ORIGINAL ARTICLE

Adjuvant Anti-PD-1 Antibody Therapy for Advanced Melanoma: A Multicentre Study of 78 Japanese Cases

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Anti-PD-1 antibodies (Abs) are among the optimal adjuvant therapies for melanoma at high risk of recurrence, especially BRAF wild-type melanoma, but the anti-tumour effects of anti-PD-1 Abs in the adjuvant setting for acral melanoma have not been evaluated previously. The aim of this study was to analyse the efficacy and safety profiles of anti-PD-1 Ab monotherapy in the adjuvant setting in an Asian population including a high ratio of acral melanoma. The efficacy and safety profiles of anti-PD-1 Ab monotherapy in the adjuvant setting were retrospectively analysed in 78 Japanese patients with advanced melanoma, including 31 cases (40%) of acral melanoma. Overall relapse-free survival was 60.3% (47 of 78 cases, 95% confidence interval (CI) 49.2–70.4%), and 39.7% of patients (31 of 78 patients, 95% CI 29.6–50.8%) relapsed during the adjuvant PD-1 Ab treatment. Six cases (7.9%) discontinued the protocol due to serious adverse events. One case (1.3%) discontinued the protocol due to trauma. The relapse-free survival of acral melanoma was 25.8%, whereas that of high cumulative sun damage was 60.0%, and that of low cumulative sun damage was 57.1%. The acral type had a significantly lower 12-month relapse-free survival than other cutaneous types ($p = 0.029$). The acral type appeared to be an independent prognostic factor on multivariate analysis ($p = 0.015$). Adverse events due to anti-PD-1 antibody were observed in 37.1% overall. The results of this study suggest that anti-PD-1 Ab therapy in the adjuvant setting is less effective for acral melanoma than for other cutaneous types.

Key words: adjuvant therapy; acral melanoma; relapse-free survival.

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SIGNIFICANCE

This study focuses on the efficacy of anti-PD1 antibodies in adjuvant setting for advanced cutaneous melanoma of 78 patients in Japan. The feature of the present cohort was that 31 cases had the acral type. In the present cohort, the anti-PD1 antibodies in the adjuvant setting is less effective in acral melanoma than in other cutaneous types, and the efficacy of anti-PD1 antibodies in the adjuvant setting in a Japanese non-acral cutaneous melanoma cohort was comparable to that in a Caucasian cohort. Thereby, the study suggests the efficacy of anti-PD1 antibodies in adjuvant setting is not sufficient for acral melanoma.

Melanoma is one of the most fatal skin tumours, with an estimated 5-year survival rate of stage III melanoma of 32–93% despite complete surgical resection (1, 2). Therefore, several adjuvant therapies for advanced melanoma have been developed over the decades (3). Anti-PD-1 antibodies (Abs) are among the optimal adjuvant therapies for melanoma at high risk of recurrence, especially BRAF wild-type melanoma (4, 5). Although resected cutaneous melanoma patients with stage IIIB-C or IV were mainly enrolled in clinical trials, the enrolled number of acral and mucosal melanoma cases was limited in Caucasian populations (4, 5). Acral melanomas are a common type in patients of Asian or African descent, predominantly affecting the palms, soles, and nail beds (non-sun-exposed areas) (6, 7). Since the rate of acral melanoma is limited in non-Hispanic white populations (1.5%) (8), investigations of the anti-tumour effects of anti-PD-1 Abs in the adjuvant setting for acral melanoma are limited (4, 9). Based on the above findings, it was hypothesized that anti-PD-1 Ab therapy in the adjuvant setting is less effective for acral melanoma than for cutaneous melanoma, unlike dabrafenib plus trametinib combination therapy in the adjuvant setting for the Japanese population (10). Therefore, it is important to evaluate the differences in the effect of anti-PD-1 Abs in the adjuvant setting between races, especially in the Asian population, to select the anti-melanoma drugs in the adjuvant setting for BRAF-mutated advanced melanoma. In this report, the anti-tumour effects and safety profiles of anti-PD-1

Abs in an adjuvant setting were evaluated in 78 cases of advanced melanoma, including 31 cases (40%) of acral melanoma in a Japanese population.

