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

Gemcitabine with or without ramucirumab as second-line treatment for malignant pleural mesothelioma. A randomised, double-blind, placebo-controlled phase 2 trial RAMES Study

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SUMMARY

Background There is a preclinical rationale for inhibiting angiogenesis in mesothelioma. The aim of the RAMES trial was to assess efficacy and safety of the anti-vascular endothelial growth factor receptor-2 antibody ramucirumab combined with gemcitabine in patients with pre-treated malignant pleural mesothelioma.

Methods RAMES was a multicentre randomised, double-blind, placebo-controlled phase 2 trial done at 26 Italian sites. Eligible patients were aged 18 years or older, had an Eastern Cooperative Oncology Group performance status 0-2, and histologically proven malignant pleural mesothelioma progressing during or after first-line pemetrexed plus platinum. Patients were randomised (1:1) to receive intravenous gemcitabine 1000 mg/m^2 on days 1,8 every 3 weeks plus intravenous placebo (arm A) or ramucirumab 10 mg/kg (arm B) on day 1 every 3 weeks, until tumour progression or unacceptable toxicity. The primary endpoint was overall survival. This trial is registered with ClinicalTrials.gov, NCT03560973.

Findings Between December 22, 2016 and July 30, 2018, 161 patients were enrolled and assigned to arm A (n=81) or arm B (n=80). With a median follow-up of 21·9 months (IQR 17 ·7-28·5), overall survival was significantly prolonged in the ramucirumab arm versus the control arm (HR 0·71; 70% CI 0·59-0·85; p=0·028). Median overall survival was 13·8 (70% CI 12·7-14·4) versus 7·5 months (70% CI 6·9-8·9); 6- and 12-month overall survival rates were 74·7% versus 63·9%, and 56·5% versus 33·9%, respectively. The frequency of adverse events was similar across the two treatment groups;

specific ramucirumab-related toxicities, including hypertension, haemorrhages, proteinuria and thromboembolic events, were uncommon and grade 1-2 in most patients.

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

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RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed for studies published from January 1, 2005, to January 31, 2021, assessing treatment options in patients with malignant pleural mesothelioma progressing to standard chemotherapy 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.

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, but responses are rarely observed, and there is no demonstrated survival advantage with these agents. Despite the encouraging results of a few phase II studies with immune checkpoint inhibitors, the phase 3 randomized PROMISE-meso trial failed to show any survival improvement with pembrolizumab versus single-agent chemotherapy (gemcitabine or vinorelbine) in relapsed mesothelioma patients with progression after or during previous platinum-based chemotherapy. On the contrary, the recently reported phase 3 randomized CONFIRM study has shown a statistically significant improvement of both progression-free and overall survival with nivolumab versus placebo in pre-treated patients.

Several preclinical studies have suggested that targeting angiogenesis could be an effective approach in mesothelioma, since its cells produce high amounts of vascular endothelial growth factor (VEGF) A and C and express VEGF receptors 1 and 2, with VEGF acting as an autocrine growth factor. Despite this, many clinical trials testing vascular targeting agents including nintedanib, cediranib and other tyrosine kinase inhibitors have failed to show a clinically meaningful advantage in any line of treatment of malignant pleural mesothelioma. In the phase 3 randomised MAPS trial, the addition of bevacizumab to standard chemotherapy in untreated patients increased median survival by nearly two months, with a higher incidence of severe adverse events. In the second-line setting the vascular-targeting agent NGR-hTNF showed no improvement in overall survival when added to single-agent chemotherapy in a randomized, double-blind, placebo-controlled phase 3 trial.

Ramucirumab is a fully humanized monoclonal antibody selectively targeting VEGFR-2, which is highly expressed on mesothelioma cells and on macrophages, with further potential on the inhibition of tumour growth and proliferation. Previous studies have demonstrated an additive effect of ramucirumab in combination with several chemotherapeutic agents. Based on this background, the RAMES study was designed as a phase 2, randomised, double-blind placebo-controlled study of gemcitabine plus ramucirumab in patients with malignant pleural mesothelioma progressing after standard platinum plus pemetrexed chemotherapy.

