


Bevacizumab plus cisplatin/pemetrexed then bevacizumab alone for unresectable malignant pleural mesothelioma: A Japanese safety study

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Abstract

Aims: Malignant pleural mesothelioma (MPM) is an aggressive malignancy with poor prognosis and limited treatment options. Cisplatin plus pemetrexed is the only approved first-line treatment for patients with unresectable MPM. Recently, promising outcomes were observed with first-line bevacizumab combined with cisplatin/pemetrexed, leading to the recommendation of this regimen as a first-line treatment option for patients with MPM. Bevacizumab plus cisplatin/pemetrexed has been shown to be safe and effective in non-small cell lung cancer, however, there are no efficacy or safety data in Japanese patients with MPM treated with this regimen. We conducted a multicenter study to evaluate tolerability and safety for Japanese patients with chemotherapy-naïve, unresectable MPM.

Methods: Eligible patients ($n = 7$) received bevacizumab plus cisplatin/pemetrexed (up to six cycles), then single-agent bevacizumab until disease progression or onset of unacceptable adverse events (AEs), according to the 3+3 design analogy.

Results: One patient (14.3%) reported an AE (gastric ulcer) meeting tolerability criteria. All patients experienced gastrointestinal disorders, including nausea (grade 1/2 only, $n = 6$, 85.7%) and constipation (grade 1/2 only, $n = 5$, 71.4%). Five patients (71.4%) had grade 3 hypertension. Two patients discontinued treatment due to gastric ulcer ($n = 1$) and proteinuria ($n = 1$). At data cut-off, four patients had stable disease, two had partial response and one had non-complete response/non-progressive disease due to the absence of target lesions.

Conclusions: Bevacizumab plus cisplatin/pemetrexed then bevacizumab was well tolerated in Japanese patients with MPM.

KEYWORDS

bevacizumab, cisplatin, malignant pleural mesothelioma, pemetrexed, safety

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1 | INTRODUCTION

Malignant pleural mesothelioma (MPM) is a rare, aggressive neoplasm with poor prognosis, which originates in the mesothelial cells lining the thoracic cavity.¹ Development of MPM is strongly associated with inhalational exposure to asbestos, and is usually caused by occupational asbestos exposure, but it can also occur from low-level exposure in the general environment.² Despite regulatory action against, and prohibition of the use of asbestos, the number of patients with MPM is increasing substantially in many countries where asbestos has been widely used historically.³ Its incidence is increasing rapidly worldwide, and the annual number of MPM deaths in Japan has risen from 500 in 1995 to 1555 in 2017.⁴ Asia has become the largest consumer of asbestos in the world and is responsible for two-thirds of global use.⁵ China continues to use asbestos and is the top consumer in the world, with an increasing trend of MPM during 2000–2013 and 1659 MPM cases in 2013, but its incidence is low compared with industrialized countries.⁵

Newly diagnosed patients with unresectable disease have a median overall survival (OS) of ~12 months when treated with the standard of care, cisplatin plus pemetrexed.⁶ The combination of cisplatin plus pemetrexed is the only currently approved regimen for unresectable first-line MPM, with approvals gained in 2004 in the USA and European Union, and in 2007 in Japan. Phase II studies demonstrated that pemetrexed in combination with carboplatin might be an alternative regimen with similar treatment outcomes.⁷ There have been no new first-line therapies approved for MPM for more than a decade. Furthermore, there is no US Food and Drug Administration (FDA)-approved or European Medicines Agency (EMA)-approved second-line treatment for MPM. In 2018, anti-programmed death-1 (PD-1) antibody nivolumab was approved in Japan for salvage use. The National Comprehensive Cancer Network (NCCN) guidelines revised their recommendation for nivolumab use with or without ipilimumab from category 2B to 2A, on the basis of recent clinical trial data for subsequent systemic MPM treatment.⁸ In view of the poor prognosis and limited approved therapies, there is an unmet need for new treatment options that further improve outcomes for patients with MPM.

