Published OnlineFirst June 4, 2019; DOI: 10.1158/1078-0432.CCR-19-0103

Clinical Trials: Immunotherapy

Clinical Cancer Research

Clinical Efficacy and Safety of Nivolumab: Results of a Multicenter, Open-label, Single-arm, Japanese Phase II study in Malignant Pleural Mesothelioma (MERIT)

Morihito Okada[1], Takashi Kijima[2], Keisuke Aoe[3], Terufumi Kato[4], Nobukazu Fujimoto[5], Kazuhiko Nakagawa[6], Yuichiro Takeda[7], Toyoaki Hida[8], Kuninobu Kanai[9], Fumio Imamura[10], Satoshi Oizumi[11], Toshiaki Takahashi[12], Mitsuhiro Takenoyama[13], Hiroshi Tanaka[14], Jun Hirano[15], Yoshinobu Namba[16], and Yuichiro Ohe[17]

Abstract

Purpose: Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy with poor prognosis. Patients with MPM who do not respond to standard first-line chemotherapy have limited treatment options. We evaluated the efficacy and safety of nivolumab, an immune checkpoint inhibitor, for the treatment of advanced or metastatic MPM.

Patients and Methods: Japanese patients with unresectable, advanced, or metastatic MPM resistant or intolerant to ≤2 regimens of chemotherapy and ≥1 measurable lesion (s) were enrolled. Patients received nivolumab 240 mg intravenously every 2 weeks until progressive disease or unacceptable toxicity. The primary endpoint was objective response rate by central assessment according to the Modified Response Evaluation Criteria in Solid Tumors. Adverse events (AEs) and treatment-related AEs (TRAEs) were evaluated.

Results: Thirty-four patients were enrolled between July 2016 and October 2016. Median follow-up was 16.8 (range: 1.8–20.2) months. Ten (29%, 95% confidence interval, 16.8–46.2) patients showed a centrally assessed objective response. The objective response rates were 26% (7/27), 67% (2/3), and 25% (1/4) patients for epithelioid, sarcomatoid, and biphasic histologic subtypes, respectively. Median duration of response was 11.1 months with a 68% disease control rate. Median overall survival and progression-free survival were 17.3 and 6.1 months, respectively. The objective response rate was 40% with programmed death-ligand 1 expression ≥1% and 8% with <1%. Thirty-two patients (94%) experienced AEs and 26 (76%) experienced TRAEs.

Conclusions: Nivolumab met the primary endpoint as second- or third-line treatment for patients with MPM and showed promising efficacy with manageable toxicity.

See related commentary by Mansfield and Zauderer, p. 5438

Introduction

Malignant pleural mesothelioma (MPM) is a rare and aggressive malignancy, responsible for 1,550 malignancy-related deaths in Japan in 2016 (1). In Japan, MPM is more common in men than women given their increased likelihood of occupational exposure to asbestos, and MPM most commonly affects elderly people (median age, 68 years; ref. 2, 3), in part, because of the long latency of the effects of asbestos exposure, which typically occur 30–50 years postexposure (4).

The median survival for patients with MPM is 7.9 months based on studies of newly diagnosed patients in Japan (2, 5).

[1]Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. [2]Division of Respiratory Medicine, Hyogo College of Medicine, Nishinomiya, Japan. [3]Department of Medical Oncology and Clinical Research, Yamaguchi-Ube Medical Center, Ube, Japan. [4]Department of Thoracic Oncology, Kanagawa Cancer Center, Yokohama, Japan. [5]Department of Medical Oncology, Okayama Rosai Hospital, Okayama, Japan. [6]Department of Medical Oncology, Kindai University Faculty of Medicine, Osakasayama, Japan. [7]Department of Respiratory Medicine, National Center for Global Health and Medicine, Tokyo, Japan. [8]Department of Thoracic Oncology, Aichi Cancer Center Hospital, Nagoya, Japan. [9]Department of Pulmonary Medicine and Oncology, Wakayama Medical University, Wakayama, Japan. [10]Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Japan. [11]Department of Respiratory Medicine, Hokkaido Cancer Center, Sapporo, Japan. [12]Division of Thoracic Oncology, Shizuoka Cancer Center, Shizuoka, Japan. [13]Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan. [14]Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan. [15]Oncology Clinical Development Planning I, Oncology Clinical Development Unit, Ono Pharmaceutical Co., Ltd., Osaka, Japan. [16]Clinical Development, Ono Pharmaceutical Co., Ltd., Osaka, Japan. [17]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan.

Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Corresponding Author: Morihito Okada, Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Graduate School of Biomedical and Health Sciences, Hiroshima University, 1-2-3 Kasumi, Minami-ku, Hiroshima 734-0037, Japan. Phone: 81-82-257-5869; Fax: 81-82-256-7109; E-mail: morihito@hiroshima-u.ac.jp

Clin Cancer Res 2019;25:5485–92

doi: 10.1158/1078-0432.CCR-19-0103

Published OnlineFirst June 4, 2019; DOI: 10.1158/1078-0432.CCR-19-0103

Translational Relevance

Malignant pleural mesothelioma (MPM) is a rare malignancy with poor prognosis, and patients who do not respond to first-line chemotherapy have limited treatment options. In this (multicenter, open-label, single-arm, Japanese phase II study in malignant pleural mesothelioma) study, we evaluated the efficacy and safety of nivolumab, an immune checkpoint inhibitor, for the treatment of advanced or metastatic MPM in patients intolerant or resistant to ≤2 regimens of chemotherapy. Nivolumab yielded an objective response rate of 29%, median overall survival of 17.3 months, and progression-free survival of 6.1 months. Its efficacy appeared promising in all histologic subtypes (epithelioid, sarcomatoid, and biphasic) and in PD-L1 ≥1% and <1% patients, although our sample size was small. Nivolumab showed manageable toxicity. While our study lacked a comparator, our findings reflect those of similar trials and suggest that nivolumab provides a clinical benefit and is a potential second- or third-line treatment option for MPM.

