Cancer Science
Japanese Cancer Association JCA
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Efficacy and safety of nivolumab in Japanese patients with previously untreated advanced melanoma: A phase II study

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Key words

Immune checkpoint inhibitor, Japanese patients, melanoma, nivolumab, programmed death 1 (PD-1) inhibitor

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Funding Information

Ono Pharmaceutical Co. Ltd.

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Received January 16, 2017; Revised February 28, 2017; Accepted March 2, 2017

Cancer Sci **108** (2017) 1223–1230

doi: 10.1111/cas.13241

Treating advanced or recurrent melanoma remains a challenge. Cancer cells can evade the immune system by blocking T-cell activation through overexpression of the inhibitory receptor programmed death 1 (PD-1) ligands. The PD-1 inhibitor nivolumab blocks the inhibitory signal in T cells, thus overcoming the immune resistance of cancer cells. Nivolumab has shown promising anticancer activity in various cancers. We carried out a single-arm, open-label, multicenter, phase II study to investigate the efficacy and safety of nivolumab in previously untreated Japanese patients with advanced melanoma. Twenty-four patients with stage III/IV or recurrent melanoma were enrolled and received i.v. nivolumab 3 mg/kg every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was overall response rate evaluated by an independent radiology review committee. The independent radiology review committee-assessed overall response rate was 34.8% (90% confidence interval, 20.8–51.9), and the overall survival rate at 18 months was 56.5% (90% confidence interval, 38.0–71.4). Treatment-related adverse events (AEs) of grade 3 or 4 only occurred in three patients (12.5%). Two patients discontinued nivolumab because of AEs, but all AEs were considered manageable by early diagnosis and appropriate treatment. Subgroup analyses showed that nivolumab was clinically beneficial and tolerable regardless of *BRAF* genotype, and that patients with treatment-related select AEs and with vitiligo showed tendency for better survival. In conclusion, nivolumab showed favorable efficacy and safety profiles in Japanese patients with advanced or recurrent melanoma, with or without *BRAF* mutations. (Trial registration no. JapicCTI-142533.)

Advanced or recurrent melanoma is a challenging disease to treat. Dacarbazine was approved for use in the USA in 1975, since when it has been a standard therapy for advanced melanoma; however, the efficacy of dacarbazine monotherapy is unsatisfactory.[1,2] Melanoma is still associated with high mortality, despite recent advancements in systemic therapy that have improved the 10-year survival rate of patients with distant metastatic melanoma from <10% in 2001[3] to approximately 30% in 2009.[4] Effective, alternative therapy options are therefore needed.

Immune checkpoint inhibitors have become a recent focus of anticancer drug discovery. T-cell activation is tightly regulated by the balance between positive and negative signals, allowing T cells to recognize and respond to pathogens while maintaining self-tolerance.[5] Checkpoint receptors are expressed in T cells and induce inhibitory signals following receptor binding. However, cancer cells overexpress immune checkpoint ligands that inhibit T-cell activation, allowing the cells to escape immune system attack,[6] whereas antagonists of such receptors can increase antigen-specific T-cell immune responses against tumor cells. Programmed death 1 and cytotoxic T-lymphocyte-associated antigen-4 are two of the most intensively investigated target receptors in cancer immunotherapy research. Unlike other antibody-based cancer therapies, immune checkpoint inhibitors do not target tumor cells directly, but rather modulate lymphocytes to enhance the body's own anticancer activities.

Nivolumab is a fully human mAb that inhibits the PD-1 checkpoint receptor. Expression of PD-1 on the T-cell surface is upregulated following activation,[7] and the PD-1 pathway negatively regulates effector T-cell activity following ligand binding. Tumor cells usually overexpress the PD-1 ligands, PD-L1 and PD-L2,[8,9] on the cell surface, thus acquiring immune resistance. Indeed, the expression level of PD-L1 was

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shown to correlate with tumor growth in primary melanomas.[10] Blockade of PD-1 by nivolumab thus represents a promising approach for enhancing the antimelanoma T cell immune response, and thereby improving clinical endpoints.[11–13]

The present study investigated the efficacy and safety of nivolumab in previously untreated Japanese patients with advanced melanoma.

Material and Methods

Patients. This was a single-arm, open-label, multicenter, phase II study to evaluate the efficacy and safety of nivolumab. Eligible patients were at least 20 years old, with histopathologically confirmed, previously untreated malignant melanoma that were unresectable stage III/IV or recurrent, an Eastern Cooperative Oncology Group performance status score of 0 or 1,[14] a predicted survival of at least 3 months, and adequate organ function. At least one tumor had to be measurable by imaging, as defined using the RECIST guidelines (version 1.1)[15] 14 days before enrollment. Enrollment of patients with previous adjuvant therapies was allowed. Patients with the following conditions were not enrolled: (i) history of hypersensitivity to other antibody-based medications; (ii) remaining influence of previous radiation or resection therapies; (iii) chronic or recurrent autoimmune diseases; (iv) genotyping for *BRAF* mutation not possible; (v) melanomas with primary tumors in the esophagus or rectum; (vi) presence of double cancer, except completely resected cancers (basal cell carcinoma, squamous cell carcinoma of stage 1, intraepithelial carcinoma, intramucosal carcinoma, or superficial bladder cancer) or other cancers without recurrence for 5 years; (vii) primary or metastatic lesions in brain or meninges; or (viii) interstitial lung disease or pulmonary fibrosis. All patients provided tumor biopsy specimens for gene analyses. The *BRAF* V600 mutation was detected using real-time PCR (Cobas 4800 BRAF V600 Mutation Test; Roche Diagnostics, Branford, CT, USA).

