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Research Article

Analysis of Pleiotropic Effects of Nivolumab in Patients with relapsed Pleural Mesothelioma: A Single center retrospective study

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[†]These authors made an equal contribution to the study.

Short Title: Pleiotropic Effects of Nivolumab in Relapsed Pleural Mesothelioma

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Keywords: anti-PD-1 Ab; Immune checkpoint inhibitor; Nivolumab; Pleiotropic Effect; Pleural mesothelioma

Abstract

Introduction: In August 2018, the Japanese PMDA approved nivolumab, an immune checkpoint inhibitor (ICI), for previously treated, unresectable, advanced, or recurrent pleural mesothelioma (PM) based on the MERIT trial, a phase II study of 34 cases. However, concerns regarding limited evidence persist.

Methods: We retrospectively analyzed 83 patients with previously treated, unresectable, advanced, or recurrent malignant pleural mesothelioma (MPM) treated with nivolumab from August 2018 to May 2022. Efficacy was evaluated using overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) per modified RECIST criteria. Safety was assessed by treatment-related adverse events (TRAEs) according to CTCAE v5.0. PD-L1 expression was analyzed with the anti-PD-1 antibody (22C3).

Results: The median age was 73 years. Histological subtypes included epithelioid (60), sarcomatoid (15), biphasic (6), and unknown (2). Lines of treatment were 2nd (62), 3rd (13), and 4th or later (8). Partial response (PR) was seen in 16 patients, stable disease (SD) in 30, progressive disease (PD) in 29, and not evaluable (NE) in 8, with an ORR of 19.3% and a disease control rate of 55.4%. Median PFS and OS were 5.1 and 12.4 months, respectively. TRAEs occurred in 45 patients (54.2%), with grade ≥3 in 6 (7.2%) and one treatment-related death. PFS correlated with male gender, TRAEs, and good performance status (PS: 0-1), while OS correlated with PS.

Conclusion: Nivolumab demonstrated efficacy and safety in clinical practice, supporting its use in patients with good PS, even in later lines.

Introduction

Pleural mesothelioma (PM) is a relatively rare tumor arising from mesothelial cells with a high mortality rate and is particularly refractory [1]. In fact, the prognosis of MPM remains poor, with an average survival of approximately 1 year after diagnosis [2]. In August 2018, the Pharmaceuticals and Medical Devices Agency (PMDA), the Japanese regulatory authority, became the first in the world to approve an ICI for the treatment of previously treated unresectable advanced or recurrent PM. The approved drug was nivolumab.

The MERIT study, a single-arm phase 2 study, demonstrated efficacy (mPFS: 6.1 m [95% CI: 2.9 -9.9], mOS: 17.3months [95% CI: 11.5 – not reached]) and safety (All Grade irAEs: 76.47% ≥ G3:32.35%) in 34 patients with previously treated PM [3]. On the other hand, weak evidence was strongly pointed out because of the single-arm phase 2 study and the small number of patients studied.

Subsequently, the CONFIRM study, a multicenter, double-blind, randomized, phase 3 study in the United Kingdom, compared placebo (n=111) with nivolumab (n=221) in 332 patients with previously treated PM and demonstrated superior efficacy in both PFS and OS [P=0.0012 for nivolumab; mPFS: 3.0months [95% CI: 2.8 -4.1] for placebo; mPFS 1.8months (95%CI 1.4-2.6)]/[p0.0090=Nivolumab group; mOS: 10.2months [95% CI: 8.5 -12.1] for Placebo;; mOS: 6.9months [95% CI: 5.0 -8.0] and safety (Nivolumab -TRAE; All Grade irAE: 73.76% ≥ G3:12.67%) [4].

However, since these results did not include Japanese patients and most of the findings were obtained from analyses of clinical big data, accumulation of data from clinical experience is considered to be extremely important for clinical application.

In addition, we previously reported the late line effect of nivolumab in lung cancer [5], but there are no studies in Japan on mesothelioma.

In this study, we evaluated the safety and efficacy of nivolumab in patients with previously treated PM in clinical practice.

The purpose of this study is to further optimize the use of nivolumab in patients with previously treated PM by confirming the actual use of nivolumab after its approval and understanding the clinical use results.

Methods

Patients

We conducted a retrospective search of the medical records at Hyogo Medical University for patients treated for PM between August 2018 and May 2022. We extracted 83 consecutive patients (64 males and 19 females) with pretreated advanced PM. Patients ware received intravenous Nivolumab administered every 2 or 4 weeks, until radiographic disease progression, unacceptable toxicity, or withdrawal was confirmed. All patients had sufficient data to evaluate their characteristics and clinical outcomes.