Most patients are diagnosed with advanced-stage MPM and receive first-line chemotherapy with pemetrexed and cisplatin (PC). This regimen provides a survival benefit over cisplatin alone (12.1 months and 9.3 months, respectively; ref. 6). Carboplatin is less toxic and more convenient than cisplatin, and combination therapy for MPM with carboplatin and pemetrexed has been evaluated, yielding an overall survival (OS) and progression-free survival (PFS) comparable with that of PC (7–9). Furthermore, adding bevacizumab to PC significantly improved survival benefit by 2.7 months in comparison with PC (10). However, patients with MPM who do not respond to first-line treatment with PC have no standard treatment. National Comprehensive Cancer Network (NCCN) guidelines recommend treatment with nivolumab with or without ipilimumab (11) and pembrolizumab is also a treatment option, but no drug had yet been approved for second-line treatment of MPM before starting this study.

Programmed death ligand 1 (PD-L1) is the ligand to the human programmed death-1 (PD-1) receptor. It is expressed in the tumors of patients with MPM (12–15): in 40% of patients with MPM according to one clinical investigation (12) and in 70% according to data from archived patient tissue (13). PD-L1 expression is correlated with a poor prognosis in MPM (12–15). Nivolumab is a human mAb to the PD-1 receptor that inhibits the interaction between PD-1 and its ligands, PD-L1 or PD-L2. Furthermore, nivolumab is approved for the treatment of various subtypes of malignancies (16).

We hypothesized that nivolumab would be a potential second- or third-line treatment option for MPM. Thus, the multicenter, open-label, single-arm, Japanese phase II study in MPM (MERIT) study evaluated the clinical efficacy and safety of nivolumab in Japanese patients with advanced or metastatic MPM resistant/intolerant to ≤2 regimens of platinum-based chemotherapy in combination with pemetrexed. This study started before the NCCN guideline recommended nivolumab for second-line treatment of MPM (11).

Patients and Methods

Study design and patients

This was a multicenter, open-label, single-arm phase II study conducted from June 16, 2016 to March 14, 2018 (data cut-off date), at 15 centers in Japan (Supplementary Table S1). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The study protocol was reviewed and approved by the institutional review board of each site before study initiation. This study is registered with clinicaltrials.jp (JapicCTI-163247). All patients provided written informed consent.

Selection and description of patients

Eligible patients were men and women ages ≥20 years with histologically confirmed MPM, unresectable advanced or metastatic MPM without surgery, or MPM resistant or intolerant to ≤2 regimens of chemotherapy including platinum-based combination therapy with pemetrexed; and had ≥1 measurable lesion(s) as defined in the Modified Response Evaluation Criteria in Solid Tumors (mRECIST) in MPM (17) and confirmed by imaging within 14 days before enrollment, available tumor tissue samples (fresh or archival) for analysis of PD-L1 expression, and an Eastern Cooperative Oncology Group performance status of 0 or 1. Main exclusion criteria were severe hypersensitivity reactions to any other drug, including antibody products; concurrent autoimmune disease or a history of chronic or recurrent autoimmune disease; multiple primary cancers; brain or meningeal metastases; current or history of interstitial lung disease or pulmonary fibrosis diagnosed on the basis of imaging or clinical findings; and previous treatment with nivolumab, anti-PD-1 antibody, anti-PD-L1, or PD-L2, or any other therapeutic antibodies or pharmacotherapies for T-cell regulation.

Procedures

Patients received 240-mg nivolumab via intravenous 30-min infusion every 2 weeks on day 1 of each cycle until any criterion for nivolumab discontinuation was met (Supplementary Table S2). Neither dose nor administration mode of nivolumab could be adjusted. Therapies prohibited during the study period included immunosuppressants, corticosteroids at doses exceeding 10 mg/day prednisone equivalent, antitumor therapies (e.g., chemotherapy, molecular-targeted therapy, and immunotherapy), concurrent radiotherapy, pleurodesis, and surgical therapies for malignant tumors.

Patients underwent tumor imaging by computed tomography or magnetic resonance imaging every three cycles. The target lesions in pleura were measured uni-dimensionally as the largest tumor thickness perpendicular to the chest wall or mediastinum according to modified RECIST (17); those in nonpleura were measured according to RECIST version 1.1.

PD-L1 expression analysis was performed in a central laboratory (Cancer Genetics, Inc.) using (fresh or archival) tumor tissue samples with 28-8 antibody (Dako). One or more formalin-fixed, paraffin-embedded (FFPE) blocks of tumor tissue samples collected by core needle biopsy, excisional biopsy, or incisional biopsy of ≥5 FFPE unstained slide samples (serial tissue sections) were analyzed for PD-L1 status. Each tumor tissue sample was required to contain ≥100 evaluable tumor cells. PD-L1–positive

Published OnlineFirst June 4, 2019; DOI: 10.1158/1078-0432.CCR-19-0103

status was defined as membranous staining in ≥1% of tumor cells. Samples were classified as "not evaluable (NE)" if the biological conditions of the sample rendered the stained cell membranes difficult to assess, even if the samples otherwise met the evaluation criteria.

Outcomes

The primary endpoint was centrally assessed objective response according to mRECIST. The objective response rate was defined as the proportion of patients whose best overall response was complete response (CR) or partial response (PR). Secondary endpoints were investigator-assessed objective response rate and percent change in the sum of tumor sizes of target lesions; disease control rate, OS, PFS, duration of response, time to response, and best overall response assessed centrally. In addition, subgroup analyses of tumor response, PFS, OS by PD-L1 expression (<1% and ≥1%), and histologic subtype were performed.