The study protocol was approved by the institutional review board at each study site. The study was carried out in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guideline for Good Clinical Practice. Written informed consent was provided by all participants before the first treatment.

Interventions. The study consisted of three stages: screening, intervention, and post-treatment follow-up. After the screening stage, eligible patients were enrolled and received i.v. nivolumab 3 mg/kg every 2 weeks in each 6-week cycle until progressive disease (PD) or unacceptable toxicity was observed. Treatment was discontinued immediately when any of following discontinuation criteria was met at any time during the intervention stage: (i) complete response (CR) based on RECIST guidelines, except patients with anticipated recurrence assessed by investigators; (ii) PD based on RECIST guidelines, and no further clinical benefit expected; (iii) clinical symptoms indicating cancer progression; (iv) interstitial lung disease of grade ≥2 regardless of the relationship to nivolumab; (v) AEs of grade ≥3 of which the relationship to nivolumab was not ruled out; or (vi) AEs (eye pain and visual acuity reduced) of grade ≥2 that were not ruled out for their relationship to nivolumab and not recovered after topical treatment. Tumors were evaluated at the end of the 6-week regimen to determine if the treatment should be continued. The follow-up stage began when the treatment was discontinued or no new cycle was started.

Assessment. *Efficacy endpoints.* Tumor images were obtained using computed tomography or magnetic resonance imaging at screening, and at the end of every 6-week treatment cycle from the 1st to 9th cycles, and thereafter at the end of every other 6-week cycle, and also at discontinuation of the treatment and on the 28th day of the follow-up period. These images were used to classify the overall response into four categories, based on the RECIST guidelines (version 1.1). The primary endpoint was the ORR, defined as the proportion of patients with CR or PR, assessed by an IRC. Secondary endpoints were the ORR assessed by investigators at each study site, OS, PFS, duration of response, disease-control rate, and change in tumor size.

Safety endpoints. Safety was assessed by recording AEs, evaluated by vital signs, and the results of 12-lead electrocardiograms and clinical tests, collected at predefined time points. Adverse events were graded using the Common Terminology Criteria for Adverse Events version 4.0. The frequency of treatment-related select AEs, defined as AEs with potential immunological causes, was also recorded.

Statistical analysis. Demographic characteristics were described as the summary statistics of the safety set, which comprised patients who had received nivolumab at least once. Efficacy endpoints were analyzed in the full-analysis set, which comprised evaluable patients in the safety set who continued to fulfill the major eligibility criteria. The proportions of patients and two-sided 90% CIs were calculated for the ORR and disease-control rate. The OS and PFS were reported as medians and two-sided 90% CIs, estimated using the Kaplan–Meier method. The proportions of patients with CR, PR, SD, PD, and not evaluable were calculated, and two-sided 90% CIs were calculated for CR, PR, and SD. The proportion of patients who showed ORR for 12 months or longer was estimated as the durable response rate using Kaplan–Meier methods. Safety was analyzed in the safety set.

Patients were stratified into two groups based on *BRAF* genotypes, and subgroup analyses were carried out to determine the nivolumab efficacy and safety endpoints in patients with *BRAF* wild-type and mutant, respectively. In addition, we undertook *a posteriori* subgroup analyses for several factors that could influence the efficacy of nivolumab. Median OS and PFS with two-sided 90% CIs were estimated for subgroups using the Kaplan–Meier method and compared using unstratified log–rank tests and unstratified Cox proportional hazards models.

The planned sample size was 20 patients. An earlier phase II study in previously treated Japanese patients who received nivolumab once every 3 weeks showed a response rate of 22.9%,[16] which were therefore set as the expected response rate for the present study. The threshold response rate was set as 6.0%, estimated based on the response rate to dacarbazine. Using these estimates, the sample size was determined to 20 patients, with a statistical power of 80% ensured to detect the response rate in a one-sided test with a 5.0% significance level. The required sample size for patients with *BRAF* wild-type was calculated as 14, using the same estimates with a statistical power of 70%, and the estimated sample size for patients with *BRAF* mutant was six, so that at least one patient would achieve a response with approximately 80% probability.

