Efficacy and safety of nivolumab in combination with ipilimumab in Japanese patients with advanced melanoma: An open-label, single-arm, multicentre phase II study

Namikawa, Kenjiro ; Kiyohara, Yoshio ; Takenouchi, Tatsuya ; Uhara, Hisashi ; Uchi, Hiroshi ; Yoshikawa, Shusuke ; Takatsuka, Sumiko ;…

(Citation)
European Journal of Cancer,105:114-126

(Issue Date)
2018-12

(Resource Type)
journal article

(Version)
Version of Record

European Journal of Cancer 105 (2018) 114–126

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Efficacy and safety of nivolumab in combination with ipilimumab in Japanese patients with advanced melanoma: An open-label, single-arm, multicentre phase II study☆

Kenjiro Namikawa [a,*], Yoshio Kiyohara [b], Tatsuya Takenouchi [c], Hisashi Uhara [d,1], Hiroshi Uchi [e], Shusuke Yoshikawa [b], Sumiko Takatsuka [c], Hiroshi Koga [d], Naoko Wada [e], Hironobu Minami [f], Masahiro Hatsumichi [g], Suguru Asada [g], Yoshinobu Namba [g], Naoya Yamazaki [a]

[a] *Department of Dermatologic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan*
[b] *Dermatology Division, Shizuoka Cancer Center Hospital, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka 411-8777, Japan*
[c] *Department of Dermatology, Niigata Cancer Center Hospital, 2-15-3 Kawagishi-cho, Niigata 961-8566, Japan*
[d] *Department of Dermatology, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-8621, Japan*
[e] *Department of Dermatology, Graduate School of Medical Sciences, Kyushu University, 3-1-1, Maidashi, Higashi-ku, Fukuoka 812-8582, Japan*
[f] *Department Medical Oncology/Hematology, Kobe University Graduate School of Medicine, 7-5-2 Kusunoki-cho, Chuo-ku, Kobe, Hyogo 650-0017, Japan*
[g] *Ono Pharmaceutical Co. Ltd., 1-8-2 Kyutaromachi, Chuo-ku, Osaka 541-8564, Japan*

Received 19 September 2018; accepted 23 September 2018
Available online 15 November 2018

KEYWORDS
Melanoma;
Immunotherapy;
Ipilimumab;

Abstract ***Aim:*** The aim of the study was to evaluate the efficacy and safety of nivolumab combined with ipilimumab in treatment-naïve Japanese patients with advanced melanoma. ***Methods:*** In this multicentre, single-arm study, treatment-naïve Japanese patients with unresectable stage III/IV or recurrent melanoma received nivolumab (1 mg/kg) plus ipilimumab

☆ Results of this study were partly presented at the European Society for Medical Oncology Asia Congress 2017, 17–19 November, Singapore. Poster number 380P.

* *Corresponding author*: Department of Dermatologic Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Fax: +81 3 3542 3815.
E-mail addresses: knamikaw@ncc.go.jp (K. Namikawa), y.kiyohara@scchr.jp (Y. Kiyohara), tatsuya@niigata-cc.jp (T. Takenouchi), uharah@sapmed.ac.jp (H. Uhara), uchihir@dermatol.med.kyushu-u.ac.jp (H. Uchi), s.yoshikawa@scchr.jp (S. Yoshikawa), sumiko-ta@niigata-cc.jp (S. Takatsuka), koga@shinshu-u.ac.jp (H. Koga), w-naoco@med.kyushu-u.ac.jp (N. Wada), hminami@med.kobe-u.ac.jp (H. Minami), hatsumichi@ono.co.jp (M. Hatsumichi), s.asada@ono.co.jp (S. Asada), y.nanba@ono.co.jp (Y. Namba), nyamazak@ncc.go.jp (N. Yamazaki).
[1] H. Uhara's present address is: Department of Dermatology, Sapporo Medical University, South 1, West 16, Chuo-ku, Sapporo 060-8543, Japan.

https://doi.org/10.1016/j.ejca.2018.09.025

Nivolumab;
Japanese;
Asian;
Mucosal;
Acral;
Survival analysis

(3 mg/kg) every 3 weeks for four doses, followed by biweekly doses of nivolumab (3 mg/kg). The primary end-point was centrally assessed objective response rate (ORR). Secondary end-points included overall survival (OS), progression-free survival (PFS), disease control rate and safety.

Results: The subtypes of the thirty patients enrolled were: 12, mucosal; eight, non-acral cutaneous; seven, acral; two, uveal and one, unknown primary melanoma. The ORR was 43.3% (95% confidence interval [CI]: 25.5, 62.6) with central and local assessment. The centrally and locally assessed disease control rate (95% CI) were 73.3% (54.1, 87.7) and 86.7% (69.3, 96.2), respectively. At the median follow-up period of 14.1 months (range 5.2–27.7), median OS and centrally assessed PFS were not reached. OS (95% CI) at 6, 12, 18 and 24 months was 93.3% (75.9, 98.3), 83.3% (64.5, 92.7), 72.9% (50.0, 86.5) and 65.6% (40.4, 82.2), respectively. Treatment-related adverse events (AEs) occurred in all patients. Grade III–IV and serious AEs occurred, mostly during the combination phase, in 23 (76.7%) and 20 (66.7%) patients, respectively. No treatment-related deaths occurred.

Conclusions: This study confirmed the efficacy and safety of nivolumab plus ipilimumab in treatment-naïve Japanese patients with advanced melanoma including rare subtypes. Incidence rates for grade III–IV AEs were high but manageable with appropriate medical attention and treatment.

Trial registration: JapicCTI-152869.

1. Introduction

Advanced-stage melanoma is primarily treated with agents targeting immune checkpoint proteins such as programmed death-1 (PD-1) and cytotoxic T-lymphocyte–associated antigen 4 or those in the mitogen-activated protein kinase pathway such as B-Raf proto-oncogene, serine/threonine kinase (BRAF) and mitogen-activated protein kinase. Dual blockade with ipilimumab and nivolumab has synergistic antitumour effects [1–4]. In phase I dose escalation assessments in advanced melanoma patients, the combination of nivolumab and ipilimumab achieved an overall survival (OS) of 79% at 2 years [5,6]. The ongoing phase II trial (CheckMate 069; NCT01927419) reported acceptable safety for the combination of nivolumab and ipilimumab in previously untreated patients with metastatic melanoma and showed more favourable response rates for the combination, compared with ipilimumab monotherapy, regardless of *BRAF* mutant status [7]. The 2-year OS in that study was 63.8% in the combination group and 53.6% in the ipilimumab monotherapy group [8]. Another ongoing international phase III study (CheckMate 067; NCT01844505) in previously untreated patients reported significantly longer progression-free survival (PFS) and OS with nivolumab alone or when combined with ipilimumab than with ipilimumab alone [9,10]. The combination of ipilimumab and nivolumab is believed to provide the greatest survival benefit at the present time [11].

Melanoma is genetically heterogeneous [12,13] and includes cutaneous, mucosal, uveal and unknown primary melanoma subgroups. Cutaneous melanoma is further categorised into superficial spreading, nodular, lentigo maligna and acral lentiginous melanoma. In Caucasians, the non-acral cutaneous type accounts for the majority of melanomas, but the acral and mucosal types are common in Asian populations [14,15]. Because the latter harbour *BRAF* mutations less frequently [16–18], immune-checkpoint inhibitors are more frequently selected for these subtypes. Some studies have shown that the anti–PD-1 antibodies alone [19,20] or in combination with ipilimumab [20] have notable clinical activities on acral or mucosal melanoma. However, the evidence to support the routine use of these agents, especially the combination of nivolumab and ipilimumab, for these rare subtypes remains less robust. Therefore, this study evaluated the efficacy and safety of nivolumab in combination with ipilimumab for treatment-naïve Japanese patients with advanced melanoma including rare subtypes.