PATIENTS AND METHODS

Patients

A database collected by the dermatology departments at Tohoku University, Nagoya City University, Kumamoto University, Kyushu University, Jichi Medical University, Tsukuba University, Tokyo Metropolitan Cancer and Infectious Disease Center Komagome Hospital, Kyushu Cancer Center, Kagoshima Medical Center, and Wakayama Medical University was retrospectively reviewed to identify 78 patients with BRAF-mutated or wild-type melanoma who had been treated with anti-PD-1 Ab (nivolumab or pembrolizumab) monotherapy in the adjuvant setting, and who started adjuvant therapy between January 2019 and September 2020. Of the total 133 postoperative melanoma cases, 36 treated with BRAF and MEK inhibitors were excluded (**Fig. 1**).

The protocol was approved by the ethics committee of Tohoku University Graduate School of Medicine, Sendai, Japan (2020-1-811), and by each of the ethics committees of the participating institutions. Patients were intravenously administered nivolumab 240 mg every 2 weeks or 480 mg every 4 weeks for 12 months. Patients were intravenously administered pembrolizumab 200 mg every 3 weeks for 12 months. Treatment continued for 12 months or until disease relapse or unacceptable toxic effects.

Safety assessment

Safety assessment involved the collection of data on adverse events (AEs), results of clinical laboratory tests and physical examinations, and vital signs. Severity grade (Common Terminology Criteria for Adverse Events version 4.0 – Japan Clinical Oncology Group) and the relationship with anti-PD-1 Ab monotherapy were determined for each AE.

Endpoints

The primary endpoint was the 1-year relapse-free survival (RFS) rate, defined as the time from the start of therapy to disease recurrence or death from any cause. Secondary endpoints included safety. All disease recurrence analyses were based on investigator assessments. The safety analyses included all patients who had received at least 1 dose of anti-PD-1 inhibitor.

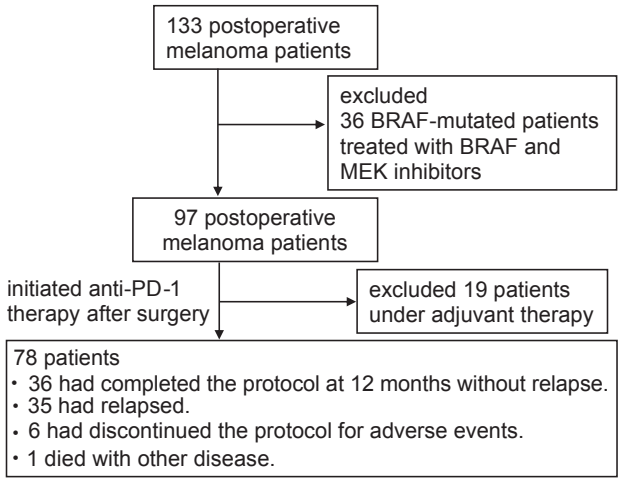

Fig. 1. Patient enrolment for adjuvant anti-PD-1 antibody monotherapy.

Statistical analysis

The RFS rate was estimated for each group using the Kaplan–Meier method. The log-rank test was used to compare survival between groups. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) were estimated using a Cox's proportional hazards model on univariate analysis. Cox proportional hazards models were also used for multivariate analyses. The significance level for all tests was a 2-sided α=0.05. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Table I. Patients' baseline characteristics (*n* = 78)