Added value of this study

The RAMES study showed a clinically meaningful improvement of overall survival in the gemcitabine plus ramucirumab arm, with a median value in the intention-to-treat population

prolonged by more than 6 months as compared to the gemcitabine plus placebo control arm (from 7·5 to 13·8 months). One-year overall survival rate was increased from 33·9% (70% CI 28·3%-39·5%) to 56·5% (70% CI 50·4%-62·1%). The survival advantage was observed in the ramucirumab arm regardless histological subtype and time to tumour progression after first-line treatment. The study data showed that the combination of gemcitabine with ramucirumab can induce a high rate of disease control, despite a response rate comparable to gemcitabine alone, consistently with the mechanism of action of anti-angiogenic drugs. Notably, these results were achieved in a study with a double-blind, placebo-controlled randomised design, having overall survival as the primary endpoint. Furthermore, 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.

Implications of all the available evidence

There is a substantial unmet need for new therapies in pre-treated malignant pleural mesothelioma. The results of the RAMES study demonstrate that the addition of ramucirumab to gemcitabine can provide a notable improvement in overall survival versus single-agent gemcitabine. The combination of ramucirumab and gemcitabine represents a novel, well-tolerated and active treatment option in patients with malignant pleural mesothelioma progressing on first-line chemotherapy with pemetrexed and platinum.

INTRODUCTION

Malignant pleural mesothelioma is a rare tumour with increasing incidence and dismal prognosis. Few patients are candidates for multimodal therapy including radical surgery, and most receive medical therapy only. Platinum and pemetrexed chemotherapy has been the standard of care for unresectable disease since 2004[1]. Recently, in the CheckMate 743 trial[2], the combination of nivolumab and ipilimumab as first-line treatment showed a significant survival benefit versus standard chemotherapy. Although the understanding 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 newest compounds such as trabectedin[6] and lurbinectedin[7] have shown limited activity. An increasing interest has been reserved to targeted therapies, but until now several compounds against intriguing targets demonstrated poor anticancer effect[8]. Indeed, two large placebo-controlled phase III trials failed to show any survival improvement with vorinostat[9] and NGR-hTNF[10]. Preliminary uncontrolled trials of immune checkpoint inhibitors suggested encouraging activity, however a randomized phase 3 study of pembrolizumab versus vinorelbine or gemcitabine showed no survival improvement[11]. On the contrary, the recently reported phase 3 placebo-controlled CONFIRM study has demonstrated a statistically significant improvement of both progression-free and overall survival with nivolumab in a heavily pre-treated population[12].

The key role of angiogenesis in the pathogenesis of mesothelioma has been demonstrated in several preclinical and translational studies. The vascular endothelial growth factor (VEGF) and its receptors (VEGFRs) are overexpressed in serum and tumour tissues of patients with mesothelioma, and higher levels are associated with poorer prognosis[13,14]. A wide range of VEGFR tyrosine kinase inhibitors and monoclonal antibodies against VEGF has been studied in both untreated and pre-treated patients[15]. In the first-line setting the addition of bevacizumab to cisplatin and pemetrexed in the phase 3 MAPS trial was associated with an improvement of progression-free and overall survival of nearly 2 months, at the cost of an increased incidence of severe adverse events[16]. On the contrary, no survival improvement was observed with the addition of nintedanib in the LUME-Meso trial[17]. Several single-arm studies of VEGFR inhibitors in pre-treated patients have shown disappointing results, as well as maintenance treatment with thalidomide after first-line chemotherapy[18].

Ramucirumab (IMC-1121B, LY3009806) is a fully humanized monoclonal antibody selectively directed against the extracellular domain of VEGFR-2, inhibiting the receptor with a much greater affinity than its natural ligands[19]. As a single drug or in combination with different chemotherapy agents, ramucirumab has been previously approved for second-line therapy of gastric adenocarcinoma, colorectal cancer, non-small cell lung cancer and hepatocellular carcinoma. Overall, ramucirumab showed a largely manageable toxicity profile across all studies[20].

