

Adjuvant Anti–PD-1 Monotherapy Versus Observation for Stage III Acral Melanoma of the Sole: A Multicenter Retrospective Study in Japanese Patients

Shigeru Koizumi, MD^{1,2} ; Naoya Yamazaki, MD, PhD³ ; Yuki Ichigozaki, MD⁴; Hiroshi Kitagawa, MD, PhD⁵; Yukiko Kiniwa, MD, PhD⁶ ; Sayuri Sato, MD, PhD⁷ ; Toshihiro Takai, MD⁸; Reiichi Doi, MD⁹; Takamichi Ito, MD, PhD¹⁰; Masahito Yasuda, MD, PhD¹¹ ; Yutaka Kuwatsuka, MD, PhD¹² ; Takeo Maekawa, MD, PhD^{13,14} ; Jun Asai, MD, PhD¹⁵; Takuya Miyagawa, MD, PhD¹⁶ ; Shigeto Matsushita, MD, PhD¹⁷ ; Takeru Funakoshi, MD, PhD¹⁸ ; Yosuke Yamamoto, MD, PhD²; Takashi Inozume, MD, PhD²; Akiko Kishi, MD¹⁹; Tatsuya Takenouchi, MD, PhD²⁰; Hiraku Kokubu, MD²¹ ; Shusaku Ito, MD²²; Yoshiyasu Umeda, MD²³; Yuki Yamamoto, MD, PhD²⁴ ; Shoichiro Ishizuki, MD, PhD²⁵; Shiro Iino, MD, PhD²⁶; Hiroshi Uchi, MD, PhD²⁷; Tomoe Nakagawa, MD, PhD²⁸; Kazuhiro Inafuku, MD, PhD²⁹ ; Takahiro Haga, MD, PhD³⁰; Takahide Kaneko, MD, PhD³¹; Masahiro Nakagawa, MD, PhD³²; Hideki Kamiya, MD, PhD³³; Masaru Arima, MD, PhD³⁴; Toshihiko Hoashi, MD, PhD³⁵ ; Azusa Hiura, MD, PhD³⁶; Nobuo Kanazawa, MD, PhD³⁷ ; Keiko Manabe, MD, PhD³⁸; Masashi Ishikawa, MD³⁹; Kenji Asagoe, MD, PhD⁴⁰; Utsugi Iwasawa, MD, PhD⁴¹ ; Takafumi Kadono, MD, PhD⁴² ; Naohito Hatta, MD, PhD⁴³ ; Shoichiro Minami, MD, PhD⁴⁴; Eiji Nakano, MD, PhD³ ; Dai Ogata, MD, PhD³ ; Satoshi Fukushima, MD, PhD⁴ ; Hisashi Uhara, MD, PhD⁷; Kenta Nakama, MD, PhD⁹ ; and Yasuhiro Nakamura, MD, PhD¹ 

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ABSTRACT

PURPOSE Adjuvant anti–PD-1 (adj PD-1) antibodies are extensively used to improve survival in patients with resected melanoma. Clinical trials on adj PD-1 antibodies have revealed significant improvements in recurrence-free survival (RFS); however, few of these trials have included patients with acral melanoma (AM).

METHODS Clinical data were retrospectively collected from Japanese patients who underwent resection of stage III sole AM between 2014 and 2021. Survival outcomes, including RFS, distant metastasis-free survival (DMFS), and overall survival (OS), were compared between patients without adjuvant therapy (OBS group) and those receiving adj PD-1 group.

RESULTS This study included 139 patients (OBS: 79; adj PD-1: 60), with a median follow-up of 2.6 years. The baseline characteristics were comparable, except for age and nodal metastasis. No significant differences in survival were observed between the OBS and adj PD-1 groups (3-year RFS: 36.7% v 27.5%, $P = .13$; 3-year DMFS: 51.0% v 45.3%, $P = .51$; 3-year OS: 65.3% v 67.4%, $P = .45$). Multivariate analysis showed no survival benefit of adj PD-1 (RFS: hazard ratio [HR], 1.25, $P = .29$; DMFS: HR, 1.03, $P = .89$; and OS: HR, 0.69, $P = .23$). Each survival outcome after propensity score matching confirmed no significant difference between the matched OBS group ($n = 52$) and adj PD-1 group ($n = 52$; 3-year RFS: 34.3% v 25.9%, $P = .22$; 3-year DMFS: 45.6% v 46.5%, $P = .85$; 3-year OS: 60.7% v 68.9%, $P = .29$).

CONCLUSION Adj PD-1 did not improve the prognosis in sole AM. However, further studies are essential to evaluate the efficacy of the adj anti–PD-1 antibody in AM.

ACCOMPANYING CONTENT

 Appendix

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INTRODUCTION

Melanoma is one of the most lethal malignant neoplasms in dermatologic oncology. Previously, surgery was the only effective treatment; however, the introduction of new therapeutic agents, including molecular-targeted therapies and immune checkpoint inhibitors (ICIs), has significantly improved the prognosis of melanoma in advanced stages.^{1–3}

These treatments also enhance survival in patients with postoperative stage IIB to IV melanoma in the adjuvant setting.^{4–6}

Acral melanoma (AM) is a clinical subtype of melanoma that is common in Asians but rare in Caucasians.⁷ The incidence of AM is reported to be 40%–70% in Asians and 1%–7% in Caucasians.⁸ Therefore, in both advanced and adjuvant

CONTEXT

Key Objective

We aimed to analyze survival differences between patients with sole acral melanoma (AM) who did not receive adjuvant therapy (OBS group) and those who received adj PD-1 (adj PD-1 group).

Knowledge Generated

After propensity score matching, the Kaplan-Meier analysis demonstrated no significant differences in recurrence-free survival, distant metastasis-free survival, and overall survival (OS) between the matched OBS and adj PD-1 groups (3-year recurrence-free survival: 34.3% v 25.9%, $P = .22$; 3-year distant metastasis-free survival: 45.6% v 46.5%, $P = .85$; and 3-year OS: 60.7% v 68.9%, $P = .29$).