Characteristics	
Age, years, median (range)	68 (14–85)
Sex, *n* (%)	
Male	45 (58)
Female	33 (42)
Clark's histological classification, *n* (%)	
Superficial spreading melanoma	19 (24)
Nodular melanoma	8 (10)
Lentigo maligna melanoma	3 (4)
Acral lentiginous melanoma	31 (40)
Not reported	17 (22)
Acral, CSD, Non-CSD grouping, *n* (%)	
High-CSD	10 (13)
Low-CSD	21(27)
Acral	31 (40)
Mucosal	11 (14)
Unknown	5 (6)
Clinical stage at adjuvant setting, *n* (%)	
IIIA	3 (4)
IIIB	12 (15)
IIIC	39 (50)
IIID	3 (4)
IV	13 (17)
Not reported	8 (10)
Type of lymph node involvement in patients with stage III disease (*n* = 57)	
Microscopic	36 (63)
Macroscopic	17 (30)
Not reported	4 (7)
Tumour ulceration in all the patients	
Present	47 (61)
Absent	23 (29)
Not reported	8 (10)
M status in patients with stage IV disease (*n* = 13)	
M1a	6 (46)
M1b	5 (38)
M1c	2 (16)
M1d	0 (0)
BRAF status	
Wild-type	73 (94)
Mutant	3 (3)
Not reported	2 (3)
Relationship between tumour ulceration and clinical subtypes	
High-cumulative sun damage (*n* = 10)	
III	43% (3/7 cases)
IV	67% (2/3 cases)
Low-cumulative sun damage (*n* = 21)	
III	63% (12/19 cases)
IV	100% (2/2 cases)
Acral (*n* = 31)	
III	81% (21/26 cases)
IV	40% (2/5 cases)

RESULTS

Demographic data

A total of 97 patients were considered, and 19 patients were excluded from the analysis because they were undergoing treatment (Fig. 1). Patient demographic data are shown in **Table I**. The subtypes of cutaneous melanoma were: 10 cases of high cumulative sun damage (CSD) (13%), 21 cases of low CSD (27%), 31 cases of acral melanoma (40%), and 5 cases of melanoma of unknown