Based on this background, the RAMES trial was aimed at assessing the efficacy and safety of the combination of gemcitabine and ramucirumab as second-line treatment in patients with advanced malignant pleural mesothelioma who had failed a pemetrexed plus platinum regimen.

METHODS

Study design and participants

RAMES (RAmucirumab MESothelioma treatment, ClinicalTrials.gov NCT03560973, EudraCT Number 2016-001132-36) was a multicentre, double-blind, placebo-controlled randomised phase II trial exploring the efficacy and safety of the addition of ramucirumab to gemcitabine as second-line treatment in patients with advanced malignant pleural mesothelioma (Figure 1). The study was conducted at 26 Italian sites, after approval by the Italian regulatory agency (AIFA) and Ethics Committees at each participating centre. Recommendations of the International Council for Harmonization - Good Clinical Practice guideline for clinical trial and of the Declaration of Helsinki were followed. Written informed consent was obtained from each patient before entering the study.

Patients were eligible for inclusion if they had a histologically confirmed diagnosis of malignant pleural mesothelioma, and documented disease progression during or after first line chemotherapy with pemetrexed plus a platinum compound, either cisplatin or carboplatin. The presence of measurable and/or evaluable lesions according to Response Evaluation Criteria in Solid Tumours (RECIST) criteria version 1.1 was mandatory[21]. Eligibility criteria included age of at least 18 years and Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. An adequate bone marrow reserve was required, with absolute neutrophil count $\geqslant 1.5 \times 10^9$ cells per L, platelets $\geqslant 100 \times 10^9$ cells per L and haemoglobin $\geqslant 9$ g /dL. Creatinine clearance, calculated by

the Cockroft and Gault formula, had to be ⩾50 mL/min, bilirubin ⩽1.5-fold the upper limit of normal (ULN), and alanine aminotransferase and aspartate aminotransferase ⩽2.5-fold ULN. A baseline urine dipstick with proteinuria <2+ was required; patients discovered to have ⩾2+ proteinuria had to undergo a 24-hour urine collection and demonstrate ⩽1 g of protein per 24 hours. Patients with uncontrolled hypertension, serious non-healing wound or ulcer, evidence of bleeding diathesis or coagulopathy, or major surgical procedure, open biopsy, or significant traumatic injury within 28 days before study treatment start were not eligible for the trial. Patients were also excluded if they were currently on treatment with anti-coagulants, high-dose aspirin (>325 mg/day) or other medications known to predispose to gastrointestinal ulceration.

Randomisation and masking

This was a multicentre, double-blind, placebo-controlled randomized phase 2 trial, in which patients were assigned in a 1:1 ratio to receive intravenous gemcitabine in combination with placebo (arm A) or with intravenous ramucirumab (arm B). Randomisation was done by a centralized web-based procedure, with a minimization algorithm using the following stratification factors: ECOG performance status (0-1 versus 2), age (≤ 70 versus > 70 years), histology (epithelioid versus non-epithelioid) and first-line time to progression (<6 versus ≥6 months). The random allocation sequence was generated at the Clinical Trials Coordinating Center, Istituto Toscano Tumori (Florence, Italy).

Procedures

Patients were randomised to receive intravenous gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 weeks, combined with 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 occurred. Dose adjustments at the start of a subsequent cycle of therapy were based on haematological and non-haematological toxicity observed during the preceding course, according to protocol-specified guidelines.

Baseline assessment included a complete medical history and physical examination, complete blood cell counts and chemistries, and creatinine clearance. A chest and abdomen CT scan was performed at baseline and repeated every 8 weeks until the end of treatment. Radiological response was evaluated according to RECIST criteria version 1.1[21]. Treatment toxicity was evaluated according to the version 4.0 of the National Cancer Institute's Common Toxicity Criteria (NCI-CTCAE). After completion of the study treatment, patients were evaluated every 3 months with chest and abdomen CT scans and followed up for survival until death or last contact if still alive.