Relevance

Adj PD-1 therapy did not improve the prognosis in patients with sole AM. Careful consideration is required when administering this therapy in clinical practice.

settings, limited cases of AM were included in major phase III clinical trials analyzing the clinical efficacy of these agents particularly in Western countries.^{1-4,6,9-12} In the CheckMate 238 and KEYNOTE-716 trials, which investigated the anti-PD-1 antibodies (nivolumab and pembrolizumab), patients with AM accounted for only 5% (34 of 672 patients) and 5% (51 of 976 patients), respectively.^{11,12} The subgroup analysis in CheckMate 238 indicated no survival benefit of adjuvant nivolumab compared with ipilimumab in the AM cohort (hazard ratio [HR], 1.04, 95% CI, 0.49 to 2.22), with no data on AM available from KEYNOTE-054.⁹ Given its rarity, conducting prospective studies on AM is challenging, making the efficacy of adjuvant anti-PD-1 (adj PD-1) in the real-world setting crucial for guiding clinical decisions regarding adjuvant therapy.

Regarding genetic analysis, the tumor mutation burden (TMB) of AM is lower than that of nonacral cutaneous melanoma, which arises in sun-exposed areas. Furthermore, the frequency of structural variants is higher in AM than in non-AM.¹³ TMB is highly associated with the response to ICIs, with tumors showing higher efficacy with ICI treatment.¹⁴

Several retrospective studies have revealed that the efficacy of ICIs in advanced melanoma varies depending on the clinical subtype.¹⁵⁻²¹ Anti-PD-1 antibody-based therapy is reported to be less effective for AM than for nonacral cutaneous melanoma.¹⁵⁻¹⁹ Although the efficacy of ICIs is limited in advanced AM, there is a knowledge gap specific to the adjuvant setting in this population. Recent retrospective studies have indicated that adj PD-1 is less effective in AM than in nonacral cutaneous melanoma.²²⁻²⁴ Although these study results raise the clinical question of whether ICIs significantly prolong survival compared with no adjuvant treatment. However, very few studies have compared the efficacy of adjuvant ICIs with that of no adjuvant treatment for AM.²⁵⁻²⁷ We retrospectively investigated the

impact of adj PD-1 on the survival outcomes of patients with sole AM.

METHODS

Patients and Study Design

We retrospectively collected the clinical data from the electronic medical records of patients with stage III resected sole AM across 44 Japanese institutions. All patients underwent wide local excision (WLE) of the primary tumor and achieved histologic complete resection of the tumor between July 2014 and August 2021. Patient ages at the time of surgery ranged from 20 to 90 years. Patients who underwent amputation were excluded. TNM staging was performed in accordance with the American Joint Committee on Cancer (8th edition). Data collected included age, sex, Breslow thickness (BT), ulceration status of the primary tumor, nodal metastasis, sentinel lymph node biopsy (SLNB), complete lymph node dissection (CLND), substage, and adjuvant therapy. Prognosis was compared between two groups: those without adjuvant therapy (OBS group) and those who received adj PD-1 (adj PD-1 group). The second group included patients who received at least one cycle of adj PD-1 regimen. Adverse events (AEs) were graded on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. This study was approved by the local institutional ethics board (IRB No.2023-022). Informed consent was waived owing to the retrospective nature of the study and the use of anonymized data. All research procedures were performed according to the principles of the Declaration of Helsinki.

Efficacy Assessment

The primary outcome measures were recurrence-free survival (RFS) and distant metastasis-free survival (DMFS). The secondary outcome measure was overall survival (OS). RFS,

DMFS, and OS were defined as the time from WLE until new radiologic or clinical development of any tumor (RFS), distant metastasis (DMFS), death from any cause (RFS, DMFS, and OS), or last follow-up (RFS, DMFS, and OS).

Statistical Analyses

We compared the baseline characteristics between the OBS and adj PD-1 groups using Fisher's exact test for categorical variables and the Mann-Whitney *U* test for continuous variables. Treatment outcomes were estimated using the Kaplan-Meier analysis and compared between the two groups. One-year and 3-year survival times, along with 95% CI, were provided for each outcome. A Cox multivariate analysis was performed, including age, sex, BT, ulceration status, nodal metastasis, CLND, and adjuvant therapy. HR and *P* values were reported for each variable. Propensity score matching (PSM) was used to balance baseline patient characteristics—age, sex, BT, ulceration status, nodal metastasis, and adjuvant therapy—between the two groups in a 1:1 ratio. After PSM, survival differences were evaluated using Kaplan-Meier analysis. All statistical analyses were performed using EZR version 1.63 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), an adjusted version of R commander.²⁸ Statistical significance was defined as a two-sided *P* value of <.05.

RESULTS

Baseline Characteristics

This study included 139 patients (OBS group: 79, adj PD-1 group: 60) with resected sole AM and a median follow-up period of 2.6 years (OBS group: 2.5 years; adj PD-1 group: 2.7 years; [Table 1](#), [Fig 1](#)). The median patient age was 73 years in the entire cohort. The OBS group included significantly older patients than the adj PD-1 group (age ≥65 years: 87% v 72%, *P* = .03). A significant difference in nodal metastasis was observed (N1: 48% v 48%, N2: 39% v 23%, N3: 13% v 28%, *P* = .03). No significant differences were found between the two groups regarding BT, ulceration status, SLNB, CLND, or substage ([Table 1](#)). In the adj PD-1 group, nivolumab was administered to 34 patients and pembrolizumab to 26 patients. Twenty-seven patients (45%) completed 12 months of adjuvant therapy (median duration: 11.5 months, interquartile range: 4.0–12.0 months). The main reasons for treatment discontinuation were disease recurrence (17 patients, 28%) and toxicity (eight patients, 13%).