Study design

Their age, gender, asbestos exposure information, Eastern Cooperative Oncology Group (ECOG) PS score, histology, stage, first-line chemotherapy regimen, toxicity were assessed. The clinical or pathological stage of the disease was based on the International Mesothelioma Interest Group (IMIG) staging system [6]. Histological subtypes were determined using the World Health Organization classification for cell types.

Safety was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0 [7] to assess TRAEs (Treatment-Related Adverse Events) during the study. Efficacy was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [8] .

Treatment was maintained in the absence of unacceptable side effects, provided that the patients were receiving clinical benefits.

Subgroup analysis

A prespecified subgroup analysis for ORR and a post-hoc subgroup analysis for PFS and OS were performed to determine the association between these efficacy variables and the patients' gender, age, histological subtype, treatment line, ECOG performance status, smoking status.

PD-L1 analysis

Tumour PD-L1 expression was assessed retrospectively in pretreatment (archival or recent) tumour-biopsy specimens using a validated, automated immunohistochemical assay (Dako North America) that used a rabbit anti-human PD-L1 antibody (clone 22C3, Dako).Tumour PD-L1 expression was confirmed when the tumour cell membranes were stained (at any intensity)at predetermined expression levels of ≥1%, 1-49%, and ≥50% in a section that included at least 100 tumour cells that could be evaluated.

Statistical analysis

Overall survival (OS) was defined as the time from the start of first nivolumab treatment to the date of death from any cause. Progression-free survival (PFS) was defined as the time from the start of treatment to the date of documented disease progression (PD) or death from any cause, whichever occurred first. Median OS and PFS, along with their 95% confidence intervals (CIs), were estimated using the Kaplan-Meier (KM) method. Differences between groups were compared using the log-rank test. Univariate and multivariate analyses were performed using Cox proportional hazards regression models to identify factors associated with OS and PFS. In the multivariate analysis, we adjusted for performance status (PS), age, sex, histological type, line of therapy, and treatment-related adverse events (TRAE). Hazard ratios (HRs) and their 95% CIs were calculated for each factor. All statistical analyses were conducted using EZR (Easy R) software version 4.2.2 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [9] and JMP software version 12.2.0 (SAS Institute, Cary, NC, USA). A p-value of less than 0.05 was considered statistically significant.

Results

Patient background characteristics

The background characteristics of all 83 patients are shown in Table 1. The median age was 73 years (Range, 45-88), 59 patients (71.08%) were 70 years or older, and 33 (39.76%) were 75 years or older. 64 patients (77.11%) were men, and 73 patients (87.95%) had ECOG PS 0-1. 61 patients (73.49%) had a history of smoking, 55 patients (66.27%) had a history of asbestos exposure, and 60 patients (72.29%) had epithelioid histology. In addition, 25.3% of patients received the drug at or after the 3rd Line.

Adverse event

Treatment-related adverse events in the 83 patients studied in this study are shown in Table 2. All adverse events were similar to those reported previously. Serious adverse events of Grade ≥ 3 were observed in 6 patients (7.23%) overall. There were no hematologic toxicities. Non-hematologic toxicities included interstitial pneumonia in 4 patients (4.82%), liver disorder in 1 patient (1.20%), and type 1 diabetes mellitus in 1 patient (1.20%). One treatment-related death was attributed to interstitial pneumonia.

Response and survival

The treatment response of all 83 patients is shown in Table 3 and Figure 1. 16 patients (19.28%) achieved PR, 30 (36.14%) had SD, 29 (34.94%) had PD, and 8 (9.64%) had NE. No patient achieved CR. The response rate was 19.28%, and the disease control rate was 55.42%. The median PFS after nivolumab treatment was 5.13months (95%CI: 3.50-6.27), and the 1-year PFS rate was 23.4% (95%CI: 13.9-34.5). The median OS and the 1-year OS rate after nivolumab treatment were 12.40months (95%CI: 8.50-16.37) and 50.3% (95%CI: 39.1-60.5), respectively.

Subgroup analysis

In the subgroup analysis, univariate analysis showed significant differences in both PFS and OS for PS (0-1 vs ≥ 2), response (yes vs no), and TRAE (no vs yes). Multivariate analysis showed significant differences in PFS for 3 items: gender [HR for PFS 2.162 (95% CI, 1.063–4.399); P=0.03338] (Figure 2), PS (0-1 vs ≥ 2) [HR for PFS 2.806 (95% CI, 1.039–7.577); P=0.04184] (Figure 3), and TRAE (no vs yes) [HR for PFS 0.5036 (95% CI, 0.2761–0.9185); P=0.02526] (Figure 4). Regarding OS, only PS (0-1 vs ≥ 2) [HR for OS 4.365 (95% CI, 1.891-10.07; P=0.0005553] showed significant differences. Multivariate analysis showed significant differences. (Figure 3). No significant differences were observed in administration LINE (2-3 vs after 4th.)[HR for PFS 0.8248 (95% CI, 0.3311–2.055); P=0.6792, HR for OS 0.8865 (95% CI, 0.8865 -0.4022); P=0.765] (Figure 5, Table 4) in either PFS or OS.