2. Materials and methods

2.1. Patients

Treatment-naïve patients aged ≥20 years with confirmed unresectable stage III/IV or recurrent melanoma who were assessed to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 were included in the study. The study was conducted in compliance with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki and local laws. All patients provided written informed consent. The study protocol and any

subsequent amendments were approved by the relevant institutional review boards or independent ethics committee at each institution.

2.2. Study design and treatments

This multicentre, open-label, uncontrolled study consisted of screening, treatment, posttreatment observation and follow-up periods (Fig. 1). Participants received two intravenous doses of nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) per cycle for two 3-week cycles, followed by 6-week cycles with biweekly nivolumab (3 mg/kg). Infusions of the study drug were administered at intervals of at least 19 days in cycles 1 and 2 and at least 14 days in cycle 3 onwards. Treatment continued until establishment of complete response (CR) or progressive disease (PD) (RECIST, version 1.1 [20]), development of unacceptable toxicity or withdrawal of consent. The trial was registered as JAPIC-CTI #152869.

2.3. Efficacy end-points and assessments

The primary end-point was the centrally assessed objective response rate (ORR) as per the RECIST guidelines, version 1.1 [21]. Secondary end-points included the ORR assessed locally by the study site investigator, disease control rate, OS, PFS, duration of response, time to response, best overall response, change in the size of target lesion and maximum change in the size of the target lesion. Participants underwent diagnostic imaging for tumour size and assessment of antitumour effects at screening, during each cycle in the treatment period, end/discontinuation of treatment and 28 days posttreatment during the follow-up.

2.4. Safety

The safety of participants was monitored through repeated laboratory tests or imaging tests. Participants were assessed for adverse events (AEs), serious AEs (SAEs) and treatment-related adverse events (TRAEs) during the treatment phase and up to 100 days after the last dose of the study drugs. AE severity was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, Japan Clinical Oncology Group Version. TRAEs occurring during the treatment period or resulting in treatment discontinuation were followed up until recovery, mitigation or stabilisation requiring no follow-up.

2.5. Biomarkers

Tumour biopsies were obtained during the screening period for central analysis of *BRAF*-mutation status using the cobas® BRAF V600 Mutation Detection kit

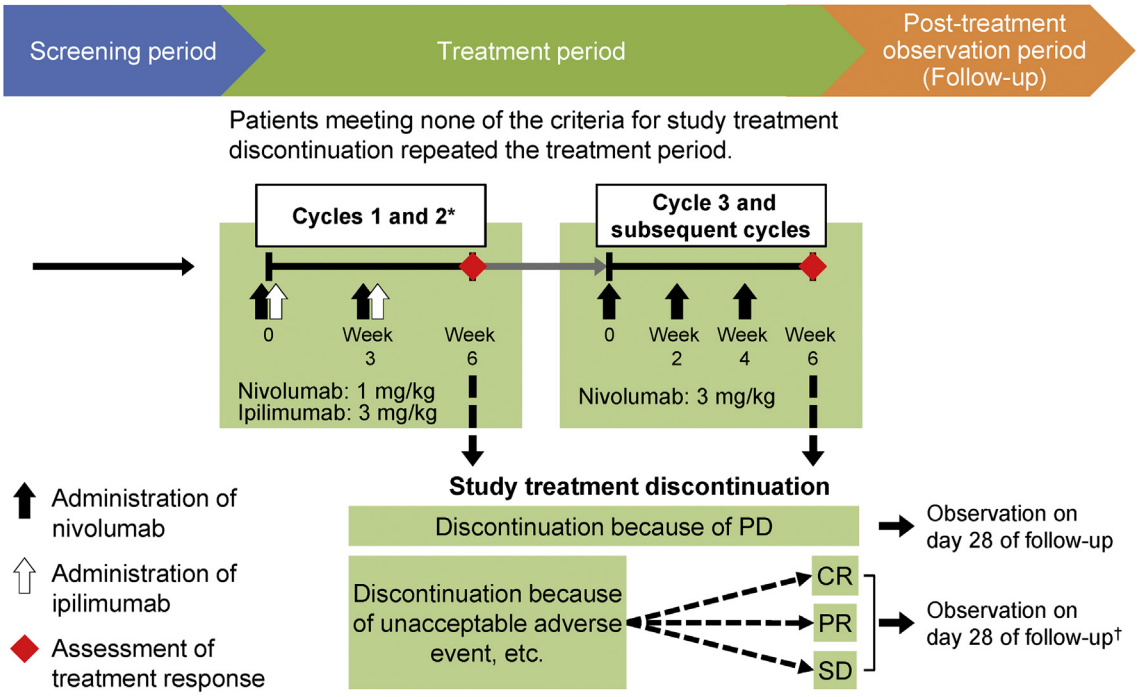


Fig. 1. Study design. *The maximum number of doses of nivolumab and ipilimumab administered was four. CR: complete response, PD: progressive disease, PR: partial response, SD: stable disease. † Diagnostic imaging (computed tomography or magnetic resonance imaging) for safety assessment was performed at 6- to 12-week intervals until post-study treatment if malignant melanoma had started or PD or recurrence was diagnosed. Treatment-related adverse events during the study period or leading to discontinuation were followed up until patients had recovered.

(Roche Diagnostics K.K., Tokyo, Japan). For consenting patients, the same sample was used to measure levels of programmed death ligand 1 (PD-L1) using the PD-L1 IHC 28-8 pharmDx assay (Dako Carpinteria, CA, USA).

2.6. Statistical methods

Based on a prior phase II study in similar patients [9,10], a response rate of 52.0% was expected in our study, and the null hypothesis was set at 23.8%. With these assumptions, data from 27 patients would provide at least 80% power to reject the null hypothesis (using the lower limit of the Clopper–Pearson 95% confidence interval [CI]). Assuming a 10% dropout rate, the planned sample size was 30.

Enrolled patients who received nivolumab or ipilimumab at least once constituted the safety set. Patients in the safety set with evaluable efficacy data were included in the full analysis set. Numbers of patients were summarised for AEs and TRAEs. AEs and TRAEs were summarised by system organ class, preferred term and grades (I–V).

For the primary end-point and all other end-points reported as percentages, the Clopper–Pearson 95% CIs were calculated. The percentage change in target lesion size was plotted against time. PFS and OS were evaluated using Kaplan–Meier analysis. PFS was analysed twice using data from both local and central assessments. Data analysis was conducted using SAS, version 9.3 (SAS Institute Inc, Cary, NC, USA).

Table 1
Demographics and baseline characteristics of the study population ($N = 30$).

Characteristic	N = 30
Sex	
Female	16 (53.3)
Male	14 (46.7)
Age, years	
<65	19 (63.3)
≥65	11 (36.7)
Median (range)	58.5 (31–81)
ECOG performance status	
0	27 (90.0)
1	3 (10.0)
Stage (at the start of the study)	
III	2 (6.7)
IV	5 (16.7)
Recurrence	23 (76.7)
Subtype	
Mucosal	12 (40.0)
Non-acral cutaneous	8 (26.7)
Acral	7 (23)
Uveal	2 (6.7)
Unknown primary	1 (3.3)
Previous resection	
Yes	23 (76.7)
Previous radiation therapy	
Yes	7 (23.3)
Number of previous adjuvant therapies	
0	22 (73.3)
1	6 (20.0)
≥2	2 (6.7)
Lactate dehydrogenase	
Normal	21 (70.0)
Elevated	9 (30.0)
BRAF	
Wild-type	27 (90.0)
Mutation	2 (6.7)
Unknown	1 (3.3)
PD-L1 expression	20 (83.3[a])
≥1%	4 (20.0[b])
<1%	16 (80.0[b])
≥5%	2 (10.0[b])
<5%	18 (90.0[b])

Values are indicated as n (%) unless otherwise stated.
BRAF: B-Raf proto-oncogene, ECOG: Eastern Cooperative Oncology Group, PD-L1: programmed death ligand 1.
[a] PD-L1 was quantifiable in 20 of the 24 (83.3%) evaluated patients.
[b] In patients with quantifiable PD-L1 results (n = 20).