Results

Patients and treatment. A total of 24 patients from nine study centers participated from May to October 2014, with a

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Table 1. Demographics and baseline characteristics of Japanese patients with previously untreated advanced melanoma given nivolumab (*n* = 24)

Characteristic	Nivolumab (*n* = 24)
Sex	
Male	14 (58.3)
Female	10 (41.7)
Age, years	
<65	13 (54.2)
≥65	11 (45.8)
Median (range), years	63.0 (26–81)
Performance status (ECOG)	
0	16 (66.7)
1	8 (33.3)
Stage	
IV	3 (12.5)
Recurrent	21 (87.5)
Melanoma type	
Lentigo maligna	0 (0.0)
Superficial spreading	6 (25.0)
Nodular	1 (4.2)
Acral lentiginous	7 (29.2)
Other	10 (41.7)
Previous resection	
Yes	23 (95.8)
Previous radiation therapy	
Yes	3 (12.5)
Number of previous adjuvant therapies	
0	9 (37.5)
1	7 (29.2)
≥2	8 (33.3)
BRAF V600 status	
Mutation	6 (25.0)
Wild-type	18 (75.0)

Data given as *n* (%) unless otherwise stated. ECOG, Eastern Cooperative Oncology Group.

Table 2. Response and survival of Japanese patients with previously untreated advanced melanoma given nivolumab (*n* = 23)

	IRC assessed, *n* (%)	Investigator assessed, *n* (%)
Total patients	23 (100.0)	23 (100.0)
Best overall response		
CR	2 (8.7)	0 (0.0)
PR	6 (26.1)	10 (43.5)
SD	7 (30.4)	8 (34.8)
PD	7 (30.4)	5 (21.7)
No lesion found†	1 (4.3)	0 (0.0)
Overall response rate (CR+PR)	8 (34.8)	10 (43.5)
90% CI, %	20.8, 51.9	28.1, 60.3
Disease control rate (CR+PR+SD)	15 (65.2)	18 (78.3)
90% CI, %	48.1, 79.2	61.6, 89.0
Duration of response (IRC assessed)		
Median, months	Not reached	–
Range, months	1.4–17.1	–
Progression-free survival		
Median, months	5.9	9.8
90% CI, months	2.8, 12.2	2.8, –
Rate at 12 months, %	38.3	42.7
90% CI, %	21.8, 54.6	25.5, 58.9
Rate at 18 months, %	28.7	37.9
90% CI, %	14.3, 44.9	21.5, 54.3
Overall survival		
Median, months	Not reached	
90% CI, months	12.02, –	
Rate at 12 months, %	16 (69.6)	
90% CI, %	50.8, 82.3	
Rate at 18 months, %	13 (56.5)	
90% CI, %	38.0, 71.4	

†Measurable lesion was found by investigator on site but not by independent radiology review committee (IRC) throughout the study. –, Censored value; CI, confidence interval; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

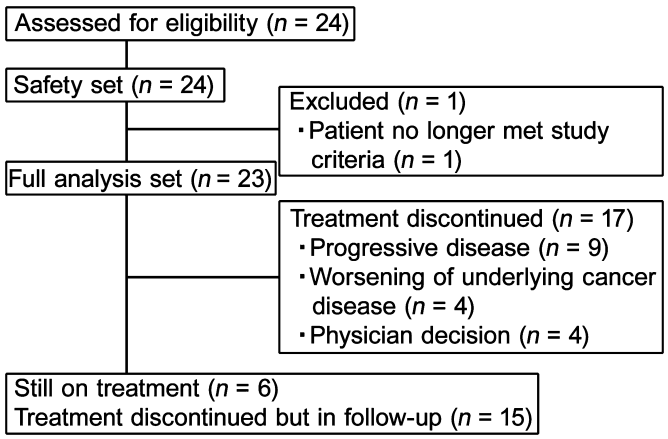


Fig. 1. Patient disposition during the study (*n* = 23).

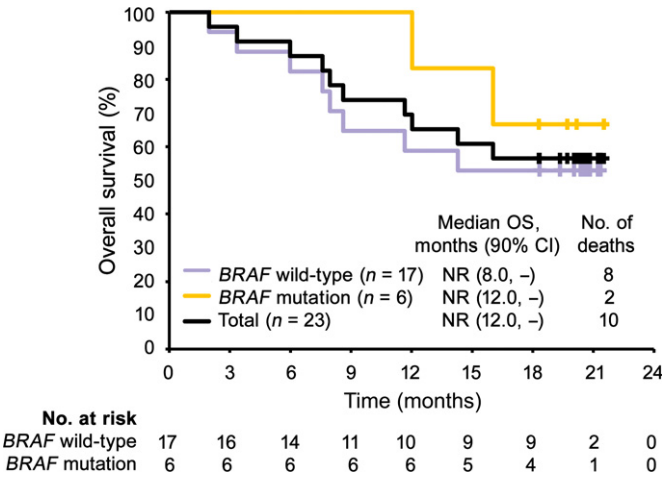


Fig. 2. Kaplan–Meier analysis of overall survival (OS) in Japanese patients with previously untreated advanced melanoma given nivolumab (*n* = 23). Purple, yellow, and black lines represent patients with *BRAF* wild-type, patients with *BRAF* mutation, and total patients, respectively. CI, confidence interval; NR, not reached.