A broad range of therapeutic targets exist in MPM, including angiogenesis, immune checkpoints, mesothelin and chemotherapeutic agents. Vascular endothelial growth factor (VEGF) is known to be a key regulator of MPM because it is an autocrine growth factor of MPM.⁹ Significantly higher serum levels of VEGF have been identified in patients with MPM compared with other tumor types¹⁰ and high VEGF level in serum or pleural effusion is a poor prognostic factor in MPM.^{11,12} Because VEGF signaling is essential for mesothelioma cell physiopathology,⁹ VEGF targeting therapy, such as the recombinant humanized monoclonal antibody bevacizumab, is a rational approach for the treatment of MPM.^{13,14} Preclinical evaluation of the therapeutic efficacy of bevacizumab in combination with pemetrexed against mesothelioma has shown a synergy for the combination, compared with pemetrexed or bevacizumab alone.¹⁵

Bevacizumab, when added to standard chemotherapy, has demonstrated effectiveness in non-small cell lung cancer (NSCLC)¹⁶ and other tumor types such as breast cancer,¹⁷ colorectal cancer¹⁸ and renal cell carcinoma.¹⁹ Bevacizumab has been evaluated as a combination therapy for MPM in randomized phase II and III clinical trials.^{20,21} Prior to the approval of pemetrexed, gemcitabine plus cisplatin was a common treatment regimen for MPM. In a randomized phase II US trial in patients with previously untreated MPM, the addition of bevacizumab to gemcitabine/cisplatin did not improve progression-free survival (PFS) or OS.²⁰ It was postulated that the trial failed to show positive results due to a potential negative interaction between bevacizumab and gemcitabine in preclinical studies.²² Therefore, other chemotherapy backbones with bevacizumab, including cisplatin plus pemetrexed, have been investigated.

The phase III Mesothelioma Avastin Cisplatin Pemetrexed Study (MAPS), which evaluated the addition of bevacizumab to cisplatin/pemetrexed followed by bevacizumab maintenance, was the first trial to demonstrate improved outcomes versus the standard of care.²¹ In MAPS, the addition of bevacizumab to cisplatin/pemetrexed significantly improved PFS and OS compared with cisplatin/pemetrexed alone (OS = 18.8 months vs 16.1 months; hazard ratio [HR] = 0.77; $P = 0.0167$; PFS = 9.2 months vs 7.3 months, HR = 0.61, $P < 0.0001$). Additionally, adverse events (AEs) reported in MAPS were consistent with the known safety profile of bevacizumab plus chemotherapy. Based on these outcomes,²¹ bevacizumab in combination with cisplatin/pemetrexed was included as a category 1 recommended first-line treatment for unresectable MPM in the NCCN guidelines.⁸ Although MAPS was conducted by the French Cooperative Thoracic Intergroup and data were from French patients only, the results confirm that first-line bevacizumab-based therapy can improve outcomes for patients with newly diagnosed MPM. Bevacizumab plus cisplatin/pemetrexed has been shown to be safe and effective in Japanese patients with NSCLC; however, there are no data showing tolerability and safety in Japanese patients with MPM treated with this triplet regimen. This article reports results from a single-arm, multicenter study evaluating the tolerability, safety and efficacy of first-line bevacizumab together with cisplatin/pemetrexed, followed by single-agent bevacizumab, in Japanese patients with unresectable MPM.

2 | PATIENTS AND METHODS

2.1 | Study design

JO39183 (JapicCTI-163294) was a multicenter, open-label, single-arm, phase II study evaluating the tolerability, safety and efficacy of bevacizumab combined with cisplatin/pemetrexed followed by single-agent bevacizumab in patients with unresectable MPM who had not previously received chemotherapy (Figure 1). The replacement of cisplatin by carboplatin was allowed in cases where a patient developed nephrotoxicity (creatinine clearance <45 mL/min, 6 weeks after administration) or ototoxicity. The target sample size for the study was six