3. Results

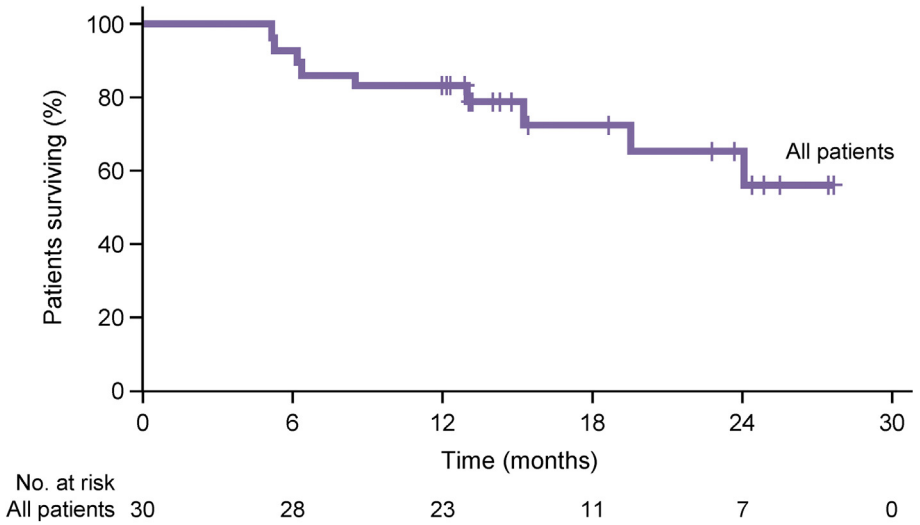
3.1. Patients

From June 2015 to November 2016, 30 patients were enrolled from five institutions in Japan. The median age of the patients was 58.5 years (Table 1). At baseline, the ECOG performance statuses were 0 and 1 in 90.0% (27/30) and 10.0% (3/30) of patients, respectively. At the data cut-off (31st October 2017), the median observation period was 14.1 months (range 5.2–27.7). The median number of doses of nivolumab was 4.0 (range

Table 2
Response to treatment in patients receiving nivolumab and ipilimumab (N = 30).

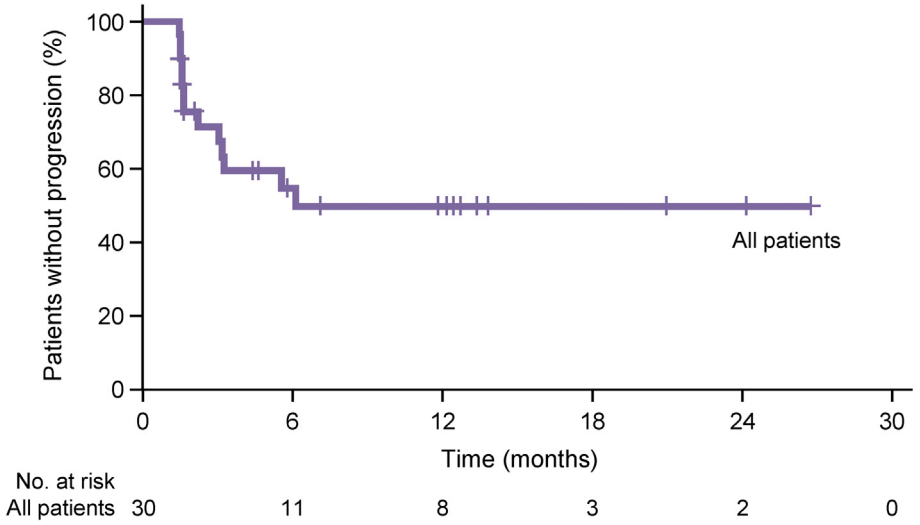
n (%) [95% CI]	Central assessment	Investigator assessment at the study site
Objective response rate (CR + PR)	13 (43.3) [25.5, 62.6]	13 (43.3) [25.5, 62.6]
Mucosal	4/12 (33.3) [9.9, 65.1]	
Non-acral cutaneous	6/8 (75.0) [34.9, 96.8]	
Acral	3/7 (42.9) [9.9, 81.6]	
Uveal	0/2 (0.0) [0.0, 84.2]	
Unknown primary	0/1 (0.0) [0.0, 97.5]	
Disease control rate (CR + PR + SD)	22 (73.3) [54.1, 87.7]	26 (86.7) [69.3, 96.2]
Best overall response		
CR	2 (6.7) [0.8,22.1]	2 (6.7) [0.8, 22.1]
PR	11 (36.7) [19.9, 56.1]	11 (36.7) [19.9, 56.1]
SD	9 (30.0) [14.7, 49.4]	13 (43.3) [25.5, 62.6]
PD	7 (23.3)	4 (13.3)
NE	1[a] (3.3)	0

CI: confidence interval, CR: complete response, PR: partial response, PD: progressive disease, NE: not evaluable, SD: stable disease. Based on RECIST Guideline, version 1.1. The Clopper–Pearson 95% CIs were determined for tumour response rates.
[a] Without measurable lesion.



	N = 30
Median OS, months (95% CI)	NE (19.5, NE)
OS rate, % (95% CI)	
6 months	93.3 (75.9, 98.3)
12 months	83.3 (64.5, 92.7)
18 months	72.9 (50.0, 86.5)
24 months	65.6 (40.4, 82.2)

Fig. 2. Overall survival. CI: confidence interval, NE: not estimable, OS: overall survival.



	N = 30
Median PFS, months (95% CI)	NE (3.0, NE)
PFS rate, % (95% CI)	
6 months	55.3 (34.4, 71.9)
12 months	50.3 (29.5, 67.9)
18 months	50.3 (29.5, 67.9)
24 months	50.3 (29.5, 67.9)

Fig. 3. Progression-free survival. CI: confidence interval, NE: not estimable, PFS: progression-free survival.

1–58). The median number of doses of ipilimumab was 3.0 (range 1–4). Seven (23.3%) patients had four combined doses of nivolumab and ipilimumab.

3.2. Efficacy end-points

The ORR was 43.3% (13/30) (95% CI: 25.5, 62.6) by both central assessment and local assessment by the investigator at the study site (Table 2). The disease control rate was 73.3% (22/30) (95% CI: 54.1, 87.7) with the central assessment and 86.7% (26/30) (95% CI: 69.3, 96.2) with the local assessment. Median OS and centrally assessed PFS were not reached (Figs. 2 and 3). OS (95% CI) at 6, 12, 18 and 24 months was 93.3% (75.9, 98.3), 83.3% (64.5, 92.7), 72.9% (50.0, 86.5) and 65.6% (40.4, 82.2), respectively. Both OS and PFS showed similar trends across subtypes. OS and PFS in accordance with tumour subtypes are shown in Figs. 4 and 5, respectively.