PD-L1 subgroup analysis

In this study, we were able to confirm the expression status of PD-L1 protein in 22 out of 83 patients. The results are shown in Table 5. The positive rate was as follows: < 1% in 13 patients (59.09%), 1 ~ 49% in 8 patients (36.36%), and ≥ 50% in 1 patient (4.55%). The median PFS by PD-L1 expression was 4.45months (95%CI: 1.47-21.23) in 13 patients with PD-L1<1% and 5.10months (95%CI: 1.17 – NA) in 9 patients with PD-L1 ≥ 1% (Table 5).

The median OS was 21.13 months (95%CI: 6.63-32.17) in 13 patients with PD-L1<1% and 7.73months (95%CI: 0.87-19.60) in 9 patients with PD-L1 ≥ 1%. Univariate analysis showed no significant difference in PFS [p=0.8950] or OS [p=0.267] (Figure 6).

Discussion

A review of 2nd-line or later nivolumab trials for previously treated PM, including the results of this study, is shown in Supplementary Table S1.

In 2018, the Japanese PMDA became the first in the world to approve the monotherapy of nivolumab, an ICI, as a treatment for previously treated PM. On the other hand, the weakness of evidence from the MERIT study, an open-label, single-arm phase II study of 34 patients, has been a major concern.

Although the efficacy of nivolumab in this study was inferior to that of the MERIT trial in PFS, OS, and ORR, the results were comparable or superior to those of the CONFIRM trial, the first randomized phase III trial in the world. The reason why the results of this study were inferior to those of the MERIT trial is that the patients included older patients (median age 73.0 years [45 -88 years]), patients with poor PS (PS ≥ 2; n=10/83 [12.05%]), and patients treated with late line (line ≥ 4th; n=8/83 [9.64%]).

However, this study shows that nivolumab is not inferior to the efficacy of the CONFIRM trial in patients with previously treated PM in an actual clinical population including these patients with unfit clinical trials, and thus justifies the judgment of the PMDA.

In addition, the present study showed that PFS and OS were significantly prolonged in patients with good PS (PS: 0-1 group) compared to those with poor PS (PS: 2 or later group), suggesting that nivolumab can be an independent predictor of treatment effect.

On the other hand, the previous studies, including MERIT, CONFIRM, NivoMes [10], and MAPS2 [11], all included patients with PS: 0-1, and the effect of nivolumab in patients with PS: 2 or later was not clear. However, the results of our study suggest that nivolumab may be beneficial for patients with poor PS (PS ≥2) in previously treated PM. This conclusion is supported by our findings in this retrospective study, which demonstrated that even among patients with PS ≥2, some cases showed a disease control rate (DCR) of 20% (n=2/10) (Supplementary Table S2) when tolerability was within acceptable limits. Based on these results, we believe this new finding is highly promising in the context of PM, where treatment options remain limited.

Furthermore, in the subgroup analysis [4] of the CONFIRM study, sufficient efficacy [HR for PFS 0.52 (95% CI, 0.22-4.20), HR for OS 0.42 (95% CI, 0.16-1.09] was confirmed in patients treated with the 4th line or later compared with placebo, but similarly in this study, no significant difference was

observed in the 2nd/3rd line group compared with those treated with the 4th line or later. In other words, based on these results, it is clear from this study that the efficacy of nivolumab for previously treated PM does not depend on the line of administration, and that nivolumab should be actively considered in patients with good PS, even in the late line, unless there is a specific reason for the patient's background.

In the subgroup analysis [12] of the Checkmate 743 study, nivolumab plus ipilimumab was shown to be more effective than chemotherapy in improving overall survival in patients with non- epithelioid histology (HR 0.86 [95% CI 0.69–1.08]) than in patients with epithelioid histology (HR 0.46 [95% CI 0.31–0.68]). In contrast, in the subgroup analysis of the CONFIRM [4] study, nivolumab seemed to suggest superiority over placebo in patients with epithelioid disease; indeed, this result was not observed in patients with non-epithelioid mesothelioma. On the other hand, in this study, there was no significant difference in PFS and OS between epithelioid and non-epithelioid tumors with regard to the difference in therapeutic effect of nivolumab by histological type, and nivolumab was effective in all histological types. As a result, the therapeutic effect by histological type was the result of 3 studies3. However, all the analyses were subgroup analyses, and it may be due to the immaturity of the number of survival events at the time of this analysis, such as the proportion by histological type and the skewed number of patients, which requires careful interpretation.