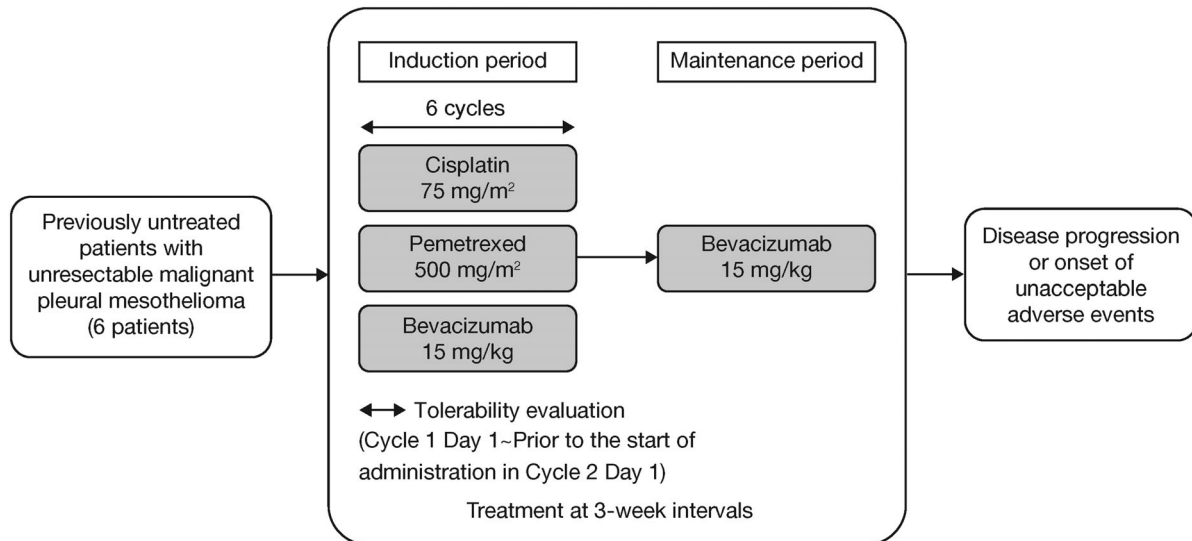


FIGURE 1 Study design

patients, which is determined as an analogy for 3+3 design, according to the methods of official recommendation issued by the Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, Japan.²³ However, it was permissible to enroll more than six patients because the main purpose of the study was to evaluate tolerability and safety in Japanese patients. Following enrollment, each patient received up to six cycles of bevacizumab, cisplatin and pemetrexed (induction period), with cycles repeated every 3 weeks. Patients then continued to receive bevacizumab monotherapy every 3 weeks during the maintenance period until disease progression or the onset of unacceptable AEs.

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice. All appropriate ethical approval was received from Institutional Review Boards or Independent Ethics Committees at each of the sites. All patients provided written informed consent prior to any study-related procedures, and agreed to their individual data being published.

2.2 | Eligibility criteria

Key inclusion criteria for patients included: age ≥ 20 years with histologically confirmed pleural mesothelioma, not considered amendable to resection; an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2; life expectancy of ≥ 12 weeks from the time of enrollment; no previous chemotherapy for MPM (including adjuvant and neoadjuvant therapy); and radiographically evident lesions. Patients with central nervous system metastases were excluded. Further exclusion criteria are detailed in the Supporting Information.

2.3 | Treatment

Patients received combination therapy with bevacizumab, cisplatin and pemetrexed, administered for up to six cycles with cycles being repeated every 3 weeks in the induction period. Pemetrexed

500 mg/m² was administered intravenously (IV) over 10 min, then 30 min later cisplatin 75 mg/m² IV was administered over 2 h. Following the cisplatin infusion, bevacizumab 15 mg/kg IV was administered over 30–90 min. If carboplatin was used in place of cisplatin, it was administered at a dose at which the target area under the curve was 5 mg/mL/min (as calculated based on the Calvert formula) over 30–60 min on Day 1 of each cycle. Following six cycles of the combination, bevacizumab 15 mg/kg was administered every 3 weeks in the maintenance period until disease progression or the onset of unacceptable AEs. The combination therapy could be discontinued before completion of six cycles; in this case, patients continued on bevacizumab monotherapy.

The study duration for each patient was from the day of consent to the last observation day (observation or assessment day that was 28 ± 7 days after the last dose of study drug).

2.4 | Study endpoints

The primary purpose was to evaluate the tolerability of bevacizumab combined with cisplatin/pemetrexed. Secondary purposes were to evaluate the safety and efficacy of bevacizumab combined with cisplatin/pemetrexed followed by single-agent bevacizumab.