data cut-off date of February 29, 2016. The demographic and baseline characteristics are summarized in Table 1. Eighteen patients (75%) had *BRAF* wild-type, and 6 (25%) had *BRAF* mutant. All 24 patients received nivolumab, however, one

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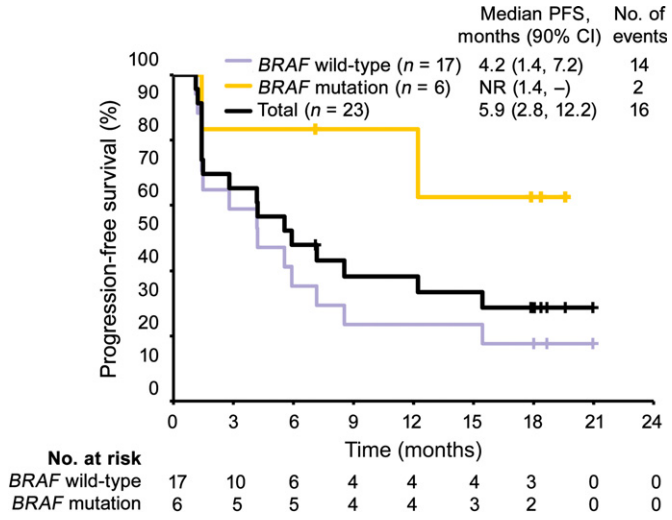


Fig. 3. Kaplan–Meier analysis of progression-free survival (PFS) in Japanese patients with previously untreated advanced melanoma given nivolumab (n = 23), estimated using data evaluated by independent radiology review committee. Purple, yellow, and black lines represent patients with *BRAF* wild-type, patients with *BRAF* mutation, and total patients, respectively. CI, confidence interval; NR, not reached.

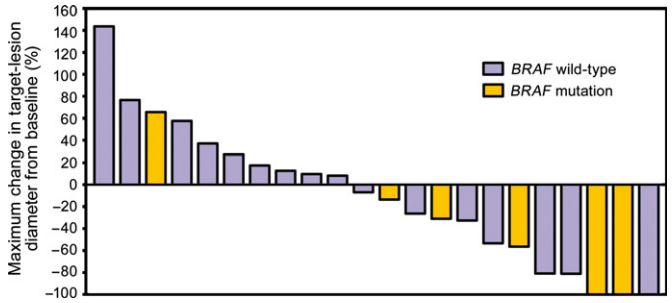


Fig. 4. Maximum change in target-lesion diameter in relation to *BRAF* genotype in Japanese patients with previously untreated advanced melanoma given nivolumab (n = 23). Maximum changes in target-lesion diameter from baseline evaluated by independent radiology review committee. Purple and yellow bars represent patients with *BRAF* wild-type and mutation, respectively.

patient was excluded from the full analysis set because the patient met one of the exclusion criteria (double cancer) after enrollment (Fig. 1). Six patients were receiving treatment at the cut-off point and continued with further treatment. Of the remaining 18 patients, 15 were in the follow-up stage at cut-off, because of PD (nine patients, 37.5%), clinical symptoms indicating cancer progression (two patients, 8.3%), or the physician's decision (four patients, 16.7%). The other three patients discontinued the study without entering the follow-up stage because of disease progression. A median of 23 doses (range, 2–46) of nivolumab were administered, with a median treatment duration of 11.9 months (range 0.5–21.0). The median follow-up was 18.8 months (range, 2.0–21.5 months).

Efficacy. The IRC-assessed and investigator-assessed ORRs are summarized in Table 2. The IRC-assessed ORR was 34.8% (90% CI, 20.8, 51.9) and the investigator-assessed ORR was 43.5% (90% CI, 28.1, 60.3), indicating similar results for both assessment methods. The lower limits of the 90% CI in both IRC-assessed and investigator-assessed ORRs were higher than the threshold response rate of 6.0% estimated using dacarbazine data. The best overall responses assessed by IRC were CR in two patients (8.7%), PR in six patients (26.1%), and SD in seven patients (30.4%), giving a disease-control rate (CR+PR+SD) of 65.2%.

The median OS was not reached, and the proportion of patients surviving at 18 months was 56.5% (Table 2, Fig. 2). The median PFS evaluated by IRC was 5.9 months (90% CI, 2.8, 12.2) (Table 2, Fig. 3).

A decrease in target-tumor diameter was observed in more than half the patients (Fig. 4), and patients who had decreased tumor diameter also had long antitumor effects (Fig. 5,6). Response was observed in eight patients and was persistent in five of eight patients until the cut-off date. The durable response rate for 12 months, estimated by Kaplan–Meier methods, was 71.4%.