The incidence of adverse drug reactions in this study was lower than in previous reports, and the safety results were favorable. The reason for this is that the use of immune checkpoint inhibitors in malignant tumors such as lung cancer has expanded and the number of cases has been accumulated, which has made it possible for physicians in charge to become familiar with immune-related adverse events and to detect them early. Another reason may be that TRAE is analyzed in detail in the Cancer board every week for serious adverse events in collaboration with other departments at our hospital. On the other hand, PFS was significantly longer in the TRAE (+) group than in the TRAE (-) group. An association between irAEs and ICIs has already been shown in NSCLC, and in our study, PFS was significantly longer in PM, suggesting that the presence or absence of irAEs may be a predictor of treatment response.

PD-L1 expression has been established as a predictive biomarker for immune checkpoint therapy in non-small cell lung cancer [13], but there is little solid evidence for PD-L1 expression as a predictor of PD-1 inhibition in mesothelioma [14]. In fact, there is no evidence to support the role of PD-L1 expression as a predictive biomarker using a Dako 22 C3 PD-L1 tumor proportion score of 1% or higher [15]. In our study, in 22 patients analyzed for PD-L1 expression, univariate analysis showed no significant difference in OS or PFS. On the other hand, it has been reported that PD-L1 overexpression is associated with a poor prognosis of PM [16,17].

In fact, according to previous reports, the CONFIRM, MERIT, and CM743 trials were considered to have no relationship between PD-L1 expression and the therapeutic effect of nivolumab, while the NivoMes and MAPS2 trials were considered to have a PD-L1 relationship.

Thus, there is no consistent view on whether the presence or absence of PD-L1 expression can be a predictive biomarker for the effect of nivolumab, and the possibility of PD-L1 expression as a predictive factor for the effect remains elusive at present.

Conclusions

This study demonstrated the efficacy and safety of nivolumab in clinical practice. It was confirmed that the appearance of TRAE can be a predictive factor for the effect as well as lung cancer. In addition, new findings suggest that nivolumab should be actively administered to patients with good PS, even in late line, unless there is a special reason for the patient's background. Furthermore, since it became clear that good therapeutic effects of nivolumab could be obtained in patients with good PS (PS: 0-1), it is proposed as a new issue that administration of nivolumab as maintenance therapy should be considered before PS decreases due to tumor progression, etc. in patients treated with cytotoxic anticancer drugs in the 1st line.

Statements

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Statement of ethics
Study Approval Statement:
This study was approved by the Institutional Ethics Review Board of Hyogo Medical University on October 18, 2022 (Approval No. 3829), and was conducted in compliance with the 2013 Declaration of Helsinki.
Consent to Participate Statement:
The requirement for written informed consent was waived by the Institutional Ethics Review Board of Hyogo Medical University due to the retrospective nature of the study. This exemption was granted as the study involved the use of anonymized patient data collected during routine clinical practice, ensuring no identifiable information was linked to the analysis.

Conflict of Interest Statement
Daichi Fujimoto has received grants and personal fees from AstraZeneca KK and Boehringer Ingelheim Japan Inc., as well as personal fees from Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., Taiho Pharmaceutical Co. Ltd., Chugai Pharmaceutical Co. Ltd., MSD KK, Eli Lilly Japan KK, Daiichi Sankyo, Novartis Pharma KK, Kyowa Kirin Co. Ltd., and Janssen Pharmaceutical K K, outside the scope of the submitted work. The other authors have no conflicts of interest to declare.

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Author Contributions
Tomoki Higashiyama: Conceptualization; Investigation; Project administration; Writing – review & editing. **Kozo Kuribayashi**: Conceptualization; Investigation; Writing – original draft; Writing – review & editing. **Hiroshi Doi**: Data curation; Formal Analysis; Methodology; Writing – review & editing. **Aki Kubota**: Data curation; Formal Analysis; Visualization; Writing – review & editing. **Taiichiro Otsuki**: Investigation; Resources; Writing – review & editing. **Yasuhiro Nakajima**: Investigation; Writing – review & editing. **Koji Mikami**: Investigation; Writing – review & editing. **Ryo Takahashi**: Investigation; Writing – review & editing. **Akifumi Nakamura**: Investigation; Resources; Writing – review & editing. **Daichi Fujimoto**: Validation; Visualization; Writing – review & editing. **Kazuhiro Kitajima**: Investigation; Visualization; Writing – review & editing. **Toshiyuki Minami**: Validation; Visualization; Writing – review & editing. **Takashi Kijima**: Funding acquisition; Supervision; Writing – review & editing.

Data Availability Statement
The data that support the findings of this study are not publicly available due to ethical and privacy restrictions, but are available from the corresponding author (K.K.) upon reasonable request.

