewed the radiological data at their respective site. CP and LB accessed and verified all the data. All authors had full access to all the study data, were responsible for the decision to submit for publication, contributed to the writing of the manuscript, and reviewed and approved the final draft. The corresponding author had final responsibility for the decision to submit for publication. All authors had full access to all the study data and took final responsibility to submit for publication.

Declaration of interests

CP reports advisory and speaker fees and travel and accommodation expenses from Amgen, Astellas, AstraZeneca, Bayer, Bristol Myers Squibb, Celgene, Clovis Oncology, Eisai, Ipsen, Janssen, Incyte, Merck-Serono, Merck Sharp and Dohme, Novartis, Roche, Sandoz, Sanofi, and Servier. PAZ reports advisory and speaker fees and travel and accommodation expenses from Merck Sharp and Dohme, Astellas, Janssen, Sanofi, Ipsen, Pfizer, Novartis, Bristol Myers Squibb, Amgen, AstraZeneca, Roche, and Bayer. FGrosso reports consultancy and speaker fees and travel and accommodation expenses from Merck Sharp and Dohme, Novocure, Bristol Myers Squibb, Boehringer Ingelheim, PharmaMar, and Novartis. GP reports advisory and speaker fees from AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Merck Sharp and Dohme, Roche, and Eli Lilly. MCG reports consultancy and advisory fees from AstraZeneca, Merck Sharp and Dohme, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Eli Lilly, Incyte, Inivata, Novartis, Pfizer, Roche, Takeda, Seattle Genetics, Mirati Threapeutics, Daiichi Sankyo, Bayer, GlaxoSmithKline, Sanofi-Aventis, Spectrum Pharmaceuticals, Blueprint Medicine, Janssen, Regeneron Pharmaceuticals; speaker fees from AstraZeneca, Merck Sharp and Dohme, and Takeda; travel and accommodation expenses from Roche; and a leadership or fiduciary role in European Society for Medical Oncology, American Society of Clinical Oncology, American Association for Cancer Research, Women for Oncology, and Italian collaborative group for thymic malignansies. MT reports advisory fees from AstraZeneca, Boehringer Ingelheim, Novartis, Roche, Takeda, and Eli Lilly; speaker fees from AstraZeneca, Boehringer Ingelheim, and Merck Sharp and Dohme; and research grants from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche. HSP reports advisory and speaker fees and travel and accommodation expenses from Amgen, AstraZeneca, Bristol Myers Squibb, Merck Sharp and Dohme, Novartis, Roche, Pfizer, and Sanofi. FGrossi reports advisory fees from AstraZeneca, Bristol Myers Squibb, Eli Lilly, Merck Sharp and Dohme, and Roche; speaker fees from Bristol Myers Squibb, AstraZeneca, Eli Lilly, Merck Sharp and Dohme, Roche, Amgen, Boehringer Ingelheim, Pierre Fabre, Pfizer, Takeda, Bayer, and Sotio; and a grant from Bristol Myers Squibb to their institution. FC reports speaker fees from Bristol Myers Squibb and advisory fees from Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, Mirati, Merck Sharp and Dohme, PharmaMar, Pfizer, and Roche. FdM reports advisory and speaker fees and travel and accommodation expenses from Merck Sharp and Dohme, Bristol Myers Squibb, Boehringer Ingelheim, Novartis, AstraZeneca, and Roche. AS reports consultancy fees from Arqule and Sanofi; speaker fees from Takeda, Bristol Myers Squibb, Roche, AbbVie, Amgen, Celgene, Servier, Gilead, AstraZeneca, Pfizer, Arqule, Eli Lilly, Sandoz, Eisai, Novartis, Bayer, and Merck Sharp and Dohme; and advisory fees from Bristol Myers Squibb, Servier, Gilead, Pfizer, Eisai, Bayer, and Merck Sharp and Dohme. GLC reports advisory speaker fees from Merck Sharp and Dohme, Astellas, and Novocure, and travel and accommodation expenses from Merck Sharp and Dohme, Astellas, and Novocure. All other authors declare no competing interests.

Data sharing

The study protocol is available in appendix 2. Individual data underlying the results reported in this article will be available after updating the survival data with correlation to the results of the translational studies, which are still in progress. Requests for patient-level data for qualified research projects should be addressed to info@goirc.org. Full details are given in appendix 2 (p 3).

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