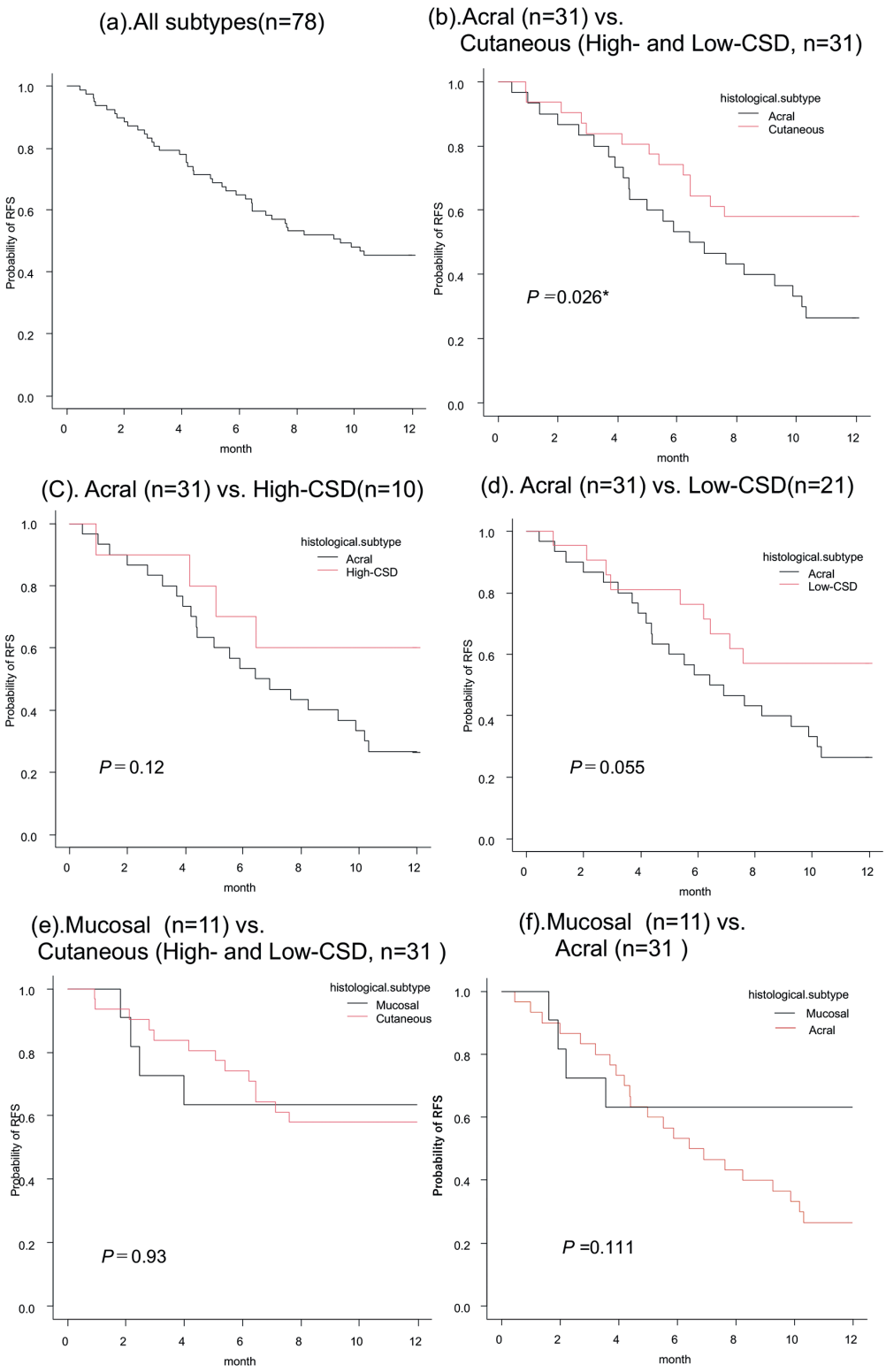

Fig. 2. Relapse-free survival of stage III cutaneous melanoma. (a) Relapse-free survival (RFS) curves of the entire cohort, (b) RFS by acral and non-acral, (c) acral and high cumulative sun damage (CSD), (d) acral and low-CSD, (e) mucosal and cutaneous, and (f) mucosal and acral melanoma.

Table II. One-year completion rate without relapse in each subtype (%)

Histological subtype($n=78$)	Staging[a]	RFS at 12 months (%)
Cutaneous	III	54% (14/26 cases)
(High- and Low-CSD, $n=31$)	IIIA	100% (1/1 case)
	IIIB	80% (4/5 cases)
	IIIC	47% (9/19 cases)
	IIID	0% (0/1 case)
	IV	80% (4/5 cases)
Acral ($n=31$)	III	23% (6/26 cases)
	IIIA	50% (1/2 case)
	IIIB	25% (1/4 cases)
	IIIC	17% (3/18 cases)
	IIID	50% (1/2 cases)
	IV	40% (2/5 cases)
Mucosal ($n=11$)	NA	64% (7/11 cases)
Unknown ($n=5$)	III	67% (2/3 case)
	IIIB	100% (2/2 cases)
	IIIC	0% (0/1 case)
	IV	50% (1/2 cases)

[a]American Joint Committee on Cancer eighth edition
RFS: relapse-free survival; CSD: cumulative sun damage.

origin (6%). Eleven patients were included as mucosal melanoma (non-cutaneous melanoma) (14%). The 62 patients without mucosal melanoma and of unknown origin were classified as stage IIIA (3 patients), stage IIIB (9 patients), stage IIIC (37 patients), stage IIID (3 patients), and stage IV (10 patients) according to the American Joint Committee on Cancer eighth edition (AJCC-8).

Efficacy

RFS was evaluated at 12 months (median RFS: 9.5 months, **Fig. 2**a). Overall RFS was 60.3% (47 of 78 cases, 95% CI 49.2–70.4%), and these 47 cases completed the observation period without recurrence (including patients who had stopped adjuvant therapy due to AEs), and 39.7% (31 of 78 patients, 95% CI 29.6–50.8) relapsed during the adjuvant PD-1 Ab treatment. Six cases (7.7%) discontinued the protocol due to serious adverse events. One case (1.3%) discontinued the protocol due to trauma. The RFS at 12 months for patients who completed the protocol was 51.3% (40 of 78 cases, 95% CI 40.4–62.1%). The RFS of acral melanoma was 25.8% (8 of 31 patients, 95% CI 14.5–43.5%). The RFS of high CSD was 60.0% (6 of 10 patients, 95% CI 31.2–83.3%), and that of low CSD was 57.1% (12 of 21 patients, 95% CI 36.5–75.6%). The RFS at 12 months in each stage and subtype is shown in **Table II**.