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Figure Legends

Fig. 1. Kaplan–Meier curves of progression-free survival (A) and overall survival (B)

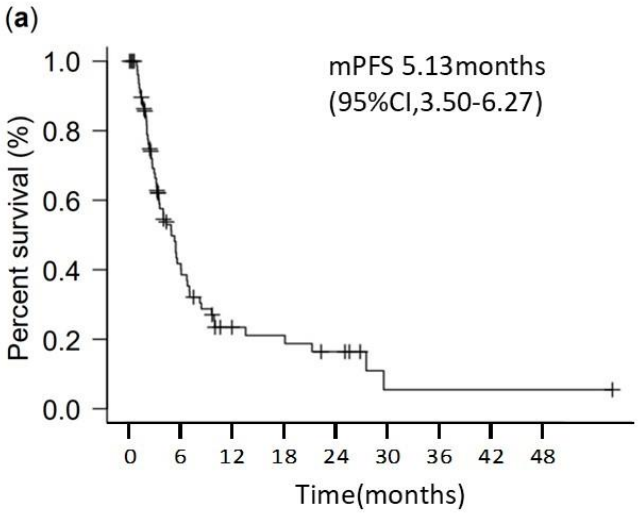
Fig. 2. Comparison of PFS (A) and OS periods (B) between patients male and Female.

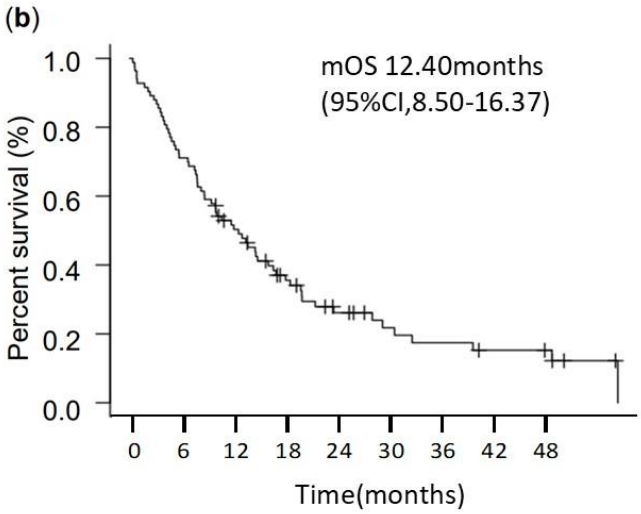
Fig. 3. Comparison of PFS (A) and over OS periods (B) for patients with PS of 0-1 and ≥2.

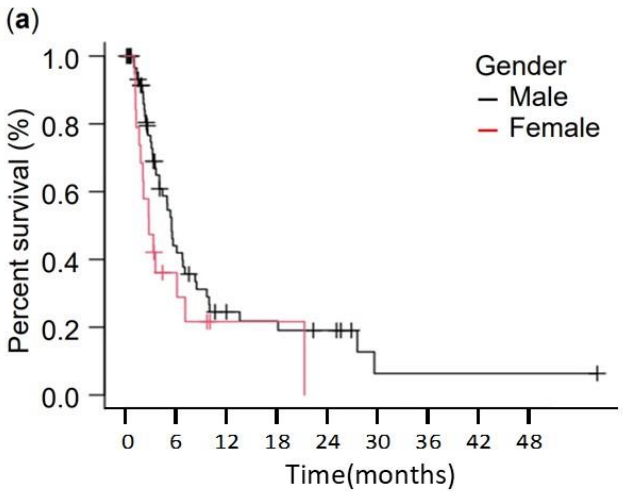
Fig. 4. Comparison of PFS (A) and OS periods (B) between patients with and without TRAEs.

Fig. 5. Comparison of PFS (A) and over OS periods (B) for patients with
treatment lines of ≥4th and 2-3 lines.

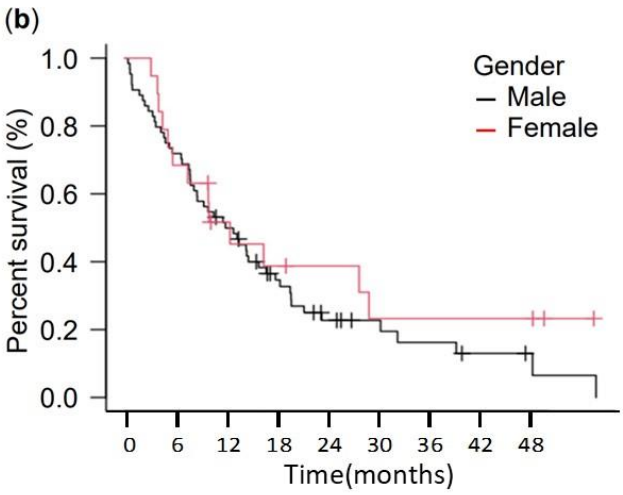
Fig. 6. Comparison of PFS (A) and over OS periods (B) for patients with PD-L1 status of ≥1% and <1%.