2.5 | Study assessments

The evaluation period for tolerability was from Day 1 of Cycle 1 until immediately prior to the start of study drug administration on Day 1 of Cycle 2. AEs predefined for tolerability criteria included grade 4 neutropenia persisting for ≥ 7 days, febrile neutropenia, grade 3/4 reductions in platelet counts and any nonhematologic toxicity with severity of grade 3 or higher (further details are provided in the Supporting Information), occurring during the tolerability evaluation period and for which a causal relationship to the combination therapy could not be ruled out. The study treatment was considered tolerable

TABLE 1 Patient characteristics at baseline

Patient characteristics	Patients (n = 7)
Sex, n (%)	
Male	4 (57.1)
Female	3 (42.9)
Median age (range), years	66 (47–73)
Histology, n (%)	
Epithelioid	6 (85.7)
Sarcomatoid or mixed	1 (14.3)
ECOG PS, n (%)	
0	5 (71.4)
1	2 (28.6)
Smoking status, n (%)	
Smoker	4 (57.1)
Never smoker	3 (42.9)

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

if these AEs were reported in $\leq 34\%$ (two out of six patients) of all enrolled patients considered evaluable for tolerability. The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

An Efficacy and Safety Evaluation Committee decided whether to continue the study and/or to amend the protocol if any AEs meeting the tolerability criteria were reported in three patients during the study period. If the occurrence of AEs meeting the criteria was estimated to be in $\leq 34\%$ of the target number of patients (e.g. corresponding AEs were not reported in the first four patients, excluding patients who were considered nonevaluable for tolerability), the Efficacy and Safety Evaluation Committee had the option of closing enrollment.

Safety was assessed using data collected until the point at which the observation period in Cycle 1 was completed for the last patient. AEs were coded using the Medical Dictionary for Regulatory Activities (version 19.0) and summarized by system organ class and preferred term.

Best overall response and median PFS were assessed in accordance with Response Evaluation Criteria in Solid Tumors version 1.1. PFS was defined as the time from the first day of study drug administration to the first documented disease progression or death, whichever occurred first.

3 | RESULTS

3.1 | Patient population

Seven patients, from four centers, were enrolled into the study and all received bevacizumab combination therapy. After four cycles of treatment with bevacizumab, cisplatin and pemetrexed, one patient changed from cisplatin to carboplatin due to reduced kidney function. Baseline patient characteristics are shown in Table 1. Patients had a median age of 66 years (range 47–73) and 57.1% were male. Although

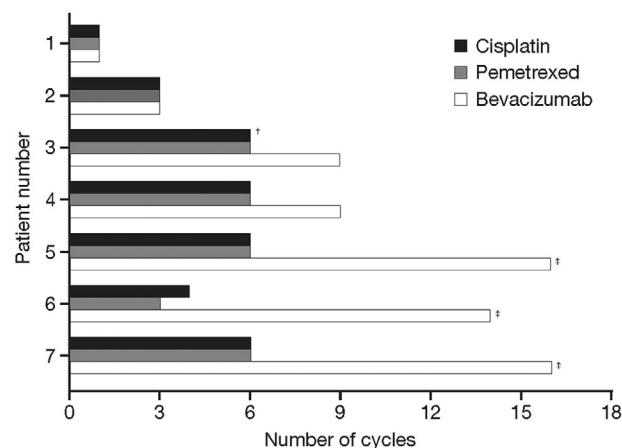


FIGURE 2 Treatment exposure. †, Cisplatin was replaced with carboplatin for Cycles 5 and 6. ‡, Ongoing

patients with an ECOG PS of 0–2 were eligible, all patients had an ECOG PS of 0 or 1. The tolerability and safety analysis sets included all seven patients. The data cut-off was September 15, 2016, for tolerability and July 6, 2017, for safety and efficacy.