Diagnostic tumour tissue samples were retrieved for each patient for molecular profile analysis[22], and a blood sample was obtained for cell-free DNA evaluation before chemotherapy start, after the first radiological re-evaluation (after 3 therapy cycles), and at the end of treatment. We assessed Quality of life by the European Organization for Research and Treatment of Cancer (EORTC) questionnaire C30 (QLQ-C30) at baseline and at day 1 of each treatment cycle.

Outcomes

The primary endpoint of the trial was overall survival, measured from the date of randomisation to the date of death for any cause. Observation time of patients alive or lost to follow-up at the end

of the study was censored at the day of the last study visit. Secondary endpoints included progression-free survival (defined as the time from randomisation to disease progression or death, whichever occurred first), objective response rate, disease control rate, safety, quality of life, and predictive biomarkers. The objective response rate was calculated as the number of randomised patients achieving complete or partial response, divided by the total number of patients included in the intention-to-treat population. The disease control rate was defined as the number of randomised patients achieving a best overall response of complete response, partial response or stable disease, divided by the total number of patients included in the intention-to-treat population. Patients without a tumour response assessment for any reason were considered as non-responders and were included in the denominator when calculating the response rate.

Statistical analysis

We planned to enrol 156 patients in order 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 was stated assuming a cumulative proportion of overall survival equal to 40% at one year in arm A, and an absolute 12% improvement at one year in arm B. All efficacy analyses were performed on a modified intention-to-treat basis. The median period of follow-up was calculated for the entire study cohort according to the reverse Kaplan–Meier method. Distributions of time-to-event variables were estimated with the use of the Kaplan–Meier product-limit method. The unstratified log-rank test was used as the primary analysis for comparison of treatment groups. Cox proportional-hazards modelling was also performed as supportive analyses. All statistical tests were one-sided, and P values of 0·15 or less were considered to indicate statistical significance. Subgroup analyses of

overall survival were performed by means of a two-sided interaction test with a significance level equal to 0·15 to determine the consistency of the treatment effect according to key baseline characteristics. Crude estimates of the hazard ratios (HRs) and associated two-sided 70% or 85% confidence intervals (CIs) were presented. Progression-free survival was analysed with the same statistical techniques described for the primary efficacy variable. The objective response rate, the disease control rate, and the incidence of adverse events in the two groups were compared with the use of the chi-square test for heterogeneity or the Fisher's exact test when appropriate. The safety analyses were done in all patients who received at least one day of study treatment. No adjustment for multiple comparisons was made. SAS System 9.2 was used as the analytical tool.

RESULTS

Between December 22, 2016 and July 30, 2018, 165 patients were randomly assigned to study treatment (gemcitabine plus placebo, arm A: n= 83; gemcitabine plus ramucirumab, arm B: n=82). Four patients were excluded from the analysis: two patients assigned to arm A, who received no treatment, and two patients assigned to arm B (one patient randomised twice by mistake, and one patient who withdrew consent immediately after randomisation). All the remaining 161 patients were included in the analysis (81 in arm A, 80 in arm B).

Baseline demographic and clinical characteristics of patients were well balanced across the two treatment groups (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 ≥6 months. At March 8, 2020, database lock, 5 (6%) patients in arm A and 6 (8%) patients in arm B

were still on treatment. The median number of gemcitabine/placebo and gemcitabine/ramucirumab cycles was 3·5 (range 1-31) and 7·5 (range 1-28), respectively. The main reasons for treatment discontinuation were radiological disease progression in 45 (55·5%) patients in arm A and in 39 (48·7%) in arm B, and worsening of clinical condition in 14 (17·2%) patients in arm A and in 11 (13·7%) in arm B. Discontinuations attributed to study drug toxicity were 0 in arm A and 1 (1·25%) in arm B.