RFS, DMFS, and OS

No significant differences were found in RFS, DMFS, or OS between the OBS and adj PD-1 groups (1- and 3-year RFS: 58.9% v 55.0% and 36.7% v 27.5%, *P* = .13; 1- and 3-year DMFS: 79.4% v 76.5% and 51.0% v 45.3%, *P* = .51; 1- and 3-year OS: 95.9% v 96.6% and 65.3% v 67.4%, *P* = .45; [Figs 2A–2C](#)).

TABLE 1. Baseline Characteristics

Variable	OBS Group	Adj PD-1 Group	<i>P</i>
Total, No.	79	60	
Age, years, No. (%)			
<65	10 (13)	17 (28)	.03
≥65	69 (87)	43 (72)	
Sex, No. (%)			
Male	45 (57)	39 (65)	.38
Female	34 (43)	21 (35)	
Breslow thickness median, mm (range)	4.90 (0.4–20.0)	4.70 (1.0–24.0)	.44
Ulceration, No. (%)			
Absent	25 (32)	19 (32)	.99
Present	54 (68)	41 (68)	
Nodal metastasis, No. (%)			
N1	38 (48)	29 (48)	.03
N2	31 (39)	14 (23)	
N3	10 (13)	17 (28)	
SLNB, No. (%)			
Not performed	12 (15)	13 (22)	.37
Performed	67 (85)	47 (78)	
CLND, No. (%)			
Not performed	41 (52)	24 (40)	.17
Performed	38 (48)	36 (60)	
Stage (AJCC 8th), No. (%)			
IIIA	6 (8)	3 (5)	.22
IIIB	18 (22)	7 (12)	
IIIC	47 (60)	39 (65)	
IIID	8 (10)	11 (18)	

Abbreviations: Adj PD-1, adjuvant PD-1 antibody monotherapy; AJCC, The American Joint Committee on Cancer; CLND, complete lymph node dissection; n, number; OBS, observation; SLNB, sentinel lymph node biopsy.

Cox Multivariate Analysis in Terms of RFS, DMFS, and OS

A higher BT negatively affected DMFS and OS (DMFS: HR, 1.08 [95% CI, 1.02 to 1.61]; *P* = .008; OS: HR, 1.09 [95% CI, 1.01 to 1.18]; *P* = .02). Other variables, including age, sex, primary tumor ulceration, and CLND, were not associated with RFS, DMFS, or OS. Similarly, adj PD-1 did not positively affect survival outcomes (RFS: HR, 1.25 [95% CI, 0.82 to 1.90]; *P* = .29; DMFS: HR, 1.03 [95% CI, 0.63 to 1.66]; *P* = .69; OS: HR, 0.69 [95% CI, 0.38 to 1.26]; *P* = .23; [Table 2](#)).

Survival Outcomes After PSM

After PSM on the basis of baseline characteristics, except for TNM stage, 52 patients from the OBS and adj PD-1 groups were identified as matched cohorts ([Table 3](#)). No significant differences in survival outcomes were observed between the

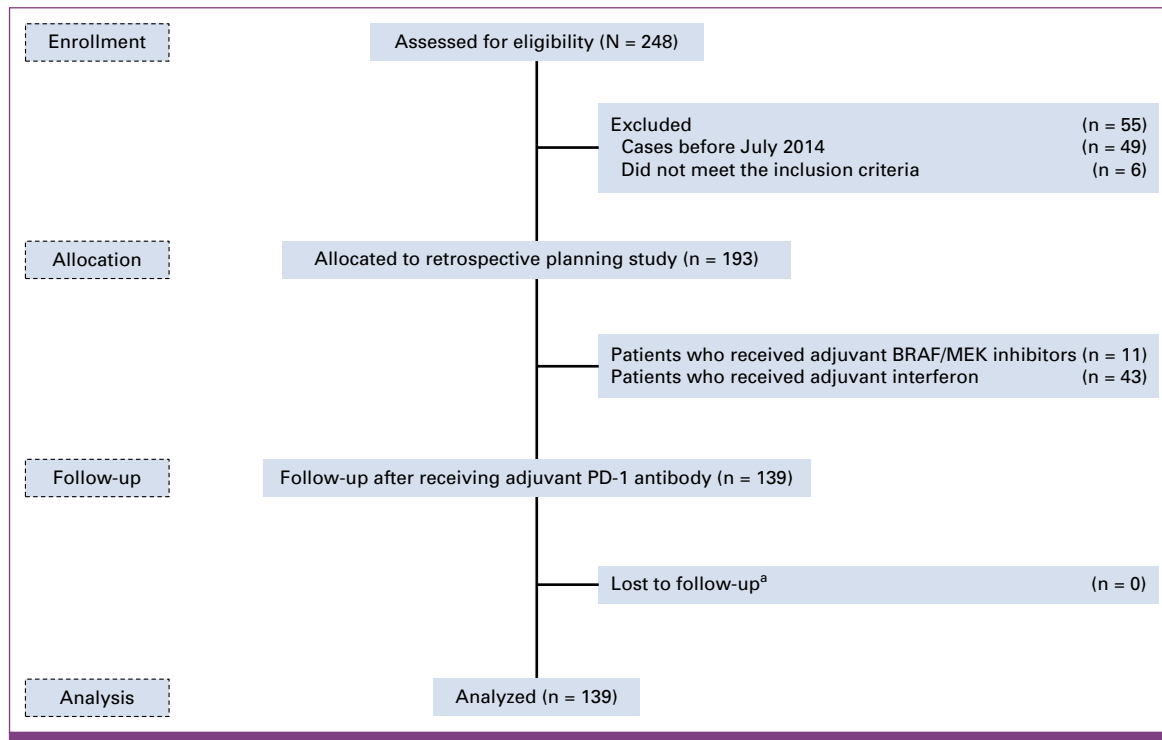


FIG 1. Flowchart on enrollment, allocation, follow-up, and analysis of this study. ^aPatients who never visited a medical examination after surgery or the initiation of adjuvant therapy. n, number.

two groups (1- and 3-year RFS: 53.6% v 53.8% and 34.3% v 25.9%, $P = .22$; 1- and 3-year DMFS: 74.7% v 78.7% and 45.6% v 46.5%, $P = .85$; 1- and 3-year OS: 95.9% v 96.1% and 60.7% v 68.9%, $P = .29$; Figs 3A–3C).