3.2 | Treatment exposure

A summary of treatment exposure is shown in Figure 2. Overall, a median of nine cycles of bevacizumab were administered, with a median treatment duration of 188 days. Dose intensity was defined as the proportion of actual doses received to planned dose. For pemetrexed and cisplatin, planned dose was defined as the initial dose for six cycles completed without dose delay or dose reduction. For bevacizumab, planned dose was defined as the initial dose for actual cycles completed without dose delay or dose reduction. The mean dose intensities of bevacizumab, pemetrexed and cisplatin were 94%, 72% and 65%, respectively.

At the time of data cut-off (July 6, 2017), four patients had discontinued treatment and three were continuing to receive single-agent bevacizumab. One patient discontinued combination therapy due to a gastric ulcer and another due to proteinuria. The remaining two patients discontinued combination therapy due to disease progression. Three out of seven patients did not complete six cycles of chemotherapy; in addition, one patient received carboplatin instead of cisplatin for Cycles 5 and 6 due to reduced creatinine clearance. In the three patients who did not complete six cycles of chemotherapy, the reasons for chemotherapy discontinuation were gastric ulcer, proteinuria (as mentioned above), systemic rash and dyspnea.

3.3 | Tolerability

During the tolerability evaluation period, one of the seven patients (14.3%) experienced an AE (gastric ulcer), which met the definition criteria for tolerability.

TABLE 2 Treatment-related adverse events ($n = 7$)

	Any grade, n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)
Nausea	6 (85.7)	3 (42.9)	3 (42.9)	0
Hypertension	6 (85.7)	0	1 (14.3)	5 (71.4)
Constipation	4 (57.1)	3 (42.9)	1 (14.3)	0
Edema peripheral	1 (14.3)	1 (14.3)	0	0
Malaise	2 (28.6)	1 (14.3)	1 (14.3)	0
Rash generalized	2 (28.6)	0	2 (28.6)	0
Epistaxis	2 (28.6)	2 (28.6)	0	0
Dysgeusia	2 (28.6)	2 (28.6)	0	0
Headache	1 (14.3)	0	1 (14.3)	0
Hiccups	1 (14.3)	1 (14.3)	0	0
Amylase increased	1 (14.3)	0	0	1 (14.3)
Gastric ulcer	1 (14.3)	0	1 (14.3)	0
Eyelid edema	1 (14.3)	1 (14.3)	0	0
Blood creatinine increased	1 (14.3)	1 (14.3)	0	0
Dyspnea	1 (14.3)	0	1 (14.3)	0
Oropharyngeal pain	1 (14.3)	1 (14.3)	0	0
Stomatitis	1 (14.3)	1 (14.3)	0	0
Neutrophil count decreased	1 (14.3)	0	1 (14.3)	0
Periodontal disease	1 (14.3)	0	1 (14.3)	0
Carpal tunnel syndrome	1 (14.3)	1 (14.3)	0	0
Pigmentation disorder	1 (14.3)	1 (14.3)	0	0
Decreased appetite	1 (14.3)	0	1 (14.3)	0
Creatinine renal clearance decreased	1 (14.3)	0	1 (14.3)	0
Bodyweight increased	1 (14.3)	1 (14.3)	0	0
Proteinuria	1 (14.3)	0	0	1 (14.3)
Injection site pain	1 (14.3)	1 (14.3)	0	0
Flushing	1 (14.3)	1 (14.3)	0	0
Hyponatremia	1 (14.3)	0	0	1 (14.3)
Protein urine present	1 (14.3)	0	1 (14.3)	0
White blood cell count decreased	1 (14.3)	0	1 (14.3)	0
Rash	1 (14.3)	1 (14.3)	0	0
Pyrexia	1 (14.3)	1 (14.3)	0	0
Abdominal distension	1 (14.3)	0	1 (14.3)	0
Peripheral neuropathy	1 (14.3)	1 (14.3)	0	0
Vomiting	1 (14.3)	0	1 (14.3)	0

No grade 4/5 treatment-related adverse events were reported.