The median follow-up was 21.9 months (IQR 17·7-28·5). Median OS was 7.5 months (70% CI 6·9-8·9) in arm A and 13.8 months (70% CI 12·7-14·4) in arm B (HR 0·71; 70 % CI 0·59-0·85; p=0·028). Overall survival rates at 6- and 12-months were 63·9% (70% CI 57·9%-69·2%) and 33·9% (70% CI 28·3%-39·5%) in arm A and 74·7% and 56·5% in arm B, respectively (Figure 2). Pre-specified subgroup analyses of overall survival data according to randomisation strata are shown in Figure 3. The progression-free survival curves are depicted in Figure 4. Median progression-free survival was 3.3 months (70% CI 2·5-3·7) in arm A and 6.2 months (70% CI 5·5-7·6) in arm B (HR 0·79; 70% CI 0·66-0·95; un-stratified log-rank test p=0·085).

The objective response rates according to RECIST version 1.1 criteria are reported in Table 2. No complete response was observed, partial response was seen in 8 (9·9%) and 5 (6·3%) patients and stable disease in 34 (42·0%) and 53 (66·3%) patients in arm A and B, respectively. Disease control rate was therefore achieved in 42 (51·9%) patients in arm A (70% CI 45·5%-58·2%) and in 58 (72·5%) in arm B (70% CI 66·4%-77·9%). Disease progression during treatment was observed in 30 patients (37·0%) in arm A and in 15 (18·8%) in arm B. The median duration of response was 5.4 months (70% CI 2·1-17·0) in gemcitabine/placebo group and 8.4 months (70% CI 4·2-11·5) in

gemcitabine/ramucirumab group. The safety results are summarized in Table 3. Grade 3-4 anaemia was reported in 4 (4·9%) patients in gemcitabine/placebo group whereas no cases were reported with gemcitabine/ramucirumab. Grade 3-4 neutropenia and thrombocytopenia were both reported in one patient (1·2%) in arm A versus 3 (3·7%) and 2 (2·5%) in arm B, respectively. One case (1·2%) of febrile neutropenia was reported in arm A and none in arm B**.** Non-haematological toxicity was comparable between the two treatment groups. Particularly, incidence of serious adverse events commonly associated with anti-angiogenic agents was similar across the two arms. Grade 3-4 thromboembolism was observed in 2 (2·4%) patients treated with gemcitabine/placebo and in 3 (3·7%) in those treated with gemcitabine/ramucirumab (p=0·64). Grade 3-4 hypertension was observed in no patients in arm A versus 5 (6·2%) patients in arm B (p=0·02). No severe bleeding events were reported in both treatment arms. No treatment-related deaths were observed in the two study groups. Analyses of biomarkers and Quality of life data are ongoing and are not reported here.

DISCUSSION

The RAMES study showed a clinically meaningful survival improvement in patients with pre-treated malignant pleural mesothelioma with the addition of ramucirumab to gemcitabine chemotherapy, with a tolerable toxicity profile. The benefit of ramucirumab was observed independently of histological subtype and outcome of first-line treatment with platinum/pemetrexed.

Due to the challenges of radiological response assessment in mesothelioma, and according to the recommendation of a recent expert consensus[23], overall survival was set as the primary endpoint of the study. The randomized and blinded design of the trial, and the stratification according to histology, first-line time to progression and ECOG performance status allowed excluding a selection of patients with a more indolent disease, a bias frequently observed in single arm studies in this setting. The addition of ramucirumab to single agent gemcitabine led to an improvement in median overall survival of more than 6 months, from 7·5 to 13·8 months (Figure 2). Moreover, the 6- and 12-month overall survival rates suggest a long-term benefit, with an increase in 1-year survival in patients treated with ramucirumab and gemcitabine larger than 20%, from 33·9 to 56·5%. The survival advantage was observed even in subgroups of patients usually showing poorer prognosis, including those with non-epithelioid histology and shorter time to progression after first-line platinum/pemetrexed (Figure 3). Disease control rate (71·6% versus 52·5%) and progression-free survival (6·2 versus 3·3 months) were also improved with the combined treatment, despite a similar response rate. This is consistent with the mechanism of action of ramucirumab, which as all the anti-angiogenics leads to tumour stabilization rather than regression.