The median duration of response was not reached (95% CI: 4.2, not estimable), and the median (range) time to response was 1.5 (1.1–19.8) months. Fig. 6 shows the change in the target tumour size from baseline (%), and Fig. 7 shows the maximum change in the target tumour size. A reduction in tumour size compared with baseline was observed, irrespective of the PD-L1 status, with all

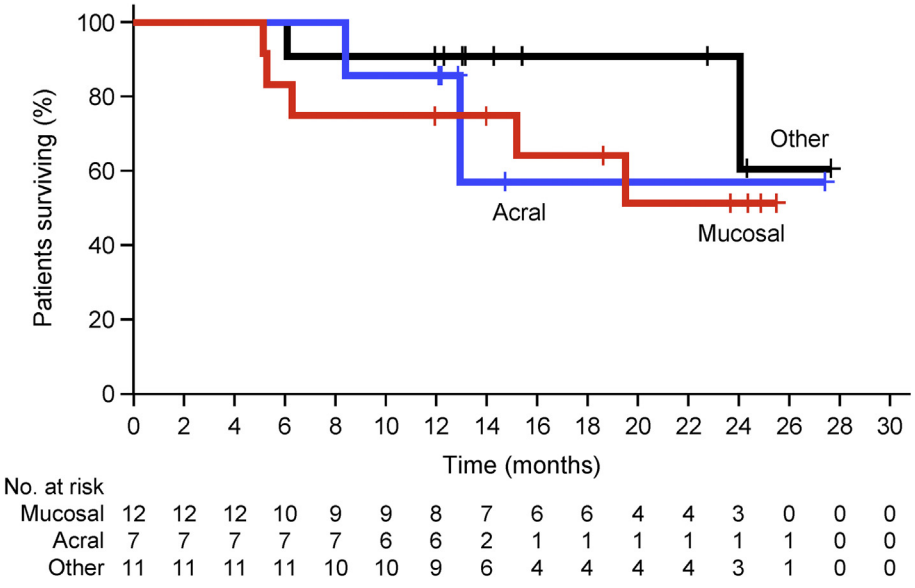


Fig. 4. Overall survival as per mucosal, acral and other subtypes. Other types include non-acral cutaneous, uveal and unknown primary subtypes.

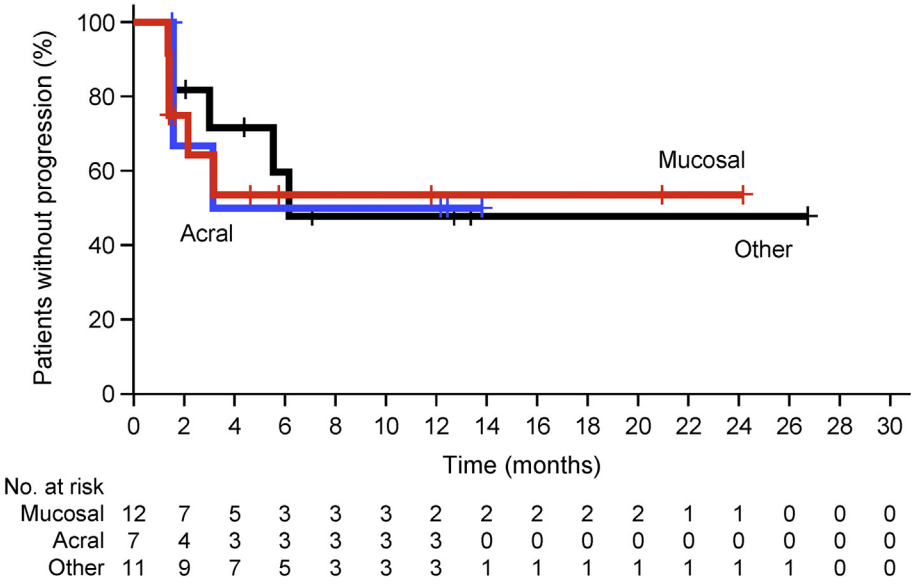


Fig. 5. Progression-free survival as per mucosal, acral and other subtypes. Other types include non-acral cutaneous, uveal and unknown primary subtypes.

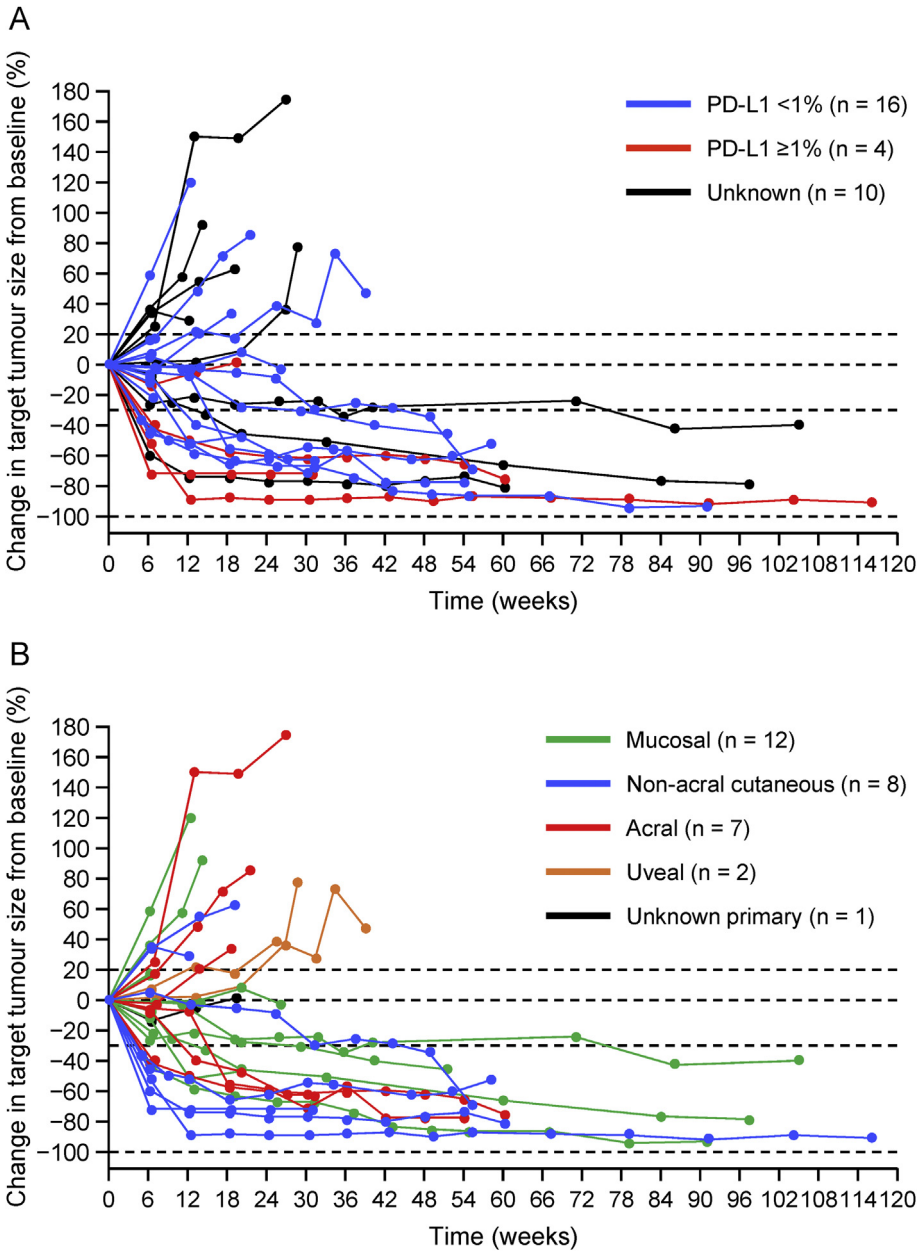


Fig. 6. Change in the target tumour size from baseline by PD-L1 status (A) and tumour subtype (B). Non-evaluable patients were excluded. There was one patient without measurable lesion. PD-L1: programmed death ligand 1.

patients with ≥1% PD-L1 status showing sustained reduction or no change from baseline (Figs. 6A and 7A). A reduction in tumour size occurred in all melanoma types except for uveal melanoma (2/30, 7%) (Figs. 6B and 7B). The ORR was 37.0% (10/27) (95% CI: 19.4, 57.6) in *BRAF* wild-type patients and 100% (2/2) in *BRAF* mutation–positive patients (95% CI: 15.8, 100.0).

