Interim analysis of a prospective observational study of the efficacy of nivolumab in Japanese patients with advanced melanoma (CREATIVE study)

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BACKGROUND

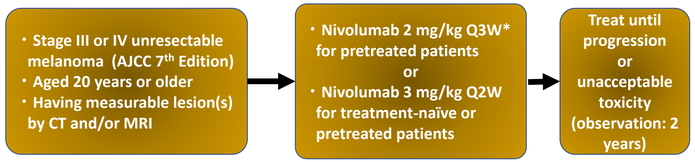
- An improved understanding of cancer pathogenesis has facilitated the development of an anti-PD-1 antibody, which is directed against the negative immunoregulatory cell surface receptor PD-1.
- The anti-PD-1 antibody nivolumab has been approved for advanced melanoma treatment in Japan.
- The rate of incidence of each clinical subtype and the status of BRAF mutation are different between Caucasian and Asian patients.
- Although the results of some clinical trials have shown the efficacy of nivolumab in patients with advanced melanoma, to date, sufficient real-world data about the efficacy of nivolumab in a cohort of Asian patients have not been generated.

OBJECTIVE

This study aimed to obtain post-marketing data on the efficacy of nivolumab in Japanese patients with advanced melanoma.

METHODS

- This prospective observational study was performed in patients with unresectable or metastatic melanoma.
- The patients were treated with nivolumab at a dose of 2 mg/kg every 3 weeks (Q3W) or 3 mg/kg every 2 weeks (Q2W).
- The primary endpoints were response rate (RR) and overall survival (OS).
- The secondary endpoints were progression-free survival (PFS) and RR according to the immune-related response criteria (irRECIST).
- In addition, biomarker analyses were planned at specific time points (before treatment and at 7, 13, 19, and 25 weeks).



*Licensed dose of nivolumab for pretreated melanoma patients in Japan

(Clinical trial information: UMIN000016608)

Comprehensive Support Project

RESULTS

Table 1. Patient demographics and clinical characteristics

No. of Patients	125
Sex	
Male	73 (58.4%)
Female	52 (41.6%)
Age (years)	
Mean	65.9
Range	35-88
Clinical subtype	
NM	19 (15.2%)
SSM	16 (12.8%)
LMM	3 (2.4%)
ALM	25 (20.0%)
Mucosal	39 (31.2%)
Unclassified	15 (12.0%)
Others	9 (7.2%)
Stage (AJCC-TNM 7th)	
III	12 (9.6%)
IV	111 (88.8%)
Others	2 (1.6%)
Radiation	
No	85 (68.0%)
Yes	40 (32.0%)
Treatment sequence	
1st line	77 (61.6%)
≥2nd line	48 (38.4%)
BRAF status	
Wild-type	94 (75.2%)
Mutant	20(16.0%)
Not investigated	11(8.8%)
Nivolumab dose	
2 mg/kg Q3W	78 (63.4%)
3 mg/kg Q2W	44 (35.8%)
Performance status	
0	80 (64.0%)
1	35 (28.0%)
≥2	10 (8.0%)

NM, nodular melanoma; SSM, superficial spreading melanoma; LMM, lentigo maligna melanoma; ALM, acral lentiginous melanoma

Table 2. Best response in all patients

Best response	RECIST	irRECIST
CR	2 (1.6%)	2 (1.6%)
PR	20 (16.0%)	19 (15.2%)
SD	36 (28.8%)	38 (30.4%)
PD	51 (40.8%)	49 (39.2%)
NE	16 (12.8%)	17 (13.6%)
CR+PR (ORR)	22 (17.6%)	21 (16.8%)
DCR	58 (46.4%)	59 (47.2%)

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

- We enrolled 125 patients from 22 institutions.
- Mucosal melanoma was the most common clinical subtype, followed by ALM, NM, SSM, and LMM.
- RECIST evaluation showed an ORR of 17.6%.

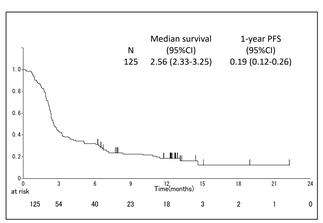


Figure 1. Progression-free survival in all patients

- The median PFS was 2.56 months and the 1-year PFS was 19%.