The overall survival gain with the addition of ramucirumab in the RAMES trial was achieved without a remarkable increase in toxicity. As expected with a VEGF-targeting agent, higher rates of hypertension and thromboembolic events were reported with ramucirumab (Table 3); however, these extra toxicities were generally mild, with only 5 (6·1%) patients experiencing a grade 3-4 hypertension and 3 (3·7%) 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 impacts VEGFR-1, VEGFR-2 and the non-catalytic co-receptors neuropilin-1 and -2. Ramucirumab leaves the VEGFR-1 receptor alone, which may 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]. Interestingly, VEGFR-2 is also expressed on macrophages, which are often abundant in mesothelioma tumour microenvironment, and are considered responsible for resistance to both chemotherapy and immunotherapy[26]. Indeed, neo-angiogenesis and immune suppression are two strictly connected key hallmarks of the pathogenesis of mesothelioma. Tumour-associated macrophages accumulate in hypoxic regions, and their recruitment and M2 polarization is promoted by hypoxia-inducible factor (HIF)-1alpha[27]. VEGF itself plays a role in cancer immune evasion by reducing lymphocyte adhesion to vessel walls. Vascular-targeting agents may restore an immune-permissive tumour microenvironment remodelling tumour vasculature, promoting T-cells priming and activation via dendritic cell maturation, and decreasing regulatory T-cells and myeloid-derived suppressor cells. On the other hand, an increasing number of studies indicate that immunotherapeutic agents might induce changes in the tumour vasculature thus improving the efficacy of anti-angiogenic drugs[28].

Three other randomized studies in pre-treated malignant pleural mesothelioma have been recently 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 consistent with those of RAMES, except that in MAPS-2 and CONFIRM one third and two thirds,

respectively, of patients were treated in third or further line of therapy. Both RAMES and CONFIRM were powered to detect a difference in overall survival between the two arms whereas the primary endpoints of MAPS-2 and PROMISE-meso were DCR at 12 weeks and PFS, respectively. Overall survival with gemcitabine and ramucirumab in RAMES (13·8 months; 70% CI 12·7-14·4) was longer than that observed in CONFIRM in the nivolumab arm (9·2 months; 95% CI 7·5-10·8), but these trials are difficult to be compared because patients enrolled in CONFIRM were more pre-treated. Interestingly, median overall survival in the control chemotherapy arm of RAMES was shorter as compared to the control arm of PROMISE-Meso (7·5 versus 11·8 months). However, nearly 60% of RAMES patients had a first-line time to progression < 6 months, whereas these data were not reported for PROMISE-Meso, suggesting that the latter study may have included a higher percentage of patients with a longer time to progression on first-line treatment, which is an established positive prognostic factor for second-line chemotherapy in malignant pleural mesothelioma.

In conclusion, in the RAMES study the combination of ramucirumab and gemcitabine is an effective and safe regimen in patients with malignant pleural mesothelioma progressing after standard first-line chemotherapy, and can therefore represent a new treatment option in this setting. The recent results of 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 likely change the therapeutic algorithm of unresectable malignant pleural mesothelioma in the near future[30]. In this new scenario, the treatment with gemcitabine plus ramucirumab after platinum/pemetrexed chemotherapy warrants to be explored in further

prospective trials stratified according to patient clinical and pathological features and previous treatment with immune checkpoint inhibitors and antiangiogenics.

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CONTRIBUTORS

All investigators were involved in data collection, and reviewed the radiological data at their respective site. All authors contributed to the writing of the manuscript, and reviewed and approved the final draft.

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All other authors declare no competing interests.

DATA SHARING

The study protocol and site enrolment data will be available in the appendix of this Article, immediately following publication and with no end date. Individual data underlying the results reported in this Article will not be available.

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