OS was defined as the time from the first nivolumab dose to death from any cause. PFS was defined as the time from the first nivolumab dose to progressive disease (PD) or death from any cause. Disease control rate was the percentage of patients whose best overall response was CR, PR, or stable disease (SD).

Adverse events (AEs) and treatment-related AEs (TRAEs) were monitored throughout the study period and graded according to the Japanese translation (Japan Clinical Oncology Group edition) of the NCI Common Terminology Criteria for Adverse Events, version 4.0. AEs of special interest were prespecified as endocrine disorders, gastrointestinal toxicity, hepatotoxicity, pulmonary toxicity, nephrotoxicity, skin toxicity, and hypersensitivity/infusion reactions.

Statistical analysis

As there was no available standard treatment for the target population, the lower threshold for response was set at 5%, and an expected objective response rate of 19% was used for this study. We calculated that ≥29 patients would be required to detect a significant difference in the objective response rate with a power of 80% and a one-sided significance level of 0.025. To account for the estimated 10% dropout rate, we planned to recruit 32 patients. The full analysis set was used for the analysis of the efficacy endpoints, and the safety analysis set for the analysis of baseline demographic and clinical characteristics and safety endpoints. Frequency distribution and summary statistics were used for baseline characteristics. The objective response and disease control rates and their two-sided 95% confidence intervals (CI) were calculated. Medians and two-sided 95% CIs for OS, PFS, and duration of response were calculated using the Kaplan–Meier method. OS and PFS rates, and their two-sided 95% CIs, were calculated at 6 and 12 months depending on the duration of follow-up. The percentages of patients with best overall response of CR, PR, SD, PD, and NE were calculated. Statistical analyses were performed with SAS version 9.3 (SAS Institute Inc.).

Results

Most patients were male (29/34 patients, 85%), with a median age of 68.0 years; 27/34 patients (79%) had an epithelioid subtype (Table 1). Patients received a median of 12.5 (range, 1–42) doses; the median duration of treatment was 6.8 (range, 0.03–19.1) months. The median relative dose intensity was 96% (range, 62%–112%). Six patients (18%) were still on treatment, and 28 (82%) discontinued treatment at data cutoff. The reasons for discontinuation included PD (22 patients, 65%); unequivocal clinical progression attributable to PD (5 patients, 15%); development of grade ≥2 interstitial lung disease or pneumonitis (4 patients, 12%); lack of nivolumab administration for 6 weeks due to AE onset (2 patients, 6%); and continuation of treatment judged as inappropriate by the principal investigator (1 patient, 3%). Some patients had more than one reason for discontinuation. All 34 patients were included in both the full and safety analysis sets. Median follow-up was 16.8 (range, 1.8–20.2) months.

Table 1. Baseline demographic and clinical characteristics

	Nivolumab *N* = 34
Sex	
Male	29 (85)
Female	5 (15)
Age, years, median (range)	68.0 (43–78)
Body mass index, kg/m^2, median (range)	22.1 (15.8–29.0)
Number of prior treatment(s)	
1	24 (71)
2	10 (29)
Performance status	
0	13 (38)
1	21 (62)
Previous systemic therapy	
First line	
Pemetrexed + cisplatin/carboplatin	31 (91)
Pemetrexed + cisplatin + BBI608	2 (6)
Pemetrexed + cisplatin + bevacizumab	1 (3)
Second line	
Gemcitabine	3 (9)
Pemetrexed + cisplatin/carboplatin	3 (9)
Pemetrexed	2 (6)
Other	2 (6)
PD-L1 status	
≥1%	20 (59)
<1%	12 (35)
NE	2 (6)
Histological subtype	
Epithelioid	27 (79)
Biphasic	4 (12)
Sarcomatoid	3 (9)

NOTE: Data are *n* (%), unless otherwise stated.

Ten (29%; 95% CI, 16.8–46.2) of 34 patients had an objective response by central assessment (Table 2), and all were PR. The response rate by site according to mRECIST was identical. The disease control rate was 68% (95% CI, 50.8–80.9; Table 2). Regarding the best overall response, 10 (29%) patients had PR, 13 (38%) had SD, 9 (26%) had PD, and 2 (6%) were NE (Table 2). In addition, central review confirmed that 1 patient had no measurable lesions.

The Kaplan–Meier curves for OS and PFS are shown in Fig. 1A and B. Median OS was 17.3 months (95% CI, 11.5–not reached), with OS rates of 85% (95% CI, 68.2–93.6) and 59% (95% CI, 40.6–73.2) at 6 and 12 months, respectively. Median PFS was 6.1 months (95% CI, 2.9–9.9), with PFS rates of 52% (95% CI, 33.5–66.9) and 32% (95% CI, 16.4–47.9) at 6 and 12 months, respectively. At data cutoff, 3 of 10 patients (30%) had an ongoing response. The median duration of response was 11.1 months (95% CI, 3.5–16.2), with median time to response of 2.63 (range, 1.0–6.9) months. Among responders, the median reduction in target lesions from baseline (depth of response) was 61% (interquartile range, 48–72).