Safety. Adverse events were reported in 22 patients (91.7%), including AEs of grade ≥3 in five (20.8%) patients. Treatment-related AEs were found in 20 patients (83.3%), including three (12.5%) with treatment-related AEs grade ≥3 (Table 3). No death occurred during the study period. The most commonly observed treatment-related AEs were vitiligo (nine patients, 37.5%), pruritus (six patients, 25.0%), hypothyroidism (six patients, 25.0%), and malaise (six patients, 25.0%). Serious treatment-related AEs were reported in three patients (12.5%), including colitis, abnormal hepatic function, renal impairment, and pleural effusion. Treatment was temporarily interrupted in two of these patients (colitis and renal impairment). Two patients (8.3%) discontinued the study because of treatment-related AEs (colitis and pleural effusion). Treatment-related select AEs were found in seven patients (29.2%). The only

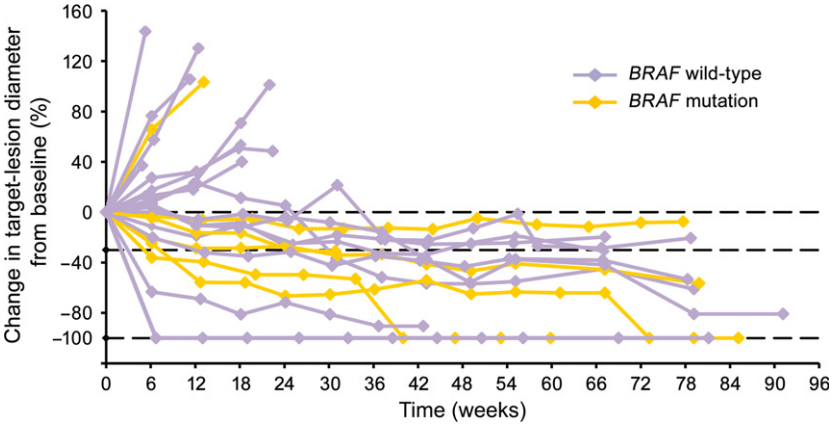


Fig. 5. Change in target-lesion diameter over time in relation to *BRAF* genotype in Japanese patients with previously untreated advanced melanoma given nivolumab (n = 23). Change in target-lesion diameter evaluated by independent radiology review committee. Purple and yellow plots represent patients with *BRAF* wild-type and mutation, respectively.

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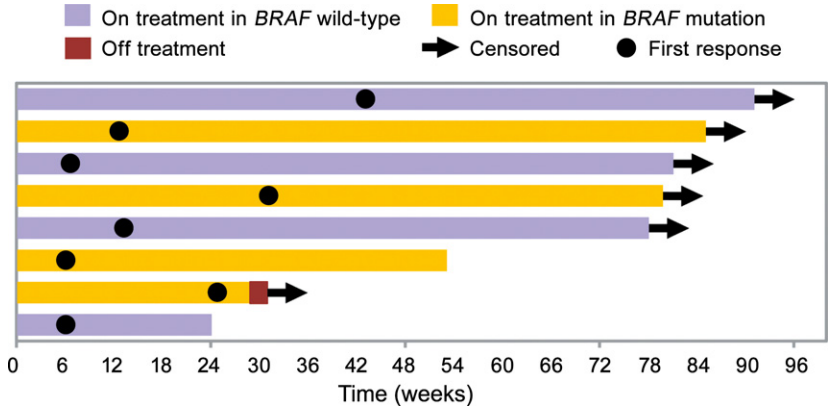


Fig. 6. Time to and duration of response in Japanese patients with previously untreated advanced melanoma given nivolumab (n = 23), in relation to *BRAF* genotype. Time to and duration of response evaluated by independent radiology review committee. Purple and yellow bars represent patients with *BRAF* wild-type and *BRAF* mutant, respectively, on treatment. Arrow, date of censor; brown bar, patients off treatment; closed circle, date of first response.

Table 3. Treatment-related adverse events (AEs) in Japanese patients with previously untreated advanced melanoma given nivolumab (n = 23)

	All grades, n (%)	Grade ≥3, n (%)
Overall	20 (83.3)	3 (12.5)
Treatment-related AEs observed in ≥10% of patients		
Vitiligo	9 (37.5)	0 (0.0)
Pruritus	6 (25.0)	0 (0.0)
Hypothyroidism	6 (25.0)	0 (0.0)
Malaise	6 (25.0)	0 (0.0)
Weight decreased	3 (12.5)	0 (0.0)
Appetite decreased	3 (12.5)	0 (0.0)
Arthralgia	3 (12.5)	0 (0.0)
Rash maculo-papular	3 (12.5)	0 (0.0)
Treatment-related AEs leading to discontinuation of treatment		
Colitis	1 (4.2)	1 (4.2)
Pleural effusion	1 (4.2)	0 (0.0)
Treatment-related serious AEs		
Colitis	1 (4.2)	1 (4.2)
Hepatic function abnormal	1 (4.2)	0 (0.0)
Renal impairment	1 (4.2)	1 (4.2)
Pleural effusion	1 (4.2)	0 (0.0)
Treatment-related select AEs		
Endocrine disorders	7 (29.2)	0 (0.0)
Infusion reactions	0 (0.0)	0 (0.0)
Gastrointestinal toxicity	2 (8.3)	1 (4.2)
Hepatotoxicity	1 (4.2)	0 (0.0)
Pulmonary toxicity	1 (4.2)	0 (0.0)
Nephrotoxicity	0 (0.0)	0 (0.0)
Skin toxicity	11 (45.8)	0 (0.0)