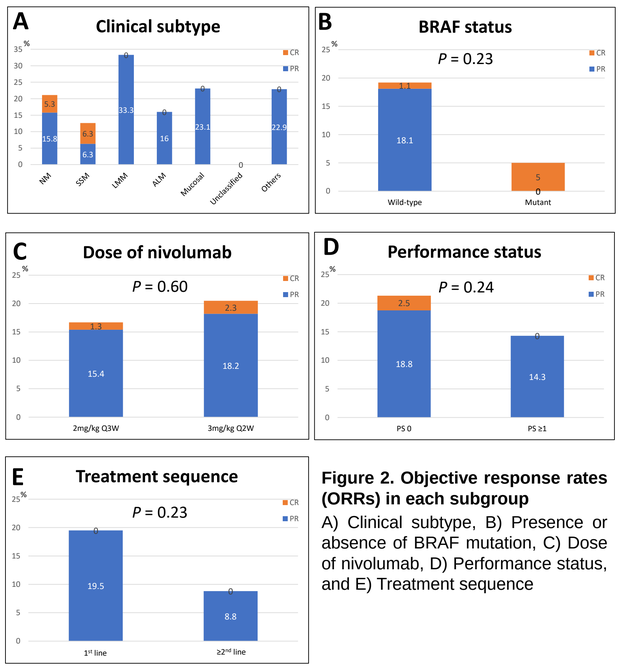


Figure 2. Objective response rates (ORRs) in each subgroup

A) Clinical subtype, B) Presence or absence of BRAF mutation, C) Dose of nivolumab, D) Performance status, and E) Treatment sequence

- Subgroup analysis according to the clinical subtype indicated that the response rate of patients with SSM and ALM was lower than that of patients with other clinical subtypes.
- Patients with BRAF wild-type melanoma, PS 0, and who received nivolumab as first-line treatment showed better response rates, but the difference in the response rates was not statistically significant.

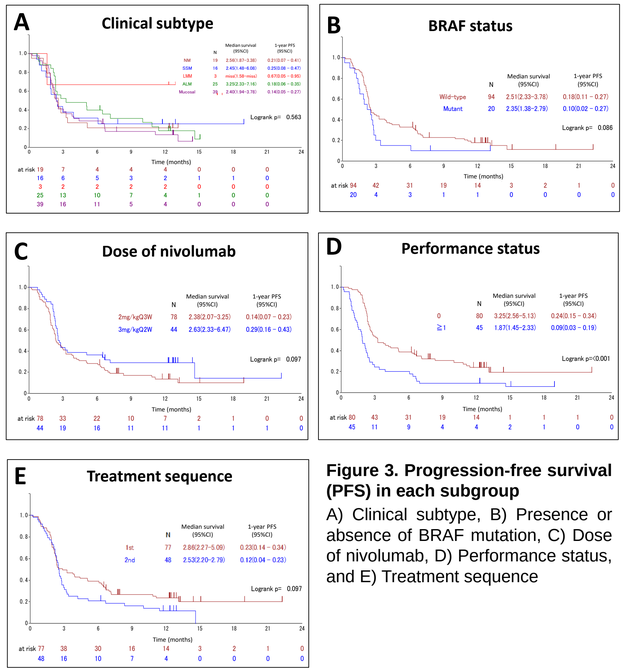


Figure 3. Progression-free survival (PFS) in each subgroup

A) Clinical subtype, B) Presence or absence of BRAF mutation, C) Dose of nivolumab, D) Performance status, and E) Treatment sequence

- Subgroup analysis indicated that the clinical subtype did not affect PFS.
- The patients with BRAF wild-type melanoma, treated with nivolumab 3 mg/kg, or those receiving nivolumab as a first-line treatment showed better PFS.
- The PFS of patients with PS 0 was better than that of patients with PS ≥ 1.

CONCLUSIONS

- The results of this interim analysis of the real-world use of nivolumab showed that the RR and PFS in Japanese patients were lower than those reported in the recent phase III randomized trials (RR, 40-44% and median PFS, 5.1 months) that included patients in western countries[1)2)].
- The difference in the incidence of the clinical subtypes and treatment sequence between Japan and the western countries is associated with a low anti-tumor efficacy of nivolumab in Japan.

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