Published OnlineFirst June 4, 2019; DOI: 10.1158/1078-0432.CCR-19-0103

Table 2. Efficacy of nivolumab

	N	Tumor response (95% CI)
Objective response rate ($n = 34$)	10	29% (16.8–46.2)
Epithelioid ($n = 27$)	7	26% (13.2–44.7)
Biphasic ($n = 4$)	1	25% (4.6–69.9)
Sarcomatoid ($n = 3$)	2	67% (20.8–93.9)
Disease control rate ($n = 34$)	23	68% (50.8–80.9)
Best overall response rate ($n = 34$)		
CR	0	0% (0.0–10.2)
PR	10	29% (16.8–46.2)
SD	13	38% (23.9–55.0)
PD	9	26%
NE	2	6%

NOTE: All results are from the central assessment according to mRECIST. 95% CIs were calculated using the Wilson method; 95% CIs were not calculated for the PD or NE categories.

Tumor shrinkage was observed in all histologic subtypes, especially in 6 of 7 patients with either sarcomatoid or biphasic histologic subtype, slight tumor growth was observed in 1 remaining patient. Therefore, the disease control rate in sarcomatoid/biphasic patients was 100% (Fig. 2A). Tumor shrinkage was observed, regardless of PD-L1 status. Among PD-L1 evaluable patients, tumor shrinkage occurred in 14 of 20 (70%) patients with PD-L1 expression ≥1% and 4 of 12 (33%) patients with PD-L1 expression <1% (Fig. 2A). A long duration of response was recorded with a median duration of 11.1 months (95% CI, 3.5–16.2; Fig. 2B). Patients with tumor shrinkage tended to maintain the tumor response (Fig. 3).

The objective response rate by histologic subtype is reported in Table 2. The objective response rates were 26%, 67%, and 25% for epithelioid, sarcomatoid, and biphasic histologic

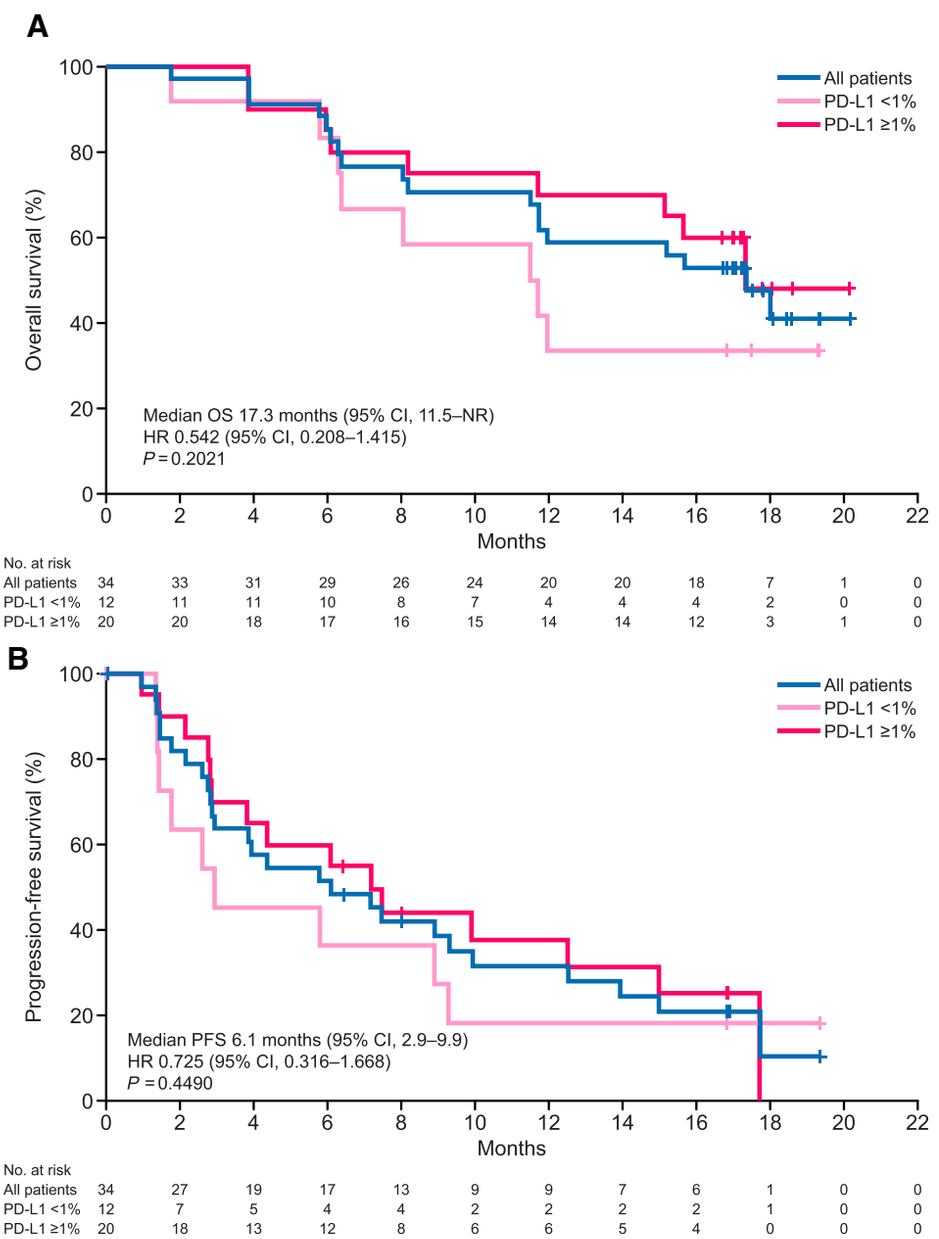

Figure 1.
Kaplan–Meier curves for OS (**A**) and PFS (**B**), for all patients and according to PD-L1 expression status. Median OS and PFS were calculated using values for all patients. HRs denote a comparison between the PD-L1 ≥1% and <1% groups. NR, not reached.