Table III. Multivariate Cox proportional hazards model analysis of potential prognostic factors affecting relapse-free survival (RFS)

Parameters	Hazard ratio (95% CI)	*p*-value
Histological subtype		
Acral type	2.27 (1.17–4.40)	0.015*
Cutaneous type	0.99 (0.22–4.45)	0.98
Mucosal type	4.45 (0.83–23.8)	0.081
Baseline characteristics		
Sex	2.12 (1.06–4.26)	0.034*
Tumor ulceration	1.49 (0.68–3.26)	0.31
Clinical staging (III vs IV)	1.79 (0.53–6.02)	0.35

95% CI: 95% confidence interval.

Melanoma subtypes

RFS at 12 months was also evaluated for each subtype (Table II and Fig. 2b–d). The acral type with stage III had a significantly lower 12-month RFS than other cutaneous types (acral type: 26% vs cutaneous type: 58%), which included high CSD (57%) plus low CSD types (60%) ($p=0.029$, Fig. 2b). In addition, the acral type did not show any significant difference in 12-month RFS compared with the high CSD (Fig. 2c) or low CSD type (Fig. 2d). The acral type with stage III tended to have ulceration of the primary tumour more than other cutaneous types (Table I). The mucosal type showed no significant difference in 12-month RFS compared with the cutaneous or the acral type (Fig. 2e–f).

Multivariate analysis of the prognostic factors

To identify the relevant prognostic factors for RFS, the relevant factors, including baseline characteristics (sex, ulceration of the primary tumour, clinical staging) and histological subtypes (cutaneous, acral, and mucosal types), were selected for multivariate analysis. Variable selection was conducted by the forward-backward stepwise method, and acral type and sex were identified as prognostic factors. The acral type (HR, 2.27; 95% CI 1.17–4.40; $p=0.015$) and sex (HR, 2.12; 95% CI 1.06–4.26.; $p=0.034$) showed significant HRs (**Table III**). Other histological subtypes (cutaneous and mucosal types) and baseline characteristics (tumour ulcerations and clinical staging) were not found to be significant on multivariate analysis.

Safety profile

Safety profiles for the nivolumab and pembrolizumab groups are shown in **Table IV**. The incidence rate of any treatment-related AEs for all patients was 37.1% (29 of 78 patients, 95% CI 27.2–48.3%). The incidence rate of serious AEs for all patients was 11.5% (9 patients, 95% CI 6.0–20.7%), including 4 cases of adrenal insufficiency, 3 cases of abnormal hepatic function, 2 cases

Table IV. Safety profile of anti-PD-1 antibody (Abs) monotherapy

	Anti-PD1 Abs ($n=78$)		
	Grade 1–2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Adrenal insufficiency	1 (1)	4 (5)	0 (0)
Abnormal hepatic function	0 (0)	3 (4)	0 (0)
Diarrhoea	0 (0)	2 (3)	0 (0)
Diabetic ketoacidosis	0 (0)	1 (1)	0 (0)
Hypoparathyroidism	0 (0)	0 (0)	0 (0)
Hypothyroidism	2 (3)	0 (0)	0 (0)
Hyperthyroiditis	4 (5)	0 (0)	0 (0)
Interstitial lung disease	4 (5)	1 (1)	0 (0)
Increased creatinine kinase	1 (1)	0 (0)	0 (0)
Vitiligo	3 (4)	0 (0)	0 (0)
Rash	4 (5)	1 (1)	0 (0)
Urticaria	2 (3)	0 (0)	0 (0)
Pemphigoid	1 (1)	1 (1)	0 (0)

of diarrhoea, and one case each of diabetic ketoacidosis, hyperthyroidism with thyroiditis, interstitial lung disease, rash, and bullous pemphigoid.

DISCUSSION

Nivolumab achieved a 4-year RFS rate of 51.7% and 4-year overall survival of 77.9% in stage III–IV melanoma patients in the adjuvant setting (4). Pembrolizumab also showed better 1-year RFS than placebo treatment for resected stage III melanoma (5). Therefore, anti-PD-1 Ab therapy is widely used in BRAF-negative cases in clinical practice. In the current study, a total of 78 melanoma cases were retrospectively examined in a Japanese population including 31 cases of acral melanoma (40%). Twelve-month RFS was significantly longer in the cutaneous type (high and low CSD) than in the acral type ($p=0.026$, Fig. 2b). Moreover, multivariate analysis showed that acral type was an independent prognostic factor ($p=0.015$, Table III). In contrast, there were no significant differences between mucosal and other subtypes in this study (Fig. 2e, f). Since the number of mucosal cases was small in the present study, further cases need to be studied in the future.