Recurrence Patterns

Recurrence pattern profiles were similar in both matched groups. The most common recurrence pattern was distant metastasis (OBS group 42%, adj PD-1 group 61%), followed by in-transit or satellite metastasis (OBS group 36%, adj PD-1 group 40%), regional lymph node metastasis (OBS group 34%, adj PD-1 group 38%), and local recurrence (OBS group 3%, adj PD-1 group 7%; Appendix Table A1).

AEs in the Adj PD-1 Group

In the adj PD-1 group, eight cases of immune-related AEs (13%) leading to treatment discontinuation were observed: pneumonitis (Grade [G] 1, one patient; G2, one patient; G3, one patient), skin disorder (G3, two patients), adrenal gland dysfunction (G3, one patient), hyperamylasemia (G3, one patient), and colitis (G1, one patient).

DISCUSSION

In this study, Kaplan–Meier analyses revealed that adj PD-1 did not prolong RFS, DMFS, or OS compared with non-adjuvant treatment in Japanese patients with sole AM. Cox multivariate and Kaplan–Meier analyses after PSM also

demonstrated that adj PD-1 therapy did not significantly affect RFS, DMFS, or OS.

In a phase III randomized trial, CheckMate 238 compared the efficacy of adjuvant nivolumab and adjuvant ipilimumab. The adjuvant nivolumab arm demonstrated a significantly longer RFS in stage IIIB, IIIC, and stage IV resected melanomas (4-year RFS: 51.7% v 41.2%, $P < .001$).¹¹ However, this trial did not compare the efficacy of nivolumab with that of nonadjuvant treatment. Similarly, in the phase III randomized trial KEYNOTE-054, the adjuvant pembrolizumab arm showed significantly improved RFS than the placebo arm in resected stage IIIA, IIIB, and IIIC melanomas (3-year RFS: 63.7% v 44.1%, $P < .001$).⁹ This result differs from that of this study. Several retrospective studies suggest that AM responds less to ICI than nonacral cutaneous melanoma in advanced stages.^{15,16} However, whether ICIs are also associated with lower responses to AM in adjuvant settings is unclear, because few studies have investigated the efficacy of adj PD-1 in AM. No prospective trials focusing on AM exist; only three retrospective studies have compared survival between the adj PD-1 group and other comparison groups, including those with no adjuvant treatment.^{25–27}

Maeda et al reported the efficacy of adjuvant nivolumab in AM.²⁵ This retrospective study involved 27 Japanese patients with resected stage III to IV AM (adj PD-1: five patients; other adjuvant therapies or no adjuvant therapy: 22 patients). The adj PD-1 did not prolong disease-free survival (DFS; $P = .15$). Although the results of this study are similar to those of this