Table 4. Response and survival in Japanese patients with previously untreated advanced melanoma given nivolumab, grouped according to wild-type and mutant *BRAF*, assessed by independent radiology review committee (IRC)

	BRAF wild-type, n (%)	*BRAF* mutation, n (%)
Total patients	17 (73.9)	6 (26.1)
Best overall response		
CR	1 (5.9)	1 (16.7)
PR	3 (17.6)	3 (50.0)
SD	6 (35.3)	1 (16.7)
PD	6 (35.3)	1 (16.7)
No lesion found†	1 (5.9)	0 (0.0)
Overall response rate (CR+PR)	4 (23.5)	4 (66.7)
90% CI, %	11.0, 43.3	34.7, 88.3
Disease control rate (CR+PR+SD)	10 (58.8)	5 (83.3)
90% CI, %	39.3, 75.9	49.8, 96.2
Progression-free survival (IRC-assessed)		
Median, months	4.21	Not reached
90% CI, months	1.41, 7.16	1.41, –
Rate at 12 months, %	23.5	83.3
90% CI, %	9.3, 41.5	38.8, 96.5
Rate at 18 months, %	17.6	62.5
90% CI, %	5.8, 34.8	21.2, 86.7
Overall survival		
Median, months	Not reached	Not reached
90% CI, months	7.95, –	12.02, –
Rate at 12 months, %	58.8	100.0
90% CI, %	37.0, 75.4	100.0, 100.0
Rate at 18 months, %	52.9	66.7
90% CI, %	31.7, 70.3	27.0, 88.2

†Measurable lesion was found by investigator on site but not by IRC throughout the study. –, Censored value; CI, confidence interval;CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

treatment-related select AE of grade ≥3 was colitis (4.2%), which was observed twice in the same patient, who recovered from the first episode after study-drug withdrawal and treatment with corticosteroids, but had another episode of colitis 146 days later, after which study treatment was discontinued. The second episode of colitis improved 71 days after its initial appearance.

***BRAF* subgroup analyses.** Among 23 patients, 17 (73.9%) had *BRAF* wild-type and six (26.1%) had *BRAF* mutation. The IRC-evaluated ORRs were 23.5% in patients with *BRAF* wild-type (90% CI, 11.0, 43.3), and 66.7% in patients with a *BRAF* mutation (90% CI, 34.7, 88.3) (Table 4). Regardless of *BRAF* genotype, the lower limit of the 90% CI was higher than the threshold response rate of 6.0% estimated using dacarbazine data. The OS rates at 18 months were 52.9% and 66.7% in patients with *BRAF* wild-type and mutation, respectively (Table 4, Fig. 2). The median OS was not reached in either subgroup. The median PFS was 4.2 months in patients with *BRAF* wild-type, but was not reached in patients with *BRAF* mutation (Table 4, Fig. 3).

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Table 5. Subgroup analyses of overall response rate (ORR) in Japanese patients with previously untreated advanced melanoma given nivolumab (*n* = 23)

	Patients, *n* (%)	ORR (IRC-assessed), % (90% CI)
Serum lactate dehydrogenase		
Normal (≤ULN)	6/16	37.5 (20.8, 57.8)
Abnormal (>ULN)	2/7	28.6 (10.0, 59.1)
Treatment-related select adverse events		
Present	7/13	53.8 (32.5, 73.9)
Absent	1/10	10.0 (2.3, 34.8)
Vitiligo as a treatment-related adverse event (including vitiligo vulgaris)		
Present	6/9	66.7 (39.8, 85.8)
Absent	2/14	14.3 (4.8, 35.3)

CI, confidence interval; IRC, independent radiology review committee; ULN, upper limit of the normal range.

Treatment-related AEs were reported in 15 (83.3%) and five (83.3%) patients with *BRAF* wild-type and mutant, respectively, and the safety profiles were similar in both genotype subgroups. However, these data were obtained from a small number of patients and therefore need to be carefully interpreted.

Other subgroup analyses. *A posteriori* subgroup analyses were carried out to identify possible factors associated with nivolumab efficacy (Table 5). Median OS was not reached (90% CI, 16.0, –) during the study period in patients with normal level (≤ULN) of LDH (determined in clinical tests) (*n* = 16). Median OS in patients with abnormal level (>ULN) of LDH (*n* = 7) was 11.7 months (90% CI, 3.4, –) (hazard ratio, 0.30; 90% CI, 0.10, 0.85) (Fig. 7a). Seven of eight responders experienced treatment-related select AEs, and the median OS was higher in patients with treatment-related select AEs (*n* = 13) (not reached; 90% CI, 0.00, –) compared with patients without treatment-related select AEs (*n* = 10) (median, 8.3 months; 90% CI, 3.4, 14.3) (hazard ratio, 0.10; 90% CI, 0.03, 0.36) (Fig. 7b). Notably, 66.7% of patients who developed vitiligo (included vitiligo vulgaris) responded to nivolumab, compared with only 14.3% without vitiligo. The median OS was not reached in patients with vitiligo (*n* = 9), but was 11.8 months (90% CI, 7.6, 16.0) in patients without vitiligo (*n* = 14) (Fig. 7c). Generally, patients with normal LDH, treatment-related select AEs, or vitiligo had longer PFS (Fig. 7d–f).