3.4 | Safety

All seven patients (100%) experienced at least one AE (any grade) and a total of 74 AEs were reported. All patients experienced gastrointestinal disorders (any grade), with the most common being nausea (any grade, $n = 6$, 85.7%) and constipation (any grade, $n = 5$, 71.4%). Six different grade 3 AEs were reported: hyperten-

sion occurred in five patients (71.4%), and elevated amylase, elevated γ -glutamyltransferase, hyponatremia, anemia and proteinuria each occurred in one patient (14.3%). There were no grade 4/5 AEs. Two patients had AEs that led to treatment discontinuation; one had a gastric ulcer ($n = 1$; 14.3%) and the other had proteinuria ($n = 1$; 14.3%). No deaths were reported. Treatment-related AEs are detailed in Table 2.

TABLE 3 Summary of efficacy

Patient number	Status	Best overall response	PFS (months)
1	Withdrawal at C1	SD ^a	0.9
2	Withdrawal at C3	SD	2.7
3	Withdrawal at C9	SD	6.7
4	Withdrawal at C9	SD	6.8
5	Ongoing	PR	10.4 ^b
6	Ongoing	Non-CR/non-PD	9.4 ^b
7	Ongoing	PR	11.1 ^b

Abbreviations: C, cycle; CR, complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

^aThe period from baseline to best overall response evaluation was ≥ 6 weeks.

^bCensored observation, treatment ongoing.

3.5 | Efficacy

Best overall response and PFS data are shown in Table 3. At the time of data cut-off (July 6, 2017), four patients had stable disease, two had a partial response and one had non-complete response/non-progressive disease (non-CR/non-PD). The four patients who had stable disease had PFS of 0.9, 2.7, 6.7 and 6.8 months, respectively; and the two patients with a partial response had censored PFS durations of 10.4 and 11.1 months, respectively. The partial response in one of the patients is illustrated in Figure 3. The non-CR/non-PD patient had a PFS of 9.4 months (censored). Three patients who had either a partial response ($n = 2$) or a non-CR/non-PD ($n = 1$) remained on treatment at the time of data cut-off.

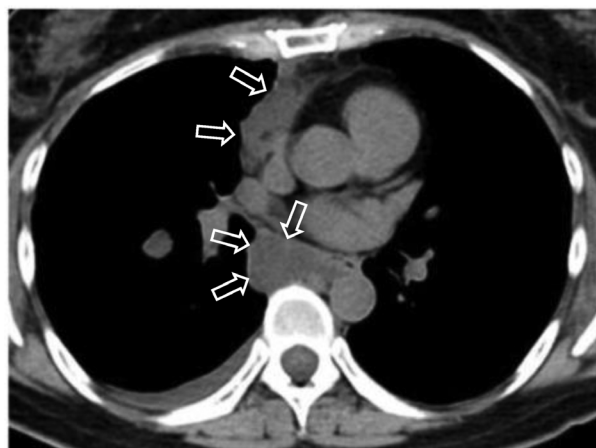
4 | DISCUSSION

This is the first study to report tolerability and safety data for Japanese patients with MPM treated with bevacizumab plus cisplatin/pemetrexed. Our results demonstrate that bevacizumab added to cisplatin/pemetrexed, followed by single-agent bevacizumab is tolerable as a first-line treatment in Japanese patients with MPM. No new safety concerns were identified for bevacizumab either in combination with cisplatin/pemetrexed or as single-agent maintenance treatment.

The overall safety profile in this study was consistent with data published for MAPS.²¹ All patients in our study experienced gastrointestinal AEs, the most common being nausea (85.7%; any grade), which was similar to the incidence reported in MAPS (78.4%). Notably, 71.4% of patients experienced grade 3 hypertension compared with only 23% of patients in MAPS.²¹ However, hypertension was manageable with administration of antihypertensive medications, allowing patients to continue receiving bevacizumab. Other grade 3 AEs included elevated amylase, elevated γ -glutamyltransferase, anemia, proteinuria and hyponatremia.