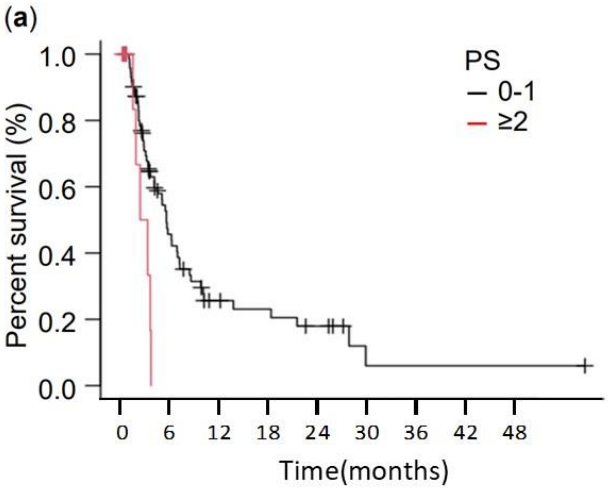




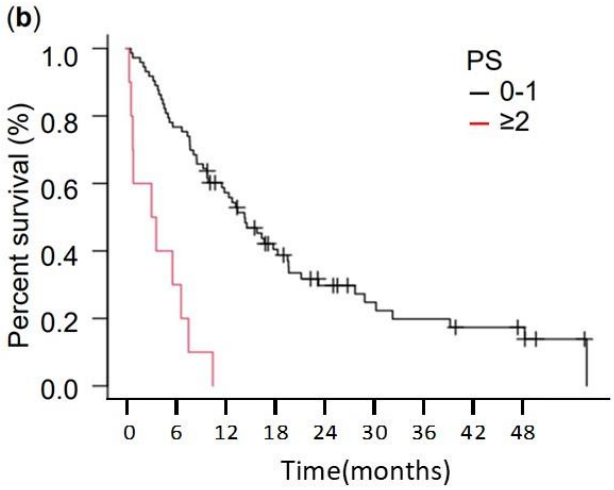
Male mPFS 5.63 months (95% CI,4.20-7.20)
Female mPFS 2.97 months (95% CI,1.83-7.23)
P=0.101 HR=1.638 (95% CI,0.9023-2.973)



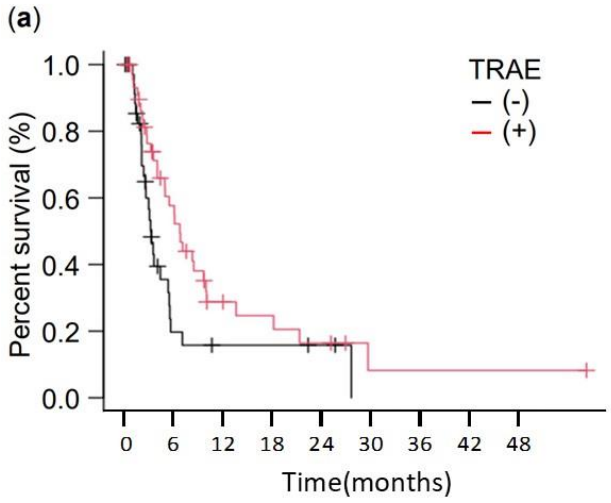
Male mOS 11.87 months (95% CI,7.73-16.67)
Female mOS 12.40 months (95% CI,1.5.07-28.80)
P=0.397 HR=0.7674 (95% CI,0.415-1.419)



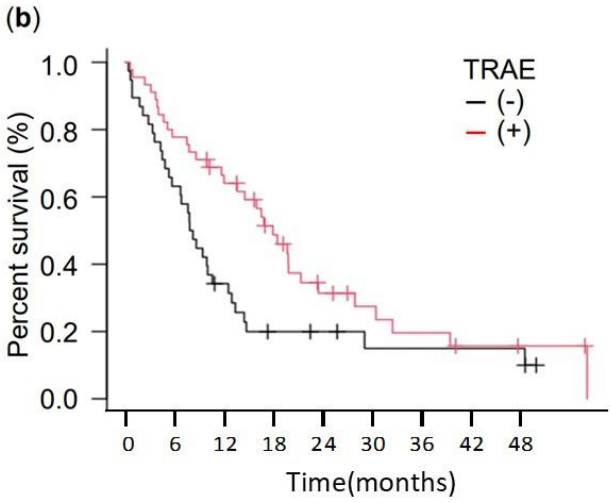
PS 0-1 mPFS 5.63 months (95% CI,4.20-7.20)
PS≥2 mPFS 2.95 months (95% CI,1.63-NA)
P=0.0034 HR=3.504 (95% CI,1.431-8.584)