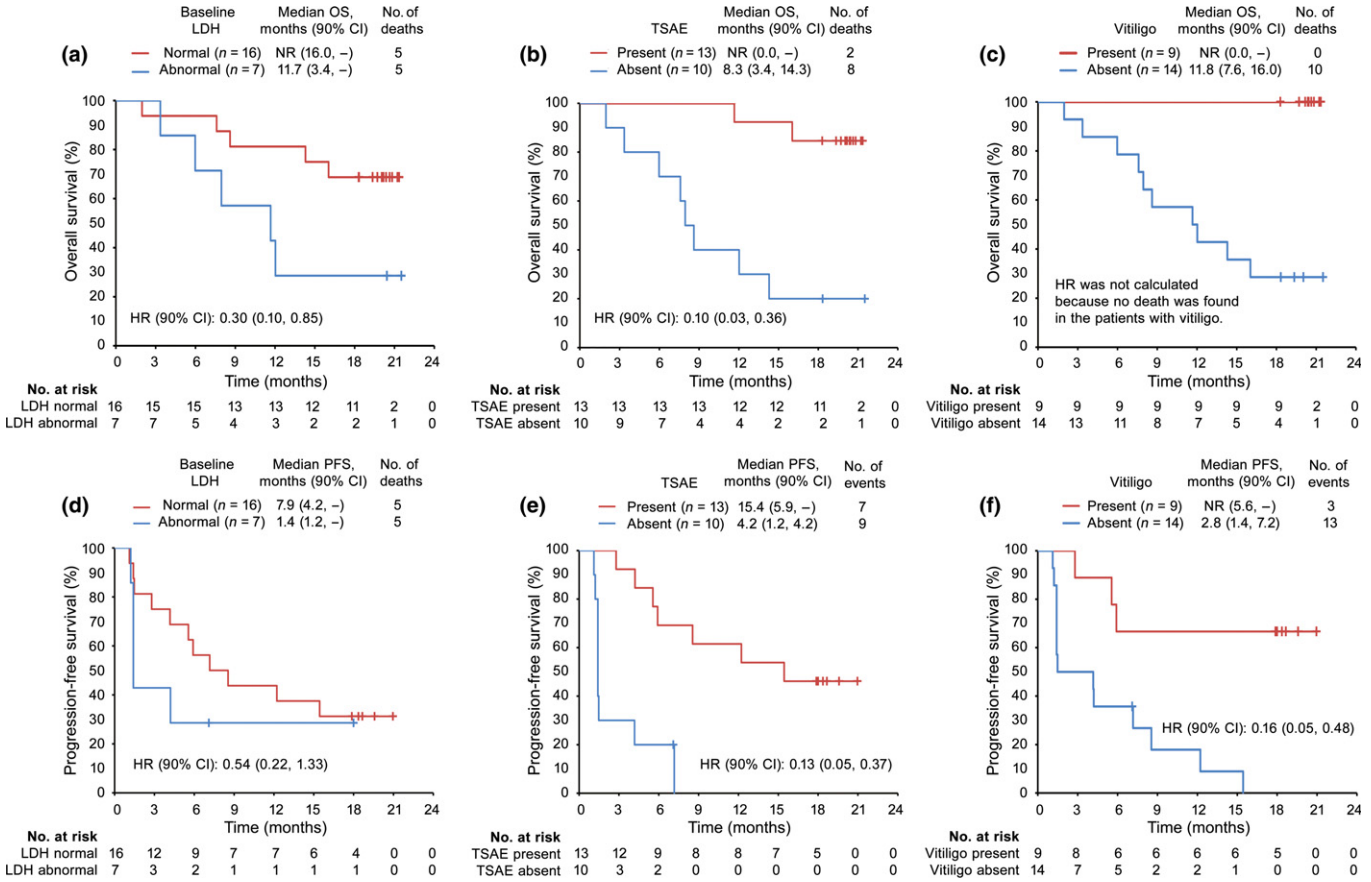


Fig. 7. Overall survival (OS; upper panels) and progression-free survival (PFS; lower panels) estimated by Kaplan–Meier analyses in subgroups of Japanese patients with previously untreated advanced melanoma given nivolumab (*n* = 23). OS (a) and PFS (d) in subgroups stratified by lactate dehydrogenase (LDH) levels at baseline (normal [≤ upper limit of the normal range [ULN], abnormal [>ULN]). Red and blue lines represent patients with low and high levels of LDH, respectively. OS (b) and PFS (e) in subgroups stratified by treatment-related select adverse events (TSAEs). Red and blue lines represent patients with and without TSAEs, respectively. OS (c) and PFS (f) in subgroups stratified by vitiligo during treatment. Red and blue lines represent patients with and without vitiligo, respectively. CI, confidence interval; HR, hazard ratio; NR, not reached.