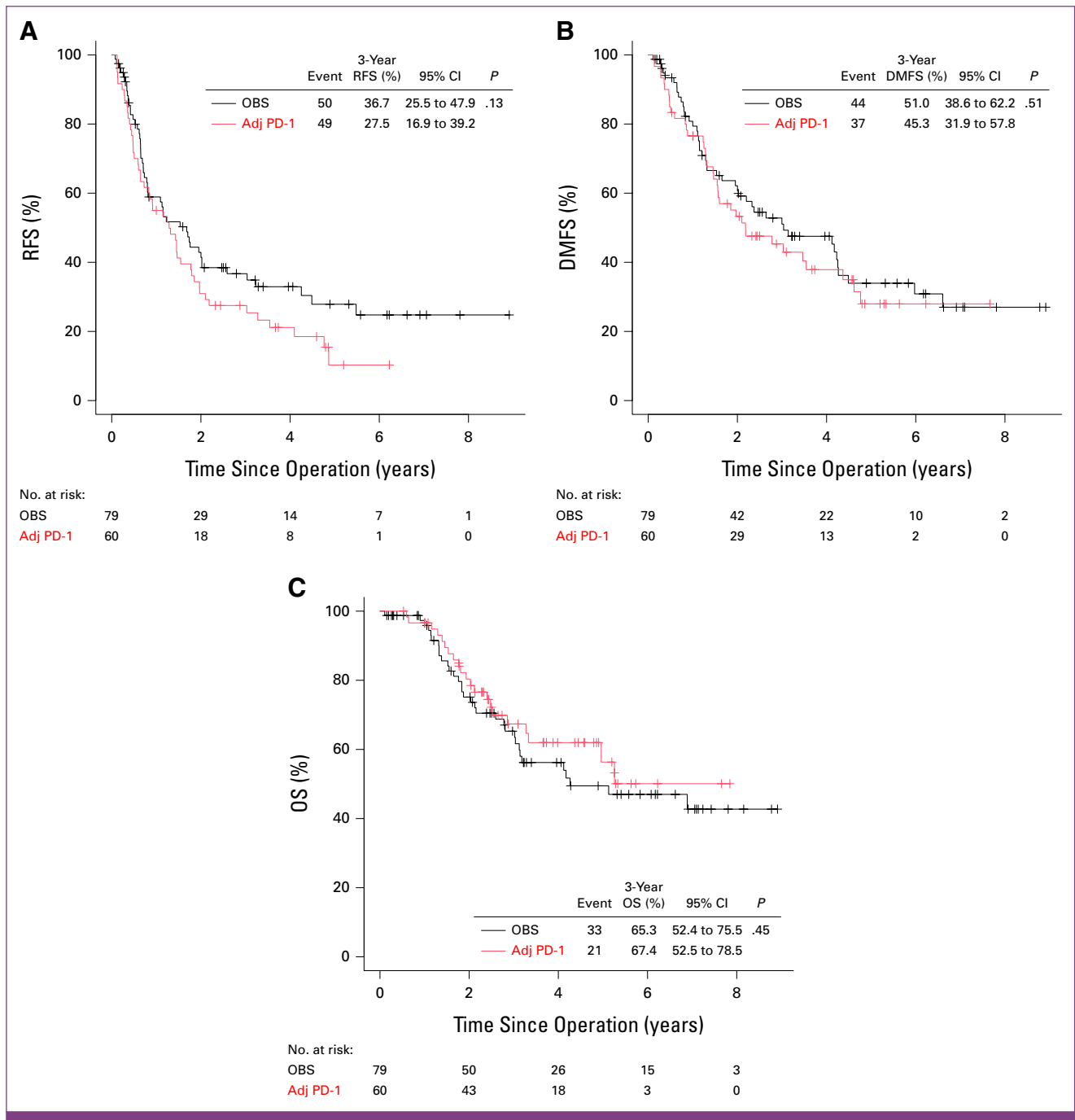


FIG 2. Kaplan-Meier survival curves of (A) RFS, (B) DMFS, and (C) OS. No significant differences in RFS, DMFS, or OS were observed between the patients who did not receive adjuvant therapy (OBS group) and those who received adjuvant anti-PD-1 antibody (adj PD-1 group). DMFS, distant metastasis-free survival; OS, overall survival; RFS, recurrence-free survival.

study, the sample size in the adj PD-1 group was extremely small compared with that in the groups with heterogeneous treatment modalities, including adjuvant chemotherapy (four patients), interferon-beta (12 patients), and no adjuvant treatment (six patients).

Arak et al reported the survival of patients treated with adjuvant therapies, including anti-PD-1 antibody, compared with those treated without adjuvant treatment in

2024.²⁷ This study included 114 Turkish patients with resected stage III to IV AM (adj PD-1 antibody, 31 patients; temozolomide, nine patients; interferon, 19 patients; BRAF/MEK inhibitors, five patients; without adjuvant therapy, 50 patients). DFS and OS in the patients who received adjuvant therapies were significantly prolonged than those in the patients without adjuvant therapy (median DFS: 24 months v 15 months, $P = .05$; median OS: 71 months v 38 months, $P = .02$). Cox multivariate analysis showed a positive impact

TABLE 2. Cox Multivariate Analysis

Variable	RFS			DMFS			OS		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Age, years									
<65	Ref			Ref			Ref		
≥65	1.37	0.81 to 2.34	.23	1.24	0.67 to 2.29	.48	1.62	0.72 to 3.63	.23
Sex									
Male	Ref			Ref			Ref		
Female	0.91	0.60 to 1.40	.69	0.68	0.42 to 1.01	.12	0.94	0.53 to 1.68	.85
Breslow thickness ^a	1.04	0.97 to 1.13	.20	1.08	1.02 to 1.61	.008	1.09	1.01 to 1.18	.02
Ulceration									
Absent	Ref			Ref			Ref		
Present	1.01	0.64 to 1.59	.95	1.14	0.69 to 1.89	.58	0.99	0.52 to 1.85	.98
Nodal metastasis									
N1	Ref			Ref			Ref		
N2	1.53	0.94 to 2.50	.08	1.19	0.68 to 2.07	.52	1.01	0.51 to 1.99	.97
N3	1.57	0.87 to 2.85	.66	1.48	0.79 to 2.76	.21	1.65	0.76 to 3.60	.20
CLND									
Not performed	Ref			Ref			Ref		
Performed	1.01	0.65 to 1.57	.93	0.99	0.61 to 1.62	.99	0.97	0.51 to 1.81	.93
Adjuvant therapy									
None	Ref			Ref			Ref		
Anti-PD-1 ab	1.25	0.82 to 1.90	.29	1.03	0.63 to 1.66	.89	0.69	0.38 to 1.26	.23

Abbreviations: Anti-PD-1 ab, anti-programmed death-1 receptor antibody; CLND, complete lymph node dissection; DMFS, distant metastasis-free survival; HR, hazard ratio; OS, overall survival; RFS, recurrence-free survival; Ref, reference.

^aContinuous category.

TABLE 3. Baseline Characteristics After Propensity Score Matching

Variable	OBS Group	Adj PD-1 Group	P
Total, No.	52	52	
Age, years, No. (%)			
<65	10 (19)	9 (17)	.99
≥65	42 (81)	43 (83)	
Sex, No. (%)			
Male	33 (64)	33 (64)	.99
Female	19 (36)	19 (36)	
Breslow thickness median, mm (range)	5.00 (1.0-20.0)	4.70 (1.6-24.0)	.88
Ulceration, No. (%)			
Absent	16 (31)	15 (29)	.99
Present	36 (69)	37 (71)	
Nodal metastasis, No. (%)			
N1	23 (45)	27 (52)	.22
N2	21 (40)	13 (25)	
N3	8 (15)	12 (23)	
CLND, No. (%)			
Not performed	26 (50)	22 (42)	.55
Performed	26 (50)	30 (58)	

Abbreviations: Adj PD-1, adjuvant PD-1 antibody monotherapy; CLND, complete lymph node dissection; n, number; OBS, observation.

on DFS and OS in adjuvant therapy (DFS: HR, 1.79, $P = .02$; OS: HR, 2.99, $P = .01$). However, univariate analysis revealed a negative impact of DFS and OS in adj PD-1 compared with no adjuvant therapy, temozolomide, interferon, or BRAF/MEK inhibitors (DFS: $P = .48$; OS: $P = .12$). Furthermore, no survival data comparing patients with adj PD-1 and without adjuvant therapy were available.