The toxicity profile of bevacizumab plus cisplatin/pemetrexed was also similar to that reported in Japanese patients with NSCLC²⁴

Before treatment (August 2016)



After treatment (Cycle 7, December 2016)

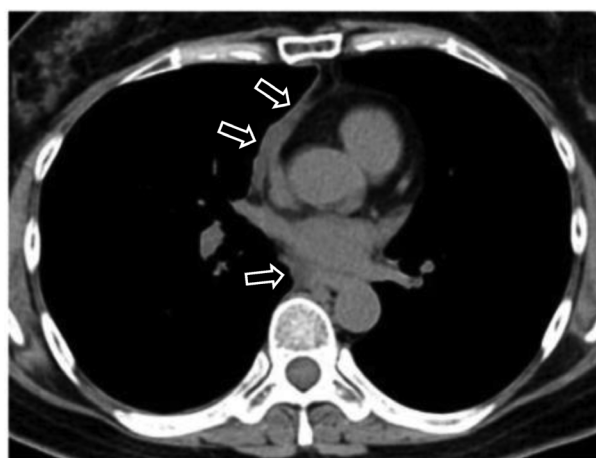


FIGURE 3 Patient case: Computed tomography scan after Cycle 7 in a 47-year-old, female patient who was diagnosed with stage III MPM, and experienced a partial response after receiving treatment without dose modification, other than cisplatin at Cycle 6, when treatment with cisplatin was discontinued mid-treatment due to the occurrence of a systemic rash (patient #5)

and with advanced cervical cancer.²⁵ Although it is difficult to make cross-trial comparisons due to differences in study designs, methods of assessment and patient populations, our safety data appear to be consistent with previous reports on bevacizumab-based therapy for MPM, and did not identify any previously unknown toxicities.^{21,22}

One patient changed from cisplatin to carboplatin due to reduced kidney function but, since there is a wealth of safety and efficacy data for carboplatin-based chemotherapy, it is unlikely that this would significantly impact the safety profile.^{16,26,27} One patient withdrew from the study due to a gastric ulcer, which was confirmed by the investigator as being associated with bevacizumab; however, because gastroendoscopy was not conducted prior to study enrollment, it is unknown whether this was present at baseline. Another patient experienced pleural effusion but continued to receive bevacizumab for ~ 1.5 years

(as of January 31, 2018). Similarly, results from the multicenter, phase II, NEJ013A trial showed that bevacizumab may be active in patients with malignant pleural effusion.²⁸

Median PFS was 6.8 months in this study, which is similar to two phase II studies in MPM that both reported median PFS of 6.9 months with the addition of bevacizumab to standard of care: the multicenter study by Dowell *et al.*²⁹ ($n = 52$) evaluated the same regimen as our study, and the randomized trial by Kindler *et al.*²⁰ ($n = 108$) added bevacizumab to cisplatin/gemcitabine. In contrast, two patients with a partial response had a longer PFS of 10.4 and 11.1 months in our study. The phase III MAPS, with a larger population of 448 patients, reported median PFS and OS durations of 9.2 and 18.8 months, respectively, with bevacizumab plus cisplatin/pemetrexed.²¹ At the data cut-off, three patients remained on treatment with bevacizumab and continue to be monitored. Patients can continue treatment for about a year, so there is potential to observe ongoing responses in these patients. As of January 31, 2018, two patients had continued to receive treatment for ~1.5 years and no new toxicity had been observed.

The combination of anti-angiogenic agents, such as bevacizumab, nintedanib and cediranib, with cisplatin/pemetrexed has been evaluated in the first-line MPM treatment setting. The most promising results have been obtained with the addition of bevacizumab to cisplatin/pemetrexed.²¹ Nintedanib is a triple angiokinase inhibitor with activity against VEGF receptor 1–3, platelet-derived growth factor (PDGF) receptors α and β , fibroblast growth factors receptors 1–3 and Src and Abl kinases. Addition of nintedanib to cisplatin/pemetrexed in the phase II LUME-Meso study improved PFS in patients with unresectable nonsarcomatoid MPM compared with the addition of placebo (median PFS 9.4 months vs 5.7 months, respectively).³⁰ However, the double-blind, randomized, placebo-controlled phase III LUME-Meso study in unresectable epithelioid MPM failed to meet its primary PFS endpoint (median PFS 6.8 months in the nintedanib arm vs 7.0 months in the placebo arm; $P = 0.91$).³¹ Cediranib is an inhibitor of VEGF receptor, PDGF receptor and stem cell factor receptor. In a phase I trial, the addition of cediranib to cisplatin/pemetrexed demonstrated promising preliminary outcomes in patients with chemotherapy-naïve MPM (median PFS = 8.6 months; median OS = 16.2 months).³² Results from the ongoing phase II study of cediranib in combination with cisplatin/pemetrexed (NCT01064648) are awaited.