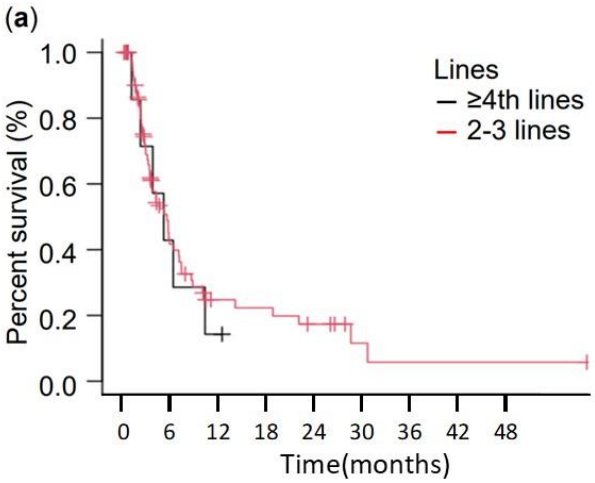
PS 0-1 mOS 14.30 months (95% CI,9.83-19.50)
PS≥2 mOS 3.35 months (95% CI,0.37-6.63)
P=0.000000062 HR=6.081 (95% CI,2.895-12.78)



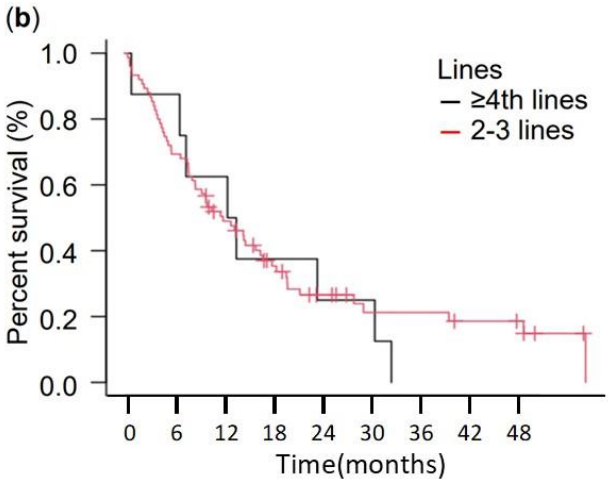
TRAE(-) mPFS 3.40 (95% CI,2.57-5.50)
TRAE(+) mPFS 6.90 (95% CI,4.20-10.03)
P=0.0328 HR=0.5637 (95% CI,0.3305-0.9614)



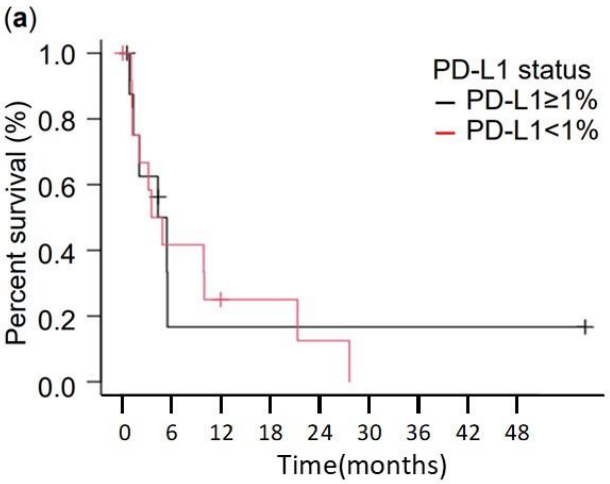
TRAE(-) mOS 7.93 (95% CI,5.23-10.47)
TRAE(+) mOS 17.77(95% CI,11.87-21.13)
P=0.0216 HR=0.5630 (95% CI,0.3427-0.9249)



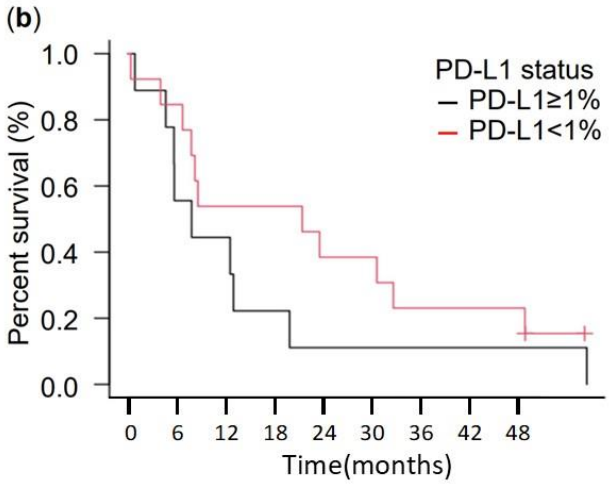
≥4th lines mPFS 5.10 months (95% CI,1.27-10.03)
2-3 lines mPFS 5.50 months (95% CI,3.43-6.97)
P=0.694 HR=0.8432(95% CI,0.3598-1.976)