3.3. Safety

AEs and TRAEs occurred in all patients, and those occurring in ≥3 patients are listed in Table 3. Specific AEs and TRAEs are shown in Table 4. Grade III or IV AEs were reported in 23 patients (77%); no grade V AEs were reported. SAEs and serious TRAEs were reported in 20 patients each (67%; grades III–IV in 57%). SAEs that occurred in multiple patients were hepatic function abnormal (4/30, 13%) and hypophysitis, hyponatraemia, decreased appetite, pyrexia, liver disorder and interstitial lung disease each in two patients (7%). Except for anaphylactic reaction and upper respiratory tract infection (each in one patient), a relationship with the study drugs could not be ruled out for any of the SAEs. Most of the SAEs resolved or improved with appropriate treatment. AEs leading to drug withdrawal (10/30, 33%; grades III–IV, 7/30, 23%) included

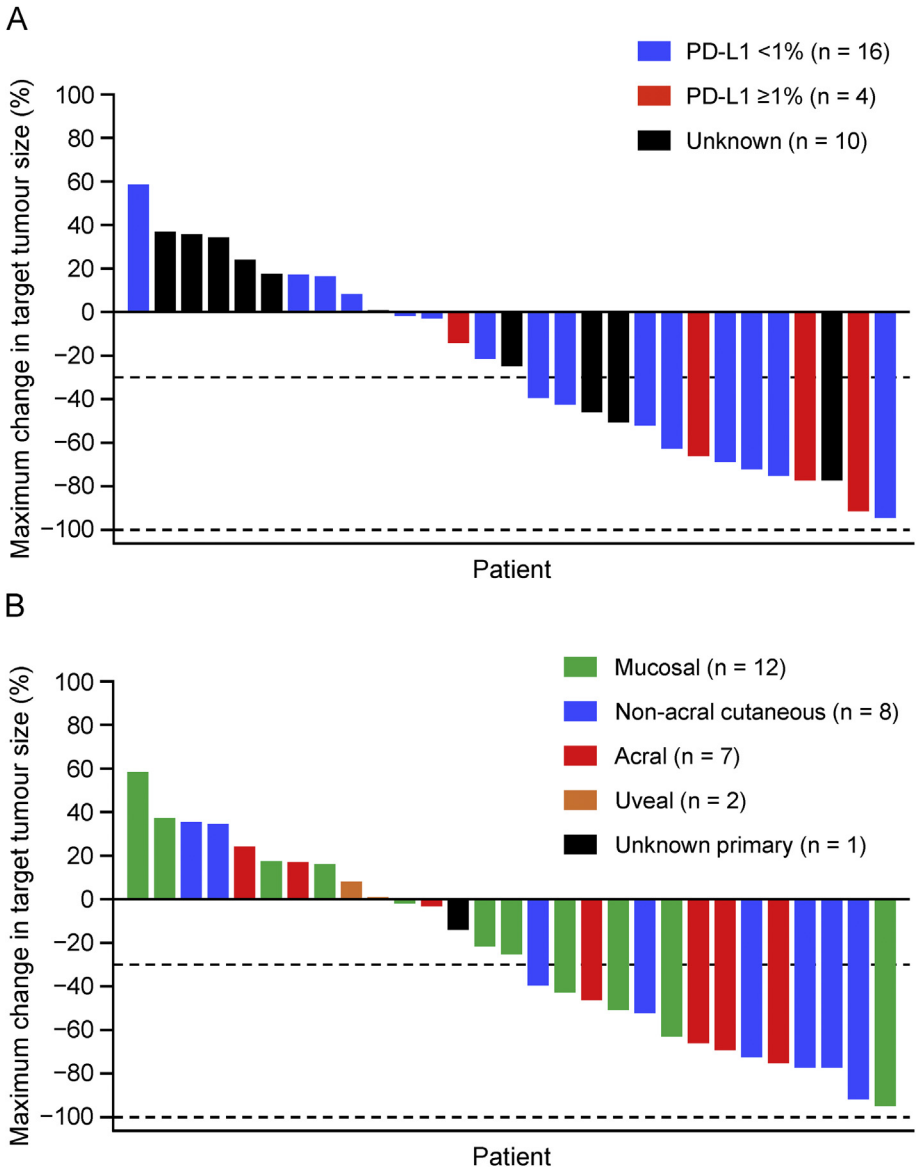


Fig. 7. Maximum change in the target tumour size by PD-L1 status (A) and tumour subtype (B). Non-evaluable patients were excluded. There was one patient without measurable legion. PD-L1: programmed death ligand 1.

hyponatremia, hepatic function abnormal and interstitial lung disease in two patients (7%), and diarrhoea, enteritis, lipase increased, hypokalaemia, and decreased appetite in one patient each (3%). AEs leading to dose interruption (16/30, 53%; grades III–IV: 11/30, 37%) included alanine aminotransferase (ALT) increased (3/30, 10%) and hypophysitis, diarrhoea, upper respiratory tract infection, pyrexia, hepatic function abnormal and lipase increased in two patients each (7%). There was no significant prolongation of Q wave to end of T wave (QT)/corrected QT interval in any patient.

Most AEs occurred within the first 3 months, during the combination treatment phase, with skin toxicity being the earliest reported event, and hypersensitivity/infusion reactions occurring the latest (Fig. 8).

3.4. Biomarkers

PD-L1 was quantifiable in 20 of the 24 (83.3%) evaluated patients. No tumour biopsies were obtained from the other six patients; thus, they were excluded. Durable tumour response was observed regardless of PD-L1 expression status (Table 5; Figs. 6A and 7A). Of the 30 patients in this study, two had *BRAF* mutations (6.7%), 27 were *BRAF* wild-type and one was not assessed (Table 1).

4. Discussion

The combination of nivolumab and ipilimumab has been reported to be efficacious with manageable toxicity

Table 3
Adverse events and treatment-related adverse events.[a]

Safety analysis set, N = 30	Adverse events		Treatment-related adverse events	
Event	All grades n (%)	Grades III–IV n (%)	All grades n (%)	Grades III–IV n (%)
Any events	30 (100)	23 (77)	30 (100)	23 (77)
Rash	18 (60)	2 (7)	18 (60)	2 (7)
Diarrhoea	17 (57)	1 (3)	17 (57)	1 (3)
Pyrexia	14 (47)	1 (3)	13 (43)	1 (3)
Lipase increased	12 (40)	7 (23)	12 (40)	7 (23)
ALT increased	11 (37)	3 (10)	11 (37)	3 (10)
AST increased	11 (37)	2 (7)	11 (37)	2 (7)
Pruritus	10 (33)	0	10 (33)	0
Decreased appetite	9 (30)	1 (3)	8 (27)	1 (3)
Hepatic function abnormal	7 (23)	4 (13)	7 (23)	4 (13)
Malaise	7 (23)	1 (3)	7 (23)	1 (3)
Hypothyroidism	7 (23)	0	7 (23)	0
Hyponatraemia	6 (20)	5 (17)	5 (17)	4 (13)
Vomiting	6 (20)	1 (3)	6 (20)	1 (3)
Headache	6 (20)	1 (3)	5 (17)	1 (3)
Gamma-glutamyltransferase increased	5 (17)	3 (10)	5 (17)	3 (10)
Constipation	5 (17)	1 (3)	5 (17)	1 (3)
Amylase increased	5 (17)	1 (3)	5 (17)	1 (3)
Fatigue	5 (17)	0	5 (17)	0
Arthralgia	5 (17)	0	5 (17)	0
Viral upper respiratory tract infection	5 (17)	0	0	0
Rash maculopapular	4 (13)	1 (3)	4 (13)	1 (3)
Nausea	4 (13)	0	4 (13)	0
Blood alkaline phosphatase increased	4 (13)	0	4 (13)	0
Stomatitis	4 (13)	0	3 (10)	0
Diabetes mellitus	3 (10)	2 (7)	1 (3)	1 (3)
Hypoalbuminaemia	3 (10)	1 (3)	2 (7)	1 (3)
Upper respiratory tract infection	3 (10)	1 (3)	0	0
Anaemia	3 (10)	0	2 (7)	0
Dysgeusia	3 (10)	0	2 (7)	0