A global retrospective study, conducted by Jacques et al²⁶ in 2024, evaluated the efficacy of adj PD-1–based therapy in AM. In this study, 330 patients with resected AM were included (adj PD-1, 138 patients; without adjuvant therapy, 192 patients). After PSM, prognosis was compared between the two groups of 138 patients. Patients who received adj PD-1 showed significantly prolonged RFS and OS compared with those who did not receive adjuvant therapy (RFS, $P = .01$; OS, $P = .01$). To our knowledge, this study is the only one to compare adj PD-1 with no adjuvant treatment. Although the results of that study were different from those of this study, a severe selection bias was observed between the two groups. The baseline characteristics between the adj PD-1 and nonadjuvant therapy groups remained significantly different at the primary site, even after PSM (palmar area: 2.2% v 78.3%, plantar area: 70.3% v 9.4%, subungual: 26.8% v 12.3%, $P < .001$). The imbalance in distribution at the primary site may lead to inaccurate evaluation of the efficacy of

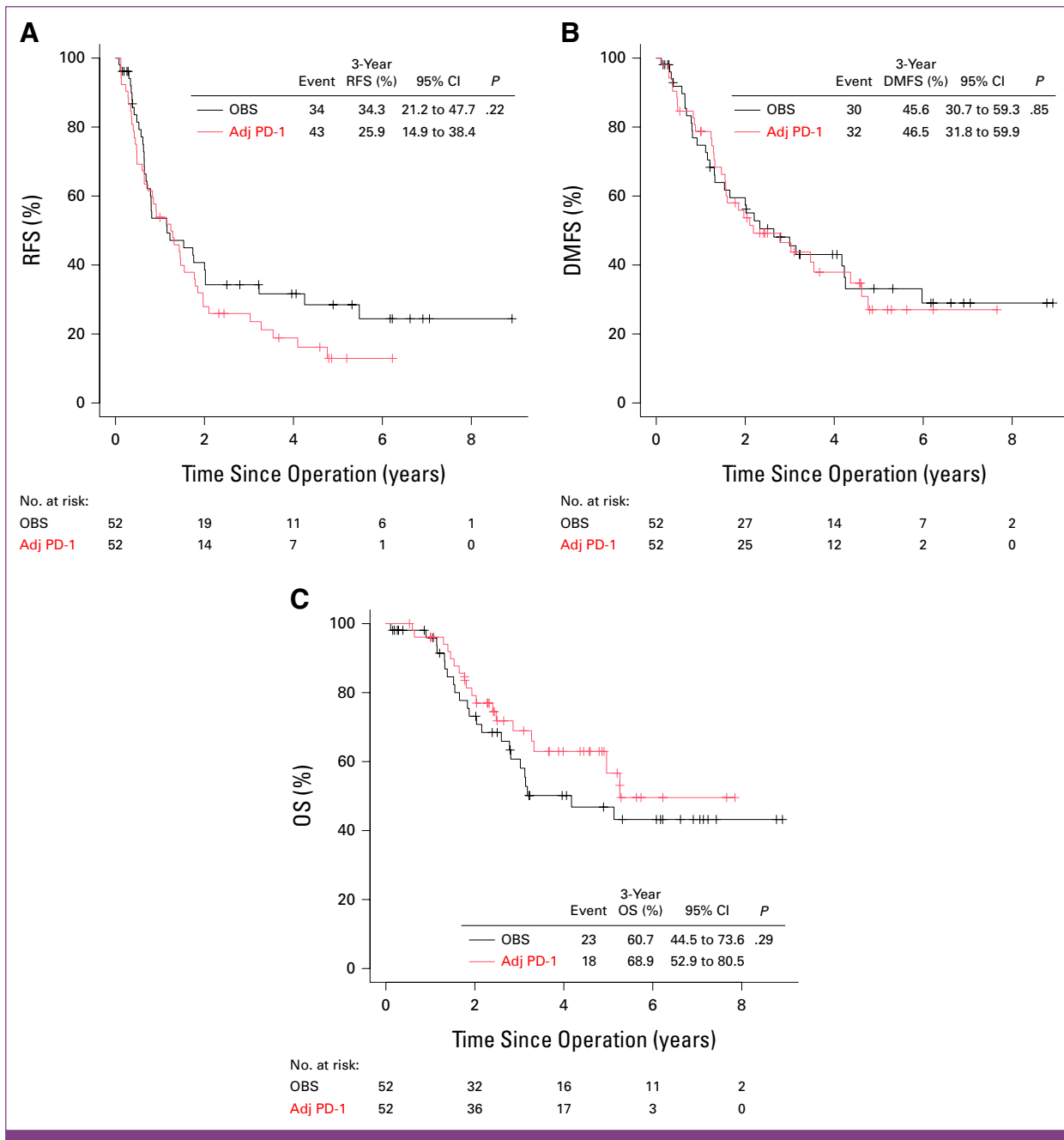


FIG 3. Kaplan-Meier survival curves of (A) RFS, (B) DMFS, and (C) OS. Even after PSM, no significant differences in RFS, DMFS, or OS were found between patients who did not receive adjuvant therapy (OBS group) and those who received adjuvant anti-PD-1 antibody (adj PD-1 group). DMFS, distant metastasis-free survival; OS, overall survival; PSM, propensity score matching; RFS, recurrence-free survival.

adjuvant ICI therapies. Several retrospective studies with larger sample sizes indicate different clinical efficacies of ICIs between subungual AM and palm and sole AM in advanced settings.

Nakamura et al¹⁹ reported that the objective response rate of anti-PD-1 antibody in subungual AM was significantly lower than that in palm and sole AM (8% v 21%, $P = .008$), and OS was significantly shorter in subungual AM (median OS:

3.3 months v 4.1 months, $P = .003$). These results suggest that the efficacy of adj PD-1 in subungual AM and palm and sole AM should be analyzed separately in the adjuvant setting. The different periods of patient selection between the two groups in this study may have had a significant impact on the differences in prognosis.²⁶ Patients who received adj PD-1 from the time of availability of anti-PD-1 antibodies as adjuvant therapy until November 2021 were included in this study. Patients who were diagnosed between 1994 and 2018,

and did not receive adjuvant therapy were included as controls. The latter group included many patients who underwent different surgical treatments and had few opportunities to receive ICIs as the disease progressed. The patients' heterogeneous ethnicity, including Caucasians, East Asians, Southeast Asians, Hispanics, and Africans, may have influenced survival and led to a difficult interpretation of the study results.