≥4th lines mOS 12.93 months (95% CI,0.80-30.17)
2-3 lines mOS 11.87 months (95% CI,8.13-16.37)
P=0.665 HR=0.8484(95% CI,0.4028-1.787)



PD-L1≥1% mPFS 5.10 months (95% CI,1.167-NA)
PD-L1<1% mPFS 4.45 months (95% CI,1.467-21.23)
P=0.8950 HR=1.07 (95% CI,0.3899-2.935)



PD-L1≥1% mOS 7.73 months (95% CI,0.8667-19.60)
PD-L1<1% mOS 21.13 months (95% CI,6.633-32.17)
P=0.267 HR=0.592 (95% CI,0.2325-1.507)

Table 1. Baseline characteristics

N=83	N	%
Median Age, years(IQR)	73(45-88)	
≥70	59	71.1
<70	24	28.9
Sex		
Male	64	77.1
Female	19	22.9
ECOG performance status score		
0	24	28.9
1	49	59.0
≧2	10	12.1
Smoking status		
Former/Current	61	73.5
Never	22	26.5
Asbestos Exposure		
Occupational	38	45.8
Environmental	17	20.5
None	24	28.9
Unknown	4	4.8
Stage		
Ⅰ	44	53.0
Ⅱ	3	3.6
Ⅲ	28	33.7
Ⅳ	8	9.7
Histology		
Epithelioid	60	72.3
Sarcomatoid	15	18.1
Biphasic	6	7.2
Unknown	2	2.4
PD-L1 status		
<1%	13	15.7
1-49%	8	9.6
≧50%	1	1.2
Unknown	61	73.5
Treatment line		
2nd	62	74.7
3nd	13	15.7
≥4th	8	9.6

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table 2. Treatment-related adverse events

	All Grade		≥Grade 3	
	N	%	N	%
Any	45	54.2	6	7.2
Diarrhea	9	10.8	0	0.0
Rash	15	18.1	0	0.0
Liver damage	2	2.4	1	1.2
Hypothyroidism	12	14.5	0	0.0
Interstitial lung disease	7	8.4	4	4.8
Adrenal insufficiency	1	1.2	0	0.0
Hypopituitarism	2	2.4	0	0.0
Neurological damage	5	6.0	0	0.0
Arthralgia	5	6.0	0	0.0
Type1 Diabetes	1	1.2	1	1.2

Table 3. Responses to nivolumab

	ALL		Epithelioid		Non-Epithelioid		Histology unknown		TRAE(+)		TRAE(-)	
	N=83		N=60		N=21		N＝2		N=45		N=38	
	N	%	N	%	N	%	N	%	N	%	N	%
CR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
PR	16	19.3	11	18.3	5	23.8	0	0.0	10	22.2	6	15.8
SD	30	36.2	19	31.7	11	52.4	0	0.0	18	40.0	12	31.6
PD	29	34.9	24	40.0	4	19.0	1	50.0	15	33.3	14	36.8
NE	8	9.6	6	10.0	1	4.8	1	50.0	2	4.5	6	15.8
ORR		19.3		18.3		23.8		0.0		22.2		15.8
DCR		55.5		50.0		76.2		0.0		62.2		47.4

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; ORR, objective response rate; DCR, disease control rate; TRAE, treatment-related adverse event.

Table 4. Baseline characteristics with prior treatment

	2nd/3rd		≥4th	
	N=75		N=8	
	N	%	N	%
CR	0	0.0	0	0.0
PR	14	18.7	2	25.0
SD	29	38.7	1	12.5
PD	25	33.3	4	50.0
NE	7	9.3	1	12.5
ORR		18.7		25.0
DCR		57.4		37.5

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate; DCR, disease control rate."

Table 5. Responses to nivolumab by PD-L1 status

	ALL		PD-L1<1%		PD-L1 1-49%		PD-L1≥50%	
	N=22		N=13		N=8		N=1	
	N	%	N	%	N	%	N	%
CR	0	0.0	0	0.0	0	0.0	0	0.0
PR	4	18.2	3	23.1	0	0.0	1	100.0
SD	6	27.3	3	23.1	2	25.0	0	0.0
PD	10	45.4	6	46.1	5	62.5	0	0.0
NE	2	9.1	1	7.7	1	12.5	0	0.0
ORR		18.2		23.1		0.0		100.0
DCR		45.5		46.2		25.0		100.0

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluated; ORR, objective response rate; DCR, disease control rate.