Severity of adverse events was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, Japanese JCOG Version.
ALT: alanine aminotransferase, AST: aspartate aminotransferase.
[a] Incidence of adverse events occurring in ≥3 patients.

in previous studies in untreated advanced melanoma [7,8]. Unlike dacarbazine [22], nivolumab appears to synergise with ipilimumab, and this combination is increasingly being used to treat advanced melanoma [7–10]. This study expands on previous results partly because the baseline characteristics of the participants in the present study differed in some notable ways from those in previous studies; these differences are typical of those between Japanese and Western patients. This study enrolled more mucosal and acral cases than earlier/early studies, including uveal cases. The prognosis for the acral and mucosal subtypes has been reported to be worse than that for the non-acral cutaneous subtype [23]. The acral and mucosal subtypes are primarily characterised by genome structural variations, and they have considerably lower rates of somatic mutations than that of non-acral cutaneous melanoma [24–26]. For these reasons, the efficacy of immune-checkpoint inhibitors was expected to be lower in these subgroups [19]. However, this study demonstrated comparable efficacy and safety of nivolumab in combination with ipilimumab between acral, mucosal and other subtypes of melanoma.

The rate of *BRAF* mutation in our study was 6.7%. The rate of *BRAF* mutations is typically about 10% in acral and mucosal melanoma [16,27] and close to 0% in uveal melanoma [27,28]. In previous studies of Japanese patients, who mostly had acral or mucosal melanoma, the *BRAF* mutation rate was approximately 30% [17,18]. However, these studies did not analyse specimens from decalcification procedures in patients who underwent digital amputation because of subungual melanoma, and the reported rate of *BRAF* mutation is likely an overestimate. In addition, fewer patients were PD-L1 positive (PD-L1 expression ≥5%) in the present study (10%) than in the CheckMate 067 study (23.5%) [10].

The safety of nivolumab and ipilimumab were comparable to those reported in previous studies [8–10]. The frequency of grade III or IV AEs (77%) was comparable to that reported (68.7%) for the combination in the CheckMate 067 study [9]. TRAEs leading to drug withdrawal in our study occurred in 33% of patients, which was similar to the 36%–40% reported in previous studies [7–10]. The most common grade III or IV AEs were lipase increased (23%), hyponatraemia (17%) and hepatic function abnormal (13%). In contrast, diarrhoea

Table 4
Serious and specific adverse events and treatment-related adverse events.

Safety analysis set, N = 30	Adverse events		Treatment-related adverse events	
	All grades n (%)	Grades III–IV n (%)	All grades n (%)	Grades III–IV n (%)
Adverse events and treatment-related adverse events leading to drug withdrawal				
Any events	10 (33)	7 (23)	10 (33)	7 (23)
Hyponatraemia	2 (7)	2 (7)	2 (7)	2 (7)
Hepatic function abnormal	2 (7)	1 (3)	2 (7)	1 (3)
Interstitial lung disease	2 (7)	0	2 (7)	0
Diarrhoea	1 (3)	1 (3)	1 (3)	1 (3)
Enteritis	1 (3)	1 (3)	1 (3)	1 (3)
Lipase increased	1 (3)	1 (3)	1 (3)	1 (3)
Hypokalaemia	1 (3)	1 (3)	1 (3)	1 (3)
Decreased appetite	1 (3)	1 (3)	1 (3)	1 (3)
Serious adverse events and treatment-related adverse events				
Any events	20 (67)	17 (57)	20 (67)	17 (57)
Hepatic function abnormal	4 (13)	3 (10)	4 (13)	3 (10)
Hypophysitis	2 (7)	2 (7)	2 (7)	2 (7)
Hyponatraemia	2 (7)	2 (7)	2 (7)	2 (7)
Decreased appetite	2 (7)	1 (3)	2 (7)	1 (3)
Pyrexia	2 (7)	0	2 (7)	0
Liver disorder	2 (7)	0	2 (7)	0
Interstitial lung disease	2 (7)	0	2 (7)	0
Constipation	1 (3)	1 (3)	1 (3)	1 (3)
Diarrhoea	1 (3)	1 (3)	1 (3)	1 (3)
Enteritis	1 (3)	1 (3)	1 (3)	1 (3)
Ileus	1 (3)	1 (3)	1 (3)	1 (3)
Malaise	1 (3)	1 (3)	1 (3)	1 (3)
Drug-induced liver injury	1 (3)	1 (3)	1 (3)	1 (3)
ALT increased	1 (3)	1 (3)	1 (3)	1 (3)
AST increased	1 (3)	1 (3)	1 (3)	1 (3)
Dehydration	1 (3)	1 (3)	1 (3)	1 (3)
Hypokalaemia	1 (3)	1 (3)	1 (3)	1 (3)
Headache	1 (3)	1 (3)	1 (3)	1 (3)
Pulmonary embolism	1 (3)	1 (3)	1 (3)	1 (3)
Rash	1 (3)	1 (3)	1 (3)	1 (3)
Rash maculopapular	1 (3)	1 (3)	1 (3)	1 (3)
Anaphylactic reaction	1 (3)	1 (3)	0	0
Upper respiratory tract infection	1 (3)	1 (3)	0	0
Fatigue	1 (3)	0	1 (3)	0
Specific adverse events and treatment-related adverse events				
Endocrine disorder	11 (37)	4 (13)	10 (33)	3 (10)
Adrenal disorder	0	0	0	0
Diabetes	3 (10)	2 (7)	1 (3)	1 (3)
Pituitary disorder	2 (7)	2 (7)	2 (7)	2 (7)
Thyroid disorder	7 (23)	0	7 (23)	0
Gastrointestinal toxicity	19 (63)	2 (7)	19 (63)	2 (7)
Hepatotoxicity	14 (47)	6 (20)	14 (47)	6 (20)
Pulmonary toxicity	3 (10)	0	3 (10)	0
Nephrotoxicity	0	0	0	0
Skin toxicity	27 (90)	3 (10)	27 (90)	3 (10)
Hypersensitivity/infusion reaction	2 (7)	1 (3)	0	0

Severity of AEs was graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, Japanese JCOG Version.
ALT: alanine aminotransferase, AST: aspartate aminotransferase.

(9.3%), ALT increased (8.6%) and colitis (8.3%) were reported in the CheckMate 067 study [9,10]. The reduced rate of diarrhoea in this study (3%) may partly result from a racial difference in gut microbiota [29]. Most AEs were manageable and resolved with study drug withdrawal, dose interruption and appropriate treatment following therapeutic algorithms for immune-related AEs. The onset of AEs tended to occur during the first combination treatment cycle. Therefore, attention to patient safety should be especially high at this stage to ensure that AEs are detected and treated early.