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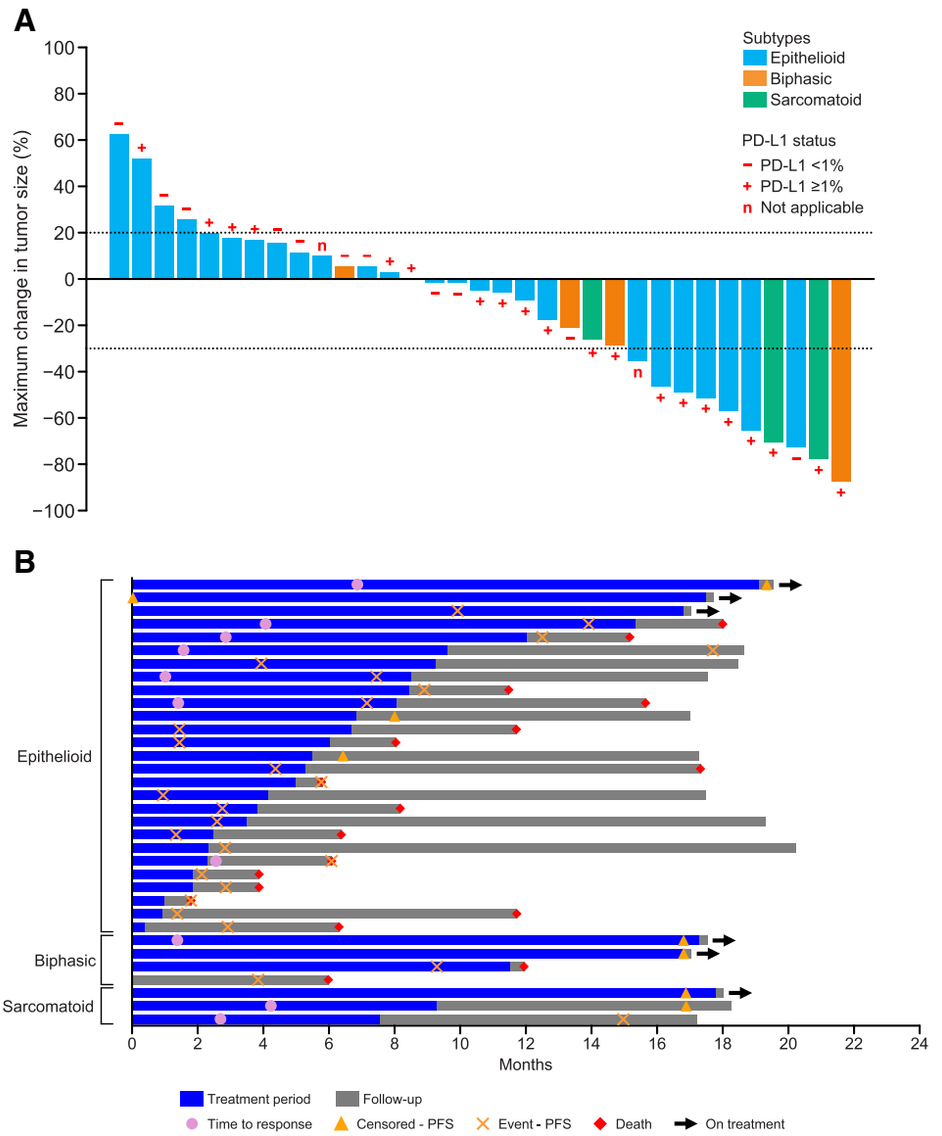

Figure 2.

Percent change in the sum of tumor size by histologic subtype and PD-L1 expression status. The waterfall plot shows the maximum percentage changes from baseline in target lesions by histologic subtype and PD-L1 expression status (**A**), with the length and direction of the bars indicating either an increase or decrease in the target lesion size of each patient. The swimmer's plot (**B**) shows treatment exposure and response duration, with bar length corresponding to the duration of treatment for each patient. Central assessment was performed with lesions defined as the largest tumor thickness perpendicular to the chest wall or mediastinum measured uni-dimensionally according to mRECIST.

subtypes, respectively. The subgroup analysis of OS and PFS by histologic subtype exhibited trends, with prolonged OS and PFS for patients with nonepithelioid subtype (Supplementary Fig. S1A and B). Results of tumor response analysis by PD-L1 expression are shown in Supplementary Table S3. The objective response rate differed by PD-L1 expression (40% for ≥1% vs. 8% for <1%, respectively). Similar trends were observed among patients with different PD-L1 expression levels (≥5% vs. <5% and ≥10% vs. <10%). The subgroup analysis of OS and PFS by PD-L1 status exhibited trends, with prolonged OS and PFS for patients with PD-L1 ≥1% versus <1% [hazard ratio (HR) for OS 0.542 (95% CI, 0.208–1.415; $P = 0.2021$); HR for PFS 0.725 (95% CI, 0.316–1.668; $P = 0.4490$); Fig. 1A and B].

All-cause AEs occurring in ≥5% of patients are shown in Table 3. Most patients (94%) experienced AEs and 16 (47%) patients experienced grade ≥3 AEs. A total of 26 patients (76%) experienced TRAEs, and 11 patients (32%) experienced Grade ≥3 TRAEs. Serious AEs occurred in 14 patients (41%), with 11 patients (32%) having serious TRAEs. Four patients (12%) experienced AEs leading to study treatment discontinuation [two events of interstitial pneumonia (1, grade 2; 1, grade 3) and two events of pneumonitis (both grade 3)]. No fatal AEs occurred between study start and either 28 days after the last nivolumab dose or the start of poststudy treatment. Regarding TRAEs with an incidence of ≥10%, rash occurred in 6 patients (18%); lipase increased, 5 (15%); and diarrhea and amylase increased, 4 each (12%).