To overcome the selection bias and heterogeneity of cohorts in previous studies, our study targeted East Asian (Japanese) patients with only sole AM. Additionally, we set the patient selection period for inclusion in this study to July 2014, when nivolumab was approved in Japan as the first ICI for advanced melanoma. This would lead to equal opportunities to use ICIs in both patient groups when they progress to an advanced stage.

This study did not include patients who underwent amputation. The current surgical standard of care for primary region of sole AM is WLE without amputation. Bulky and

deep-penetrating primary disease that requires amputation is extremely rare, and ICIs are usually used for limb preservation in unresectable cases.²⁹

Our study has several limitations. First, we focused on East Asian patients with only sole AM, and the efficacy of adj PD-1 in other forms of AM, such as palmar and subungual AM, or in different ethnic groups, remains unclear. Second, the follow-up period was limited because nivolumab and pembrolizumab were approved for use in Japan between 2018 and 2021, respectively. Finally, we did not collect detailed treatment information after the patients progressed to an advanced stage.

In conclusion, despite these limitations, this study did not demonstrate a survival benefit of adj PD-1 in contrast to no adjuvant treatment in Japanese patients with resected stage III sole AM, thus contradicting the findings of a previous study.²⁶ Although further studies are needed to validate the use of adjuvant ICI for AM, adj PD-1 therapy should be used with caution, at least in East Asian patients with sole AM.

AFFILIATIONS

¹Department of Skin Oncology/Dermatology, Saitama Medical University International Medical Center, Saitama, Japan

²Department of Dermatology, Chiba University, Chiba, Japan

³Department of Dermatologic Oncology, National Cancer Center Hospital, Tokyo, Japan

⁴Department of Dermatology and Plastic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

⁵Department of Dermatology, Mie University, Mie, Japan

⁶Department of Dermatology, Shinshu University, Matsumoto, Japan

⁷Department of Dermatology, Sapporo Medical University School of Medicine, Sapporo, Japan

⁸Department of Dermatology, Hyogo Cancer Center, Akashi, Japan

⁹Department of Dermatology, Kurume University School of Medicine, Kurume, Japan

¹⁰Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

¹¹Department of Dermatology, Gunma University, Gunma, Japan

¹²Department of Dermatology and Allergology, Nagasaki University Hospital, Nagasaki, Japan

¹³Department of Dermatology, Jichi Medical University, Tochigi, Japan

¹⁴Department of Dermatology, Jichi Medical University, Saitama Medical Center, Saitama, Japan

¹⁵Department of Dermatology, Kyoto Prefectural University of Medicine, Kyoto, Japan

¹⁶Department of Dermatology, University of Tokyo, Tokyo, Japan

¹⁷Department of Dermato-Oncology, NHO Kagoshima Medical Center, Kagoshima, Japan

¹⁸Department of Dermatology, Keio University School of Medicine, Tokyo, Japan

¹⁹Department of Dermatology, Toranomon Hospital, Tokyo, Japan

²⁰Department of Dermatology, Niigata Cancer Center Hospital, Niigata, Japan

²¹Department of Dermatology, Shiga University of Medical Science, Otsu, Japan

²²Department of Dermatology, Hitachi General Hospital, Hitachi, Japan

²³Department of Dermatology, Kawasaki Medical School, Kurashiki, Japan

²⁴Department of Dermatology, Wakayama Medical University, Wakayama, Japan

²⁵Department of Dermatology, University of Tsukuba, Tsukuba, Japan

²⁶Department of Dermatology, University of Fukui, Fukui, Japan

²⁷Department of Dermato-Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

²⁸Department of Dermatology, Asahikawa Medical University, Asahikawa, Japan

²⁹Department of Dermatology, Kimitsu Chuo Hospital, Kisarazu, Japan

³⁰Department of Dermatology, Kesennuma City Hospital, Miyagi, Japan

³¹Department of Dermatology, Juntendo University Urayasu Hospital, Urayasu, Japan

³²Department of Plastic and Reconstructive Surgery, Hamamatsu University School of Medicine, Hamamatsu, Japan

³³Department of Dermatology, Central Japan International Medical Center, Gifu, Japan

³⁴Department of Dermatology, Fujita Health University School of Medicine, Aichi, Japan

³⁵Department of Dermatology, Nippon Medical School Hospital, Tokyo, Japan

³⁶Department of Dermatology, Teikyo University, Tokyo, Japan

³⁷Department of Dermatology, Hyogo Medical University, Hyogo, Japan

³⁸Department of Dermatology, Takamatsu Red Cross Hospital, Takamatsu, Japan

³⁹Department of Dermatology, Saitama Cancer Center, Saitama, Japan

⁴⁰Department of Dermatology, NHO Okayama Medical Center, Okayama, Japan

⁴¹Department of Dermatology, Metropolitan Hiroo Hospital, Tokyo, Japan

⁴²Department of Dermatology, St Marianna University, Kawasaki, Japan

⁴³Department of Dermatology, Toyama Prefectural Central Hospital, Toyama, Japan

⁴⁴Department of Dermatology, Itami City Hospital, Itami, Japan

CORRESPONDING AUTHOR

Yasuhiro Nakamura, MD, PhD; e-mail: ynakamur@saitama-med.ac.jp.