Overall, our outcomes were comparable with those reported for previous studies. In the present study, the ORR by the central and local investigator assessments

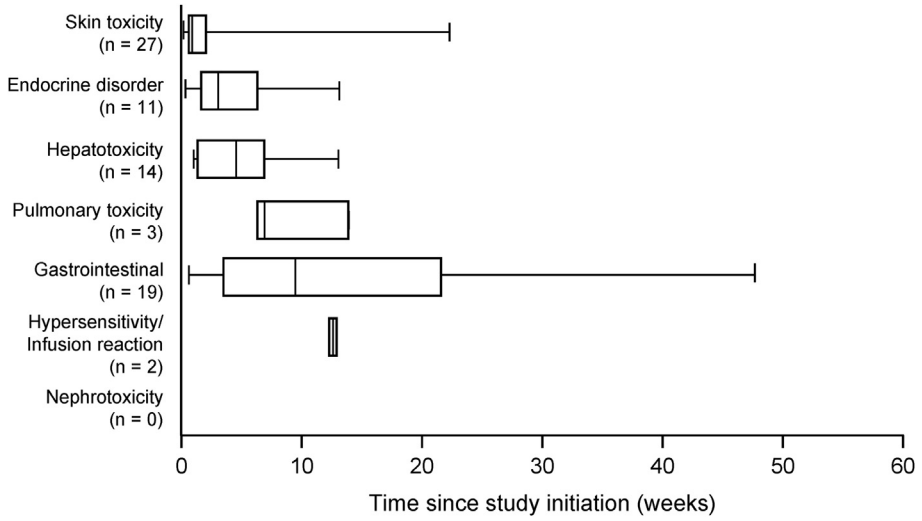


Fig. 8. Timeline of occurrence of selected adverse events.

Table 5
Response to treatment in patients receiving nivolumab and ipilimumab stratified by PD-L1 expression.

PD-L1 expression	Objective response rate n/N (%)	[95% CI]
≥1%	3/4 (75.0)	[19.4, 99.4]
<1%	8/16 (50.0)	[24.7, 75.3]
≥5%	2/2 (100.0)	[15.8, 100.0]
<5%	9/18 (50.0)	[26.0, 74.0]
Indeterminate or not evaluable	1/4 (25.0)	[0.6, 80.6]

CI: confidence interval, PD-L1: programmed death ligand 1.

at the study site were both 43.3%. This is lower than the investigator-assessed ORR of 57.6% in the CheckMate 067 study [9]. However, the centrally assessed disease control rate in our study was higher (73.3%) than the investigator-assessed disease control rate (70.7%) for the combination in the phase III study [9].

After a median observation period of 14.1 months, median PFS and OS were not reached. A median PFS of 11.5 months was reported for CheckMate 067 [9]. The OS at 12 months in the present study (83.3%) was comparable to that in CheckMate 067 (73%) [9,30]. Similarly, PFS at 12 months was 50.3% in the present study and 49% in CheckMate 067 [9,30]. The ORR, PFS and OS at 12 months in the published phase II study of nivolumab monotherapy in previously untreated Japanese patients were 34.8%, 38.3% and 69.6%, respectively [31]. Thus, the present study showed a similar ORR but much higher PFS and OS rate of nivolumab and ipilimumab combination than those of nivolumab monotherapy. Because long-term survivors of the ipilimumab group included those with a best overall response of CR, partial response, stable disease or even PD [32], the radiographic response may not necessarily correlate to long-term survival in this setting [33].

This study was small, which limited any analysis of efficacy within patient subgroups; because only two patients had *BRAF* mutations. Further development of this combination should be powered to assess the efficacy and safety of tailoring therapy for patients with confirmed genetic mutations or disease-related biomarkers such as PD-L1. Finally, only Japanese patients were included in this study; therefore, the results may not be generalised to wider population groups.

4.1. Conclusions

This study established the efficacy and safety of nivolumab combined with ipilimumab in a small number of Japanese patients with treatment-naïve advanced melanoma including rare subtypes. The ORR was lower than that in the previous phase III trial CheckMate 067, although the disease control rate was higher, and OS and PFS were comparable [9]. Incidence rates for grade III–IV AEs were high, but all were manageable and tolerable with appropriate medical attention and treatment following therapeutic algorithms for immune-related AEs. These results suggest a wider utility of this combination for treating patients with advanced melanoma.

Role of the funding source

The conduct of this research and preparation of the manuscript were funded by Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb. The sponsors contributed to the study design; collection, analysis, and interpretation of data; drafting of the manuscript and approved the final version to submit for publication. Specific contributions of three authors, M. Hatsumichi,

S. Asada and Y. Namba, who are employees of Ono Pharmaceutical Co., Ltd., and their declarations of interest have been detailed in the following sections.

Contributor statements

All authors contributed to manuscript review and manuscript approval. K. Namikawa prepared and edited the manuscript. S. Asada contributed to study design, and Y. Kiyohara, H. Uhara, H. Minami, M. Hatsumichi and N. Yamazaki contributed to both study conception and design. S. Asada contributed to quality control of data and algorithms. K. Namikawa, H. Minami, M. Hatsumichi, S. Asada and Y. Namba contributed to data analysis and interpretation. Y. Kiyohara, H. Uhara, T. Takenouchi, H. Uchi, K. Namikawa, S. Yoshikawa, S. Takatsuka, H. Koga, N. Wada and N. Yamazaki contributed to data acquisition.

Conflict of interest statement

K. Namikawa has received a grant from Ono Pharmaceutical Co., Ltd. during the conduct of the study and personal fees from Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis Pharmaceutical, Toray Industries, Takara Bio Inc., Eisai Co., Ltd. and Chugai Pharmaceutical Co., Ltd. outside the submitted work. Y. Kiyohara has received research funding from Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb during the conduct of the study and research funding from Chugai Pharmaceutical Co., Ltd., Novartis Pharma K.K., Merck Sharp & Dohme, Merck Serono, Takara Bio Inc. and Amgen Inc. outside the submitted work. N. Wada has received research funding from Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb during the conduct of this study. H. Minami has received grants, personal fees and other financial support from Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb during the conduct of the study and grants, personal fees and other financial support from Novartis Pharma K.K, Bayer AG, Chugai Pharmaceutical Co., Ltd., Daiichi Sankyo Co., Ltd., Sumitomo Dainippon Pharma Co., Ltd., Merck Sharp & Dohme and Taiho Pharmaceutical; grants and personal fees from Boehringer Ingelheim, Eisai Co., Ltd., Kyowa Hakko Kirin Co., Ltd., Lilly, Nippon Chemiphar, Pfizer Inc., Sanofi S.A. and Takeda Pharmaceutical Co., Ltd.; grants from Asahi-Kasei Corporation, Astellas Pharma Inc., AstraZeneca, Nippon Shinyaku Co. Ltd., Taisho Toyama Pharmaceutical Co., Ltd., Teijin Pharma Ltd. and Yakult Honsha Co., Ltd. and personal fees from Celgene, Janssen, Kowa Co., Ltd., Merck Serono, Mochida Co., Ltd., Otsuka Pharmaceutical Co., Ltd. and Shire Japan outside the submitted work. S. Takatsuka, S. Yoshikawa, H. Koga, T. Takenouchi and H. Uchi have received research funding from Ono Pharmaceutical Co., Ltd. during the conduct of the study. N. Yamazaki has received research funding from Ono Pharmaceutical Co., Ltd. during the conduct of the study and grants and personal fees from Bristol-Myers Squibb and Novartis Pharma K.K. outside the submitted work. H. Uhara has received a grant, honorarium and non-financial support from Ono Pharmaceutical Co., Ltd; honoraria and non-financial support from Bristol-Myers Squibb during the conduct of this study and grants, personal fees and non-financial support from Ono Pharmaceutical Co., Ltd, Chugai Pharmaceutical Co., Ltd., Novartis Pharma K.K., Merck Sharp & Dohme, Kyowa Hakko Kirin Co., Ltd., Maruho Co., Ltd., Pola Pharma Inc. and Mochida Pharmaceutical Co., Ltd.; personal fees and non-financial support from Bristol-Myers Squibb and Janssen Pharmaceutical K.K.; grants and personal fees from Mitsubishi Tanabe Pharma Corporation, Eisai Co., Ltd. and Daiichi Sankyo Co., Ltd. and grants from AbbVie Inc., Tsumura & Co., Nippon Kayaku Co., Ltd., Actelion Pharmaceuticals Ltd., Torii Pharmaceutical Co., Ltd. and Kaken Pharmaceutical Co., Ltd. outside the submitted work. M. Hatsumichi, S. Asada, and Y. Namba are employees of Ono Pharmaceutical Co., Ltd.