The following AEs of special interest occurred: type 1 diabetes mellitus in 1 patient (3%), hypopituitarism in 1 patient (3%), hypothyroidism in 2 patients (6%); and blood thyroid stimulating hormone decreased, blood thyroid stimulating hormone increased, and thyroid function test abnormal in 1 patient (3%) each; diarrhea in 6 (18%) patients; gamma-glutamyltransferase increased in 2 patients (6%); alanine aminotransferase increased, aspartate aminotransferase increased, blood bilirubin increased, and blood alkaline phosphatase

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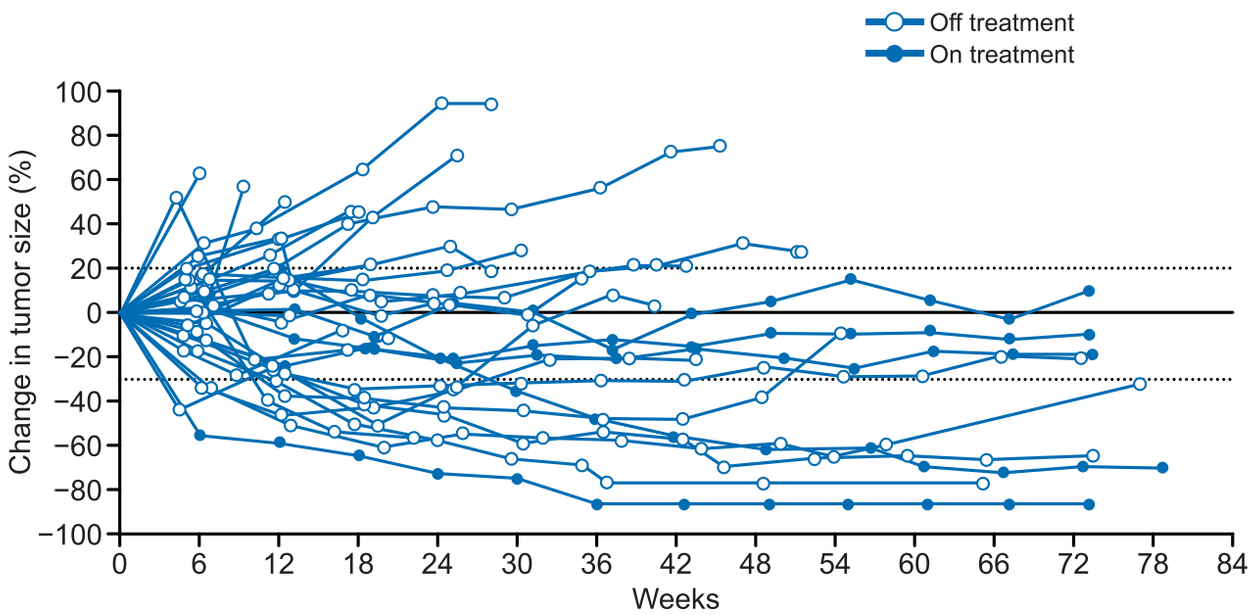

Figure 3.
Percent change in target tumor size over time. Central assessment was performed according to mRECIST.

increased in 1 patient (3%) each; interstitial lung disease and pneumonitis in 2 patients (6%) each; blood creatinine increased in 1 patient (3%); rash in 6 patients (18%), rash maculopapular in 2 patients (6%), and blister, eczema, rash pruritic, skin exfoliation, and urticaria in 1 patient (3%) each; and hypersensitivity in 1 patient (3%). Grade 3–4 AEs of special interest were diarrhea, gamma-glutamyltransferase increased, and pneumonitis in 2 patients (6%) each, and type 1 diabetes mellitus, hypopituitarism, alanine aminotransferase increased, aspartate aminotransferase increased, interstitial lung disease, and rash and hypersensitivity in 1 patient each (3%).

Discussion

MPM is a very aggressive malignancy with a poor prognosis. To develop better therapies for mesothelioma, recent research has focused on the role of immune cells within the tumor microenvironment. Treatment with immune checkpoint inhibitors, which reactivate immune responses that are silenced by immune checkpoints, has shown promising results (18).

The present results suggest that patients with advanced or metastatic MPM resistant or intolerant to the standard treatment may benefit from treatment with nivolumab. Previous studies of standard treatment in advanced or recurrent MPM reported response rates of 0%–2% with placebo or best supportive care and 0%–4.5% with investigational products (19–21). Efficacy of nivolumab for pretreated MPM was reported in previous studies (MAPS2 and NivoMes trials; ref. 22, 23). In addition, the KEYNOTE-028 study showed an objective response rate (investigator assessed according to RECIST guideline, version 1.1) of 20% (95% CI, 6.8–40.7) in previously treated patients with PD-L1–positive MPM receiving pembrolizumab 10 mg/kg every 2 weeks (24). In this study, an objective response rate of 29% was confirmed by central assessment according to mRECIST in patients with MPM and was concordant with the results of other similar studies (22–24). These results suggest that anti-PD-1 antibodies have a high potential for becoming a new treatment option for MPM.

Sarcomatoid or biphasic histologic subtypes are known predictors of poor prognosis (25), and PC therapy has little effect on these histologic subtypes (26). In this study, the objective response in patients with sarcomatoid and biphasic histologic subtypes was 2 of 3 and 1 of 4 patients, respectively. These results indicate that nivolumab had a beneficial effect in these histologic subtypes for which no previous treatment has been shown to be effective. This further supports the use of immune checkpoint inhibitors as potential treatment options to manage MPM. Interestingly, the PD-L1 expression rate was $\geq$50% in the three responders with sarcomatoid and biphasic histologic subtype (data not shown). However, these results should be interpreted with caution as there were only 7 patients with these subtypes. Further study in a larger number of patients with these histologic subtypes is warranted to confirm our findings.