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AUTHOR CONTRIBUTIONS

Conception and design: Shigeru Koizumi, Takahide Kaneko, Toshihiko Hoashi, Masashi Ishikawa, Utsugi Iwasawa, Hisashi Uhara, Yasuhiro Nakamura

Financial support: Utsugi Iwasawa, Yasuhiro Nakamura

Administrative support: Shigeru Koizumi, Yutaka Kuwatsuka, Utsugi Iwasawa, Hisashi Uhara, Yasuhiro Nakamura

Provision of study materials or patients: Shigeru Koizumi, Naoya Yamazaki, Takuya Miyagawa, Yosuke Yamamoto, Takashi Inozume, Shusaku Ito, Yuki Yamamoto, Shoichiro Ishizuki, Kazuhiro Inafuku, Takahiro Haga, Masahiro Nakagawa, Masaru Arima, Azusa Hiura, Utsugi Iwasawa, Shoichiro Minami, Hisashi Uhara, Kenta Nakama, Yasuhiro Nakamura

Collection and assembly of data: Shigeru Koizumi, Naoya Yamazaki, Yuki Ichigozaki, Hiroshi Kitagawa, Yukiko Kiniwa, Sayuri Sato, Toshihiro Takai, Reiichi Doi, Takamichi Ito, Masahito Yasuda, Yutaka Kuwatsuka, Takeo Maekawa, Jun Asai, Takuya Miyagawa, Shigeto Matsushita, Yosuke Yamamoto, Takashi Inozume, Akiko Kishi, Tatsuya Takenouchi, Hiraku Kokubu, Shusaku Ito, Yoshiyasu Umeda, Yuki Yamamoto, Shoichiro Ishizuki, Shiro Iino, Hiroshi Uchi, Tomoe Nakagawa, Kazuhiro Inafuku, Takahiro Haga, Takahide Kaneko, Masahiro Nakagawa, Hideki Kamiya, Masaru Arima, Toshihiko Hoashi, Azusa Hiura, Nobuo Kanazawa, Keiko Manabe, Masashi Ishikawa, Kenji Asagoe, Utsugi Iwasawa, Takafumi Kadono, Naohito Hatta, Shoichiro Minami, Eiji Nakano, Dai Ogata, Satoshi Fukushima, Hisashi Uhara, Kenta Nakama, Yasuhiro Nakamura

Data analysis and interpretation: Shigeru Koizumi, Takeru Funakoshi, Takahide Kaneko, Masahiro Nakagawa, Toshihiko Hoashi, Masashi Ishikawa, Utsugi Iwasawa, Hisashi Uhara, Yasuhiro Nakamura

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Naoya Yamazaki

Consulting or Advisory Role: Ono Pharmaceutical, Otsuka, AstraZeneca, Astellas Pharma, Eisai, Chugai Pharma, Merck

Speakers' Bureau: Ono Pharmaceutical, Bristol Myers Squibb Japan, Novartis, MSD

Research Funding: Bristol Myers Squibb Japan (Inst), Novartis (Inst), Takara Bio (Inst), HUYA Bioscience International (Inst), MSD (Inst), Regeneron (Inst)

Yukiko Kiniwa

Honoraria: Ono Pharmaceutical, Bristol Myers Squibb Japan, Sanofi, Otsuka, Novartis, AstraZeneca, Mitsubishi Tanabe Pharma

Toshihiro Takai

Speakers' Bureau: Ono Pharmaceutical

Takeo Maekawa

Speakers' Bureau: Ono Pharmaceutical, Novartis, Bristol Myers Squibb Japan

Jun Asai

Speakers' Bureau: MSD, Ono Yakuhin

Shigeto Matsushita

Speakers' Bureau: Ono Pharmaceutical, Novartis

Takeru Funakoshi

Honoraria: Maruho

Speakers' Bureau: Ono Pharmaceutical, Bristol Myers Squibb Japan, Maruho, Kyowa Kirin International, MSD, Novartis

Research Funding: Ono Pharmaceutical

Takashi Inozume

Speakers' Bureau: Ono Pharmaceutical, Maruho, BMS, Novartis

Research Funding: Maruho (Inst), Sun Pharma (Inst), Sato Pharmaceutical (Inst), Torii Pharmaceutical (Inst)

Tatsuya Takenouchi

Speakers' Bureau: Ono Pharmaceutical, MSD, Novartis, Bristol Myers Squibb Japan

Hiroshi Uchi

Speakers' Bureau: Ono Pharmaceutical, MSD

Masahiro Nakagawa

Stock and Other Ownership Interests: Medin Co

Uncompensated Relationships: Medin Co

Dai Ogata

Research Funding: MSD

Satoshi Fukushima

Speakers' Bureau: Sanofi, Taiho Pharmaceutical Co, Ltd

Research Funding: Sanofi, Taiho Pharmaceutical, Kyowa Kirin Co, Ltd, Nippon Kayaku

Hisashi Uhara

Consulting or Advisory Role: Ono Pharmaceutical

Speakers' Bureau: Ono Pharmacy, Novartis, Bristol Myers Squibb Japan, MSD

Yasuhiro Nakamura

Honoraria: Bristol Myers Squibb Japan, Ono Pharmaceutical, Novartis Pharmaceuticals UK Ltd, MSD Oncology, Mitsubishi Tanabe Pharma, Kyowa Kirin International, Maruho, Sun Pharma, LEO Pharma, Pierre Fabre

Consulting or Advisory Role: Novartis Pharmaceuticals UK Ltd, MSD Oncology

Research Funding: MSD Oncology (Inst), Parexel/CALYX (Inst)

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APPENDIX

TABLE A1. Pattern of Recurrence in the OBS and Adj PD-1 Groups After Propensity Score Matching

Group	Local Recurrence, No. (%)	In-Transit or Satellite Metastasis, No. (%)	Regional Lymph Node Metastasis, No. (%)	Distant Metastasis, n (%)
OBS group (n = 52)	2 (3)	19 (36)	18 (34)	22 (42)
Adj PD-1 group (n = 52)	4 (7)	21 (40)	20 (38)	32 (61)

Abbreviations: Adj PD-1, adjuvant PD-1 antibody monotherapy; n, number; OBS, observation.