Compared with Western European countries, Asian regions including Japan tend to have more acral type, which have higher BRAF-wild status than other cutaneous types (acral: 3.6–33.3% vs other cutaneous subtypes: 40–60%) (11, 12). Moreover, since the number of structural variant mutations is significantly lower in acral melanoma than in cutaneous melanoma (13), and since the efficacy of anti-PD-1 Abs, at least in part, depends on tumour mutation burden (14), the efficacy of anti-PD-1 Abs for advanced acral melanoma should be limited (15, 16). Moreover, since the number of $CD8^+$ T cells in acral melanoma is significantly lower than in cutaneous melanoma, the efficacy of anti-PD-1 Abs for unresectable acral melanoma is limited (17). Notably, among $CD8^+$ T cells, $CD103^+$ tumour-resident $CD8^+$ T cells increased significantly with anti-PD-1 Ab monotherapy in the first-line setting in unresectable melanoma (18) and could even be a biomarker for the prediction of efficacy of anti-PD-1 Ab monotherapy. In addition, other reports suggested that both tumours expressing immune check points and TIL-related chemokines that recruit CD8+ T cells at a tumour site are important to predict the efficacy of anti-PD-1 Abs in unresectable melanoma treated by anti-PD-1 Ab monotherapy (19, 20). These reports suggest the possible mechanisms for the lower efficacy of anti-PD-1 Ab monotherapy for unresectable acral melanoma, and such studies are needed to evaluate resectable acral melanoma in the adjuvant setting. Two previous independent studies might be helpful to explain this hypothesis (15, 21), although these results could not be compared directly, because 1 was an intervention trial, and the other was a retrospective study. Indeed, the objective response rate (ORR) of anti-PD-1 Abs is lower for unresectable acral melanoma (16.6%) (15) than for cutaneous melanoma (43.7%) (21). However, the BRAF status of acral melanoma is generally lower than for other subtypes (22). Given the above reason, despite an expected lower ORR in acral melanoma, anti-PD-1 Ab treatment is mainly selected for postoperative adjuvant therapy for acral melanoma.

Adverse events due to anti-PD-1 Ab therapy were observed in 37.1% (29 of 78 cases) of subjects overall. In past reports, the rate of adverse events with anti-PD-1 Ab was 18–93.3% (4, 5). Discontinuations in the present cohort were for skin disorders in 2 patients (dermatomyositis and pemphigoid), interstitial pneumonia in 2 patients, liver disorder in 1 patient, and adrenal insufficiency in 1 patient. In aggregate, anti-PD-1 Ab in the adjuvant setting is a highly tolerable protocol for advanced melanoma even in the Japanese population.

Study limitations

Since nivolumab monotherapy in the adjuvant setting has been covered by health insurance since 2018, follow-up is now ongoing; therefore, the follow-up time with real-world data is still limited. The number of patients with melanoma, especially patients with mucosal melanoma, is limited for further statistical analysis in each subpopulation (e.g. divide high CSD and low CSD). Further cases are needed to confirm the current results in future studies.

Conclusion

The unique feature of the current study cohort was that 31 cases had the acral type, suggesting a higher number of cases than in the checkmate 238 trial (16 of a total 453 cases) (4). Moreover, the acral type had a significantly lower 12-month RFS than other cutaneous types. The results of the current study suggest that anti-PD-1 Ab therapy in the adjuvant setting is less effective for acral type (25.8%) than for other cutaneous types (high and low CSD) (58.1%), similar to the anti-tumour effects for unresectable melanoma (15). In addition, the efficacy of anti-PD-1 Abs in the adjuvant setting in a Japanese non-acral cutaneous melanoma cohort was comparable with that in a Caucasian cohort (4). In contrast to acral melanoma, there was no significant difference in RFS between mucosal and other types. This result might be caused by the lower number of mucosal cases in the current cohort.

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