Previous studies have shown that positive PD-L1 expression status has been associated with worse survival outcomes compared with negative PD-L1 expression status (14, 15). In this study, both PD-L1–positive and PD-L1–negative patients responded to nivolumab, and although not significant, differences in OS and PFS with PD-L1 expression status favored positive PD-L1 expression. While promising, these results must be considered in the context of the study design and size, and the fact that the PD-L1 analysis was exploratory. A greater number of patients showing PD-L1 expression responded to nivolumab, although some patients without PD-L1 expression also showed responses. This study was not powered to study differences in response or survival between categories of PD-L1 expression, but this is a critical area for future study in larger, comparative trials.

Patients who have PD after initial chemotherapy are generally expected to have a poor prognosis, advanced symptoms, and worsened condition compared with chemotherapy-naïve

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Table 3. AEs

	Nivolumab *N* = 34	
	Any grade	Grade 3–4
Any AEs	32 (94)	16 (47)
Most common AEs by preferred term (≥5% of patients)		
Viral upper respiratory tract infection	10 (29)	0 (0)
Weight decreased	7 (21)	0 (0)
Diarrhea	6 (18)	2 (6)
Rash	6 (18)	1 (3)
Pyrexia	6 (18)	0 (0)
Lipase increased	5 (15)	4 (12)
Stomatitis	5 (15)	1 (3)
Nausea	5 (15)	0 (0)
Amylase increased	4 (12)	2 (6)
Decreased appetite	4 (12)	2 (6)
Arthralgia	4 (12)	0 (0)
Vomiting	3 (9)	0 (0)
Fatigue	3 (9)	0 (0)
Malaise	3 (9)	0 (0)
Upper respiratory tract infection	3 (9)	0 (0)
Gamma-glutamyltransferase increased	2 (6)	2 (6)
Pneumonitis	2 (6)	2 (6)
Anemia	2 (6)	1 (3)
Hypophosphatemia	2 (6)	1 (3)
Interstitial lung disease	2 (6)	1 (3)
Hypothyroidism	2 (6)	0 (0)
Constipation	2 (6)	0 (0)
Dental caries	2 (6)	0 (0)
Mucosal inflammation	2 (6)	0 (0)
Edema peripheral	2 (6)	0 (0)
Lymphocyte count decreased	2 (6)	0 (0)
Hyperkalemia	2 (6)	0 (0)
Hypoalbuminemia	2 (6)	0 (0)
Myalgia	2 (6)	0 (0)
Dyspnea	2 (6)	0 (0)
Pneumothorax	2 (6)	0 (0)
Rash maculo-papular	2 (6)	0 (0)
AEs leading to discontinuation of study treatment	4 (12)	3 (9)
AEs leading to interruption of study treatment	15 (44)	10 (29)

NOTE: Data are presented as *n* (%).

patients. In fact, a PFS of 1.6–1.7 months and an OS of 5.4–4.9 months was reported in patients with MPM resistant/intolerant to standard treatment who received single-agent vinorelbine, single-agent gemcitabine, or both agents (27). Conversely, in this study, the median PFS and median OS were 6.1 months and 17.3 months, respectively, which were comparable with the results of previous studies in patients requiring second- and third-line treatment with nivolumab with or without ipilimumab (22, 23) and pembrolizumab (24). These findings suggest that nivolumab provides a clinical benefit and could be considered an option for second- or third-line treatment for MPM.

Regarding the safety profile, of the 34 patients receiving nivolumab, 32 (94%) and 26 (76%) patients experienced AEs and TRAEs, respectively. No deaths related to AEs were reported. Nivolumab is approved for the treatment of various cancer types and has been administered to many patients. In our opinion, the safety profile of nivolumab in this study did not differ greatly from that in other cancer types for which nivolumab has already been approved.

In conclusion, the primary endpoint was met in patients with advanced or metastatic MPM resistant or intolerant to maximally two regimens of chemotherapy including platinum-based combination therapy with pemetrexed who received nivolumab as second- or third-line treatment. Nivolumab showed a promising overall response rate of 29% and appeared to yield encouraging PFS and OS results across a range of histologic subtypes, and in patients with PD-L1 expression. Nivolumab had a manageable toxicity profile. Adequately powered, randomized, controlled trials are needed before definitive conclusions can be drawn regarding the survival benefits of nivolumab.