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Discussion

Programmed death 1 inhibitors have been tested in clinical studies and have shown encouraging antitumor activities and tolerability in a wide range of advanced or refractory cancers, including renal cell carcinoma,[17,18] non-small-cell lung cancer,[19–21] Hodgkin's or non-Hodgkin's lymphoma,[22,23] ovarian cancer,[24] and melanoma.[11–13]

In this study we investigated the efficacy and safety of the PD-1-blocking mAb nivolumab in Japanese patients with previously untreated advanced or recurrent melanoma. The efficacy in responding patients was sustainable, with the median OS not being reached during the course of this study. These results showed that nivolumab had good efficacy and was clinically more beneficial than standard dacarbazine therapy in Japanese patients with previously untreated advanced or recurrent melanoma.

The safety profile of nivolumab was similar to that observed in previous large, international, phase III studies.[11,12] All treatment-related AEs in the present study were considered to be manageable by early diagnosis and appropriate treatment, such as with corticosteroids. These results indicated that nivolumab was tolerable in Japanese patients with previously untreated advanced melanoma.

We also compared the efficacy and safety profiles of nivolumab in patients with and without *BRAF* mutations. Nivolumab showed effective anti-\tumor activity regardless of *BRAF* genotype, with apparently better OS and PFS in patients with *BRAF* mutant, although the sample sizes were insufficient to draw a statistically relevant conclusion. Our results were consistent with previous studies that reported clinical benefits of nivolumab, regardless of *BRAF* genotype.[25,26] Melanomas have been reported to be more aggressive and resistant to chemotherapy in patients with *BRAF* mutations,[27–29] and the available therapeutic options have been limited in these patients. Nivolumab may thus represent a promising option for these patients.

High pretreatment serum LDH has been associated with shorter survival in patients with metastatic melanoma,[30,31] and the similar tendency was observed in our study. Nevertheless, some patients with high LDH levels showed a response to nivolumab, suggesting that it might offer an effective therapeutic option in melanoma patients with elevated LDH.

Patients experiencing treatment-related select AEs and vitiligo showed a tendency for better survival in nivolumab-treated patients in the current study. Immune-related AEs have previously been shown to be characteristic of PD-1 inhibitors,[32,33] and have a reported association with increased survival.[32] However, it cannot be ruled out that non-responder patients discontinued nivolumab so early that immune-related AEs never appeared.[34]

The present study was limited by the small study group and the lack of a control group. However, several controlled clinical studies have previously been carried out in patients from the USA and Europe.[11,12] The efficacy and safety profiles of nivolumab in the current study were similar to those in previous trials, suggesting that the clinical data from those controlled clinical studies were likely to be applicable to the current Japanese study group.

The present study did not address the antitumor activity of nivolumab in relation to tumor PD-L1 status. Furthermore, although nivolumab alone showed an ORR >30% in this study, combination therapy with another checkpoint inhibitor with a different mechanism of action, such as the cytotoxic T-lymphocyte-associated antigen-4 inhibitor ipilimumab, may further enhance the therapeutic benefit,[6,13] and patients may respond differently.[11,35]

In conclusion, nivolumab given at a dose of 3 mg/kg once every 2 weeks is tolerable and shows favorable anticancer activity in Japanese patients with previously untreated advanced or recurrent melanoma, irrespective of *BRAF* mutation status.

Acknowledgments

The authors are grateful to the patients and their families, and to the investigators, nurses, and staff members who participated in this study. We also acknowledge the statistical support of Eiichiro Morishima (Ono Pharmaceutical Co. Ltd., Osaka, Japan). The work was funded by Ono Pharmaceutical Co. Ltd.

Disclosure Statement

Honoraria was received from Ono Pharmaceutical Co., Ltd. (N.Y., Y.K., H.U., T.T.), Takeda Pharmaceutical Co., Ltd. (N.Y.), Bristol-Myers Squibb (N.Y., Y.K., H.U.), Chugai Pharmaceutical Co., Ltd. (N.Y., Y.K., H.U., T.T.), and Boehringer Ingelheim (N.Y.). Research funding was received from Ono Pharmaceutical Co., Ltd. (N.Y., Y.K., H.M.), Bristol-Myers Squibb (N.Y., Y.K., H.M.), Chugai Pharmaceutical Co., Ltd. (Y.K., H.M.), MSD (Y.K.), Glaxo Smith Kline (Y.K.), and Novartis Pharma (N.Y., H.M.). The other authors have no conflict of interest. This study was funded by ONO Pharmaceutical, Japan, including the writing and editing service provided by ASCA Corporation, Japan. The study was planned, conducted, and analyzed independently by the authors.

Abbreviations

AE	adverse event
CI	confidence interval
CR	complete response
IRC	independent radiology review committee
LDH	lactate dehydrogenase
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed death 1
PD-L	programmed death 1 ligand
PFS	progression-free survival
PR	partial response
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
ULN	upper limit of the normal range

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