Funding

This work was supported by Ono Pharmaceutical Co., Ltd. and Bristol-Myers Squibb.

Acknowledgements

The authors wish to express their gratitude to the patients who participated in the study, their families, the doctors and other medical staff at the study centres for their contribution to this study. They thank Dr. Tarveen Jandoo, MD, MBA, and Dr. Susan Cottrell, PhD, of Edanz Medical Writing for providing medical writing support, which was funded by Ono Pharmaceutical Co., Ltd.

References

[1] Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. Nat Immunol 2013;14:1212–8.

[2] Yang Y, Pei J, Gao G, Yang Z, Guo S, Yue B, et al. Pharmacological interventions for melanoma: comparative analysis using Bayesian meta-analysis. Oncotarget 2016;7:80855–71.

[3] Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. Proc Natl Acad Sci U S A 2010;107:4275–80.

[4] Selby M, Engelhardt JJ, Lu LS, Quigley M, Wang C, Chen B, et al. Antitumor activity of concurrent blockade of immune checkpoint molecules CTLA-4 and PD-1 in preclinical models. J Clin Oncol 2013;(15_Suppl):3061.

[5] Wolchok JD, Kluger H, Callahan MK, Postow MA, Rizvi NA, Lesokhin AM, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med 2013;369:122–33.
[6] Sznol M, Kluger H, Callahan MK, Postow MA, Gordon RA, Segal NH, et al. Survival, response duration, and activity by BRAF mutation (MT) status of nivolumab (NIVO, anti-PD-1, BMS-936558, ONO-4538) and ipilimumab (IPI) concurrent therapy in advanced melanoma (MEL). J Clin Oncol 2014;32:5s.
[7] Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med 2015;372:2006–17.
[8] Hodi FS, Chesney J, Pavlick AC, Robert C, Grossmann KF, McDermott DF, et al. Combined nivolumab and ipilimumab versus ipilimumab alone in patients with advanced melanoma: 2-year overall survival outcomes in a multicentre, randomised, controlled, phase 2 trial. Lancet Oncol 2016;17:1558–68.
[9] Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23–34.
[10] Wolchok JD, Chiarion-Sileni V, Gonzalez R, Rutkowski P, Grob JJ, Cowey CL, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2017;377:1345–56.
[11] Ugurel S, Rohmel J, Ascierto PA, Flaherty KT, Grob JJ, Hauschild A, et al. Survival of patients with advanced metastatic melanoma: the impact of novel therapies-update 2017. Eur J Cancer 2017;83:247–57.
[12] Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, et al. Distinct sets of genetic alterations in melanoma. N Engl J Med 2005;353:2135–47.
[13] Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol 2006;24(26):4340–6.
[14] Tomizuka T, Namikawa K, Higashi T. Characteristics of melanoma in Japan: a nationwide registry analysis 2011–2013. Melanoma Res 2017;27:492–7.
[15] Ishihara K, Saida T, Otsuka F, Yamazaki N. Statistical profiles of malignant melanoma and other skin cancers in Japan: 2007 update. Int J Clin Oncol 2008;13:33–41.
[16] Sullivan RJ, Fisher DE. Understanding the biology of melanoma and therapeutic implications. Hematol Oncol Clin N Am 2014;28:437–53.
[17] Sakaizawa K, Ashida A, Uchiyama A, Ito T, Fujisawa Y, Ogata D, et al. Clinical characteristics associated with BRAF, NRAS and KIT mutations in Japanese melanoma patients. J Dermatol Sci 2015;80:33–7.
[18] Yamazaki N, Tanaka R, Tsutsumida A, Namikawa K, Eguchi H, Omata W, et al. BRAF V600 mutations and pathological features in Japanese melanoma patients. Melanoma Res 2015;25:9–14.
[19] Shoushtari AN, Munhoz RR, Kuk D, Ott PA, Johnson DB, Tsai KK, et al. The efficacy of anti-PD-1 agents in acral and mucosal melanoma. Cancer 2016;122:3354–62.
[20] D'Angelo SP, Larkin J, Sosman JA, Lebbé C, Brady B, Neyns B, et al. Efficacy and safety of nivolumab alone or in combination with ipilimumab in patients with mucosal melanoma: a pooled analysis. J Clin Oncol 2017;35(2):226–35.
[21] Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228–47.
[22] Yamazaki N, Uhara H, Fukushima S, Uchi H, Shibagaki N, Kiyohara Y, et al. Phase II study of the immune-checkpoint inhibitor ipilimumab plus dacarbazine in Japanese patients with previously untreated, unresectable or metastatic melanoma. Cancer Chemother Pharmacol 2015;76:969–75.
[23] Kuk D, Shoushtari AN, Barker CA, Panageas KS, Munhoz RR, Momtaz P, et al. Prognosis of mucosal, uveal, acral, nonacral cutaneous, and unknown primary melanoma from the time of first metastasis. Oncologist 2016;21:848–54.
[24] Furney SJ, Turajlic S, Stamp G, Thomas JM, Hayes A, Strauss D, et al. The mutational burden of acral melanoma revealed by whole-genome sequencing and comparative analysis. Pigment Cell Melanoma Res 2014;27:835–8.
[25] Furney SJ, Turajlic S, Stamp G, Nohadani M, Carlisle A, Thomas JM, et al. Genome sequencing of mucosal melanomas reveals that they are driven by distinct mechanisms from cutaneous melanoma. J Pathol 2013;230(3):261–9.
[26] Hayward NK, Wilmott JS, Waddell N, Johansson PA, Field MA, Nones K, et al. Whole-genome landscapes of major melanoma subtypes. Nature 2017;545:175–80.
[27] Glitza IC, Davies MA. Genotyping of cutaneous melanoma. Chin Clin Oncol 2014;3:27.
[28] Jovanovic P, Mihajlovic M, Djordjevic-Jocic J, Vlajkovic S, Cekic S, Stefanovic V. Ocular melanoma: an overview of the current status. Int J Clin Exp Pathol 2013;6:1230–44.
[29] Chaput N, Lepage P, Coutzac C, Soularue E, Le Roux K, Monot C, et al. Baseline gut microbiota predicts clinical response and colitis in metastatic melanoma patients treated with ipilimumab. Ann Oncol 2017;28:1368–79.
[30] European Medicines Agency. Opdivo: EPAR – product information. 2018. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/003985/WC500189765.pdf. [Accessed 20 July 2018].
[31] Yamazaki N, Kiyohara Y, Uhara H, Uehara J, Fujimoto M, Takenouchi T, et al. Efficacy and safety of nivolumab in Japanese patients with previously untreated advanced melanoma: a phase II study. Cancer Sci 2017;108(6):1223–30.
[32] Wolchok JD, Weber JS, Maio M, Neyns B, Harmankaya K, Chin K, et al. Four-year survival rates for patients with metastatic melanoma who received ipilimumab in phase II clinical trials. Ann Oncol 2013;24:2174–80.
[33] Khushalani NI. Duration of anti-programmed death-1 therapy in advanced melanoma: how much of a good thing is enough? J Clin Oncol 2018. JCO2017768275.