Disclosure of Potential Conflicts of Interest

M. Okada reports receiving commercial research grants from Ono Pharmaceutical and Bristol-Myers Squibb and speakers bureau honoraria from Ono Pharmaceutical and Bristol-Myers Squibb. T. Kijima reports receiving speakers bureau honoraria from Ono Pharmaceutical. K. Aoe reports receiving commercial research grants from Ono Pharmaceutical, Bristol-Myers Squibb, AstraZeneca, MSD, Novartis, and Eli Lilly. T. Kato reports receiving speakers bureau honoraria from AbbVie, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eli Lilly, Kyowa Hakko Kirin, Merck Serono, MSD, Nitto Denko, Novartis, Ono Pharmaceutical, Pfizer, Sumitomo Dainippon Pharma, Taiho Pharmaceutical, Takeda Pharmaceutical, and F. Hoffman-La Roche, is a consultant/advisory board member for AstraZeneca, Eli Lilly, MSD, and Chugai Pharmaceutical, and reports that an immediate family member is an employee of Eli Lilly. N. Fujimoto reports receiving speakers bureau honoraria from Ono Pharmaceutical, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, Chugai Pharmaceutical, Hisamitsu Pharmaceutical, Daiichi Sankyo, and Astellas Pharma, and is a consultant/advisory board member for Ono Pharmaceutical, Bristol-Myers Squibb, Nippon Boehringer Ingelheim, and Kyorin Pharmaceutical. K. Nakagawa reports receiving commercial research grants from MSD, Eli Lilly Japan, Bristol-Myers Squibb, Taiho Pharmaceutical, Ono Pharmaceutical, Chugai Pharmaceutical, Merck Serono, AstraZeneca, Astellas Pharma, Novartis Pharma, Pfizer Japan, and Nippon Boehringer Ingelheim, other commercial research support from ICON Japan, Takeda Pharmaceutical, PAREXEL International, IQVIA Services Japan, A2 Healthcare, AbbVie, SymBio Pharmaceuticals, EP-CRSU, Linical, Otsuka Pharmaceutical, EPS International, Quintiles, CMIC Shift Zero, Eisai, Kissei Pharmaceutical, Kyowa Hakko Kirin, EPS, Daiichi Sankyo, Bayer Yakuhin, inVentiv Health Japan, Gritstone Oncology, GlaxoSmithKline, Yakult Honsha, and Covance, and speakers bureau honoraria from MSD, Bristol-Myers Squibb, Eli Lilly Japan, Ono Pharmaceutical, Chugai Pharmaceutical, AstraZeneca, Astellas Pharma, Novartis Pharma, Nippon Boehringer Ingelheim, Pfizer Japan, Takeda Pharmaceutical, SymBio Pharmaceuticals, Daiichi Sankyo, Kyorin Pharmaceutical, CareNet, Nichi-Iko Pharmaceutical, Hisamitsu Pharmaceutical, Yodosha, Clinical Trial Co., MEDICUS SHUPPAN Publishers, AYUMI Pharmaceutical, Nikkei Business Publications, Thermo Fisher Scientific, Nanzando, Medical Review Co., Yomiuri Telecasting, and Reno. Medical. T. Hida reports receiving speakers bureau honoraria from Ono Pharmaceutical, Bristol-Meyers Squibb, Chugai Pharmaceutical, AstraZeneca, and MSD. S. Oizumi reports receiving other commercial research support from Bristol-Myers Squibb, Kyowa Hakko Kirin, Merck Serono, and Pfizer, and speakers bureau honoraria from AstraZeneca and Eli Lilly. F. Imamura reports receiving speakers bureau honoraria from AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceutical, Eli Lilly Japan, MSD, Ono Pharmaceutical, and Taiho Pharmaceutical. T. Takahashi reports receiving speakers bureau honoraria from Ono Pharmaceutical, MSD, and Chugai Pharmaceutical. M. Takenoyama reports receiving commercial research grants and speakers bureau honoraria from Bristol-Myers Squibb, AstraZeneca, Chugai Pharmaceutical, MSD, and Ono Pharmaceutical. H. Tanaka reports receiving speakers bureau honoraria from Ono Pharmaceutical and Bristol-Myers Squibb. Y. Ohe reports receiving commercial research grants from AstraZeneca, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Bristol-Myers Squibb, Kyorin Pharmaceutical, Dainippon Sumitomo Pharma, Pfizer, Taiho Pharmaceutical, Novartis, Kissei Pharmaceutical, Ignyta, Takeda Pharmaceutical, Daiichi Sankyo Pharmaceutical Co., Ltd, and Janssen, speakers bureau honoraria from AstraZeneca, Chugai Pharmaceutical, Eli Lilly, Ono Pharmaceutical, Bristol-Myers Squibb, Boehringer Ingelheim, Bayer, Pfizer, MSD, and Taiho Pharmaceutical, and is a consultant/advisory board member for AstraZeneca, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Kyorin Pharmaceutical, Celltrion, and Amgen. No potential conflicts of interest were disclosed by the other authors.

Published OnlineFirst June 4, 2019; DOI: 10.1158/1078-0432.CCR-19-0103

Authors' Contributions

Conception and design: M. Okada, K. Nakagawa, J. Hirano, Y. Namba, Y. Ohe
Development of methodology: M. Okada, J. Hirano, Y. Namba
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Okada, T. Kijima, K. Aoe, T. Kato, N. Fujimoto, K. Nakagawa, Y. Takeda, T. Hida, K. Kanai, F. Imamura, S. Oizumi, T. Takahashi, M. Takenoyama, H. Tanaka, Y. Ohe
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Okada, T. Kato, Y. Takeda, J. Hirano
Writing, review, and/or revision of the manuscript: M. Okada, T. Kijima, T. Kato, K. Nakagawa, Y. Takeda, T. Hida, K. Kanai, F. Imamura, S. Oizumi, T. Takahashi, M. Takenoyama, H. Tanaka, J. Hirano, Y. Namba, Y. Ohe
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): Y. Takeda, J. Hirano
Study supervision: M. Okada, K. Nakagawa, Y. Takeda, Y. Ohe

Acknowledgments

We wish to express our gratitude to the patients who participated in the study, their families, and the doctors and all the medical staff at the study centers for their contribution to this study. In addition, we thank Takanori Yoshikawa for conducting the statistical analysis and Michelle Belanger, MD, and Keyra Martinez Dunn, MD, of Edanz Medical Writing for providing medical writing assistance. This work was supported by Ono Pharmaceutical Co., Ltd., and Bristol-Myers Squibb.

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Received January 17, 2019; revised April 1, 2019; accepted May 30, 2019; published first June 4, 2019.

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Published OnlineFirst June 4, 2019; DOI: 10.1158/1078-0432.CCR-19-0103

Clinical Cancer Research

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Morihito Okada, Takashi Kijima, Keisuke Aoe, et al.

Clin Cancer Res 2019;25:5485-5492. Published OnlineFirst June 4, 2019.