Recently, nivolumab was approved in Japan as salvage therapy in MPM patients, and is now being evaluated in the first-line setting in combination with standard of care treatment in Japan.³³ Pre-clinical studies suggest that combining anti-angiogenic agents with immunotherapy may have a synergistic effect, enhancing the efficacy of both treatments.³⁴ A phase I trial is currently assessing nintedanib in combination with the PD-1 inhibitor pembrolizumab in patients with various tumors including MPM (NCT02856425), whereas a phase II study is evaluating bevacizumab in combination with atezolizumab in MPM and peritoneal mesothelioma (NCT03074513).

We reported safety and efficacy data for first-line bevacizumab in combination with cisplatin/pemetrexed in Japanese patients with MPM, for whom data are currently limited. Our safety data are com-

parable with other similar studies and show that the addition of bevacizumab to the current standard of care is tolerable.

5 | CONCLUSION

The combination of bevacizumab, cisplatin and pemetrexed followed by maintenance treatment with bevacizumab was well tolerated and had satisfactory efficacy in this small patient dataset, warranting its first-line use in Japanese patients with MPM, on the basis of the phase III study in France.

In terms of systematic chemotherapy for MPM, cisplatin plus pemetrexed is the only approved regimen in the untreated setting. Data from this single-arm trial are encouraging for patients with unresectable MPM; the addition of bevacizumab to standard chemotherapy would offer an alternative treatment option and may extend survival in patients with this aggressive neoplasm.

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CONFLICTS OF INTEREST

Takashi Nakano has received honoraria from MSD, Olympus Corporation, ISHIHARA Sangyo, KYORIN Pharmaceutical, Nippon Boehringer Ingelheim and ONO Pharmaceutical; acted in a consulting or advisory role for Nippon Boehringer Ingelheim; and reports personal fees from Cancer and Chemotherapy Publishers, Ishiyaku Publishers, IGAKU-SHOIN, Elsevier Japan K.K., Asakura Publishing, Ministry of the Environment Japan and Amagasaki City, outside the submitted work. Kozo Kuribayashi has received honoraria from AstraZeneca, Astellas Pharma, Boehringer Ingelheim, Chugai Pharmaceutical, Kyowa Hakko Kirin, KYORIN Pharmaceutical, Meiji-Seika-Pharma, Novartis, Ono Pharmaceutical and Taiho Pharmaceutical. Masashi Kondo has received honoraria from Eli Lilly, MSD, Chugai Pharmaceutical, Pfizer, Novartis, AstraZeneca, Nippon Boehringer Ingelheim, Taiho Pharmaceutical and Kyowa Hakko Kirin. Masahiro Morise has received honoraria from Chugai Pharmaceutical, Eli Lilly Japan K.K., Ono Pharmaceutical, Bristol-Myers Squibb, Pfizer, AstraZeneca, Boehringer Ingelheim, Merck Serono and Novartis. Yuji Tada has received honoraria from Chugai Pharmaceutical. Katsuya Hirano reports personal fees from AstraZeneca K.K., Chugai Pharmaceutical, Eli Lilly, Nippon Boehringer Ingelheim, Ono Pharmaceutical, Pfizer, Taiho Pharmaceutical and Novartis, outside the submitted work. Morihiko Hayashi and Misa Tanaka are employees of Chugai Pharmaceutical, and Misa Tanaka owns stock in Chugai Pharmaceutical.

Masataka Hirabayashi has received honoraria from AstraZeneca K.K., Ono Pharmaceutical, KYORIN Pharmaceutical, Taiho Pharmaceutical, MSD, Chugai Pharmaceutical, Pfizer, Boehringer Ingelheim and Eli Lilly.

DATA AVAILABILITY STATEMENT

Chugai Pharmaceutical Co., Ltd. provide qualified researchers access to individual patient-level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details of Chugai's Data Sharing Policy are available here (https://www.chugai-pharm.co.jp/english/profile/rd/ctds_request.html).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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