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IMMUNO-ONCOLOGY AND TECHNOLOGY

ORIGINAL ARTICLE

Phase II trial on nivolumab plus hypofractionated radiotherapy in patients with metastatic mucosal melanoma: PORTER-M3 trial

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Background: The response rate of nivolumab monotherapy for mucosal melanoma is only ∼20%. The objective of this phase II trial was to evaluate the efficacy and safety of nivolumab in combination with radiotherapy for metastatic mucosal melanoma.

Patients and methods: The eligibility criteria were: histological diagnosis of metastatic mucosal melanoma, Eastern Cooperative Oncology Group performance status of 0 or 1, and presence of measurable lesions. Patients received nivolumab with concurrent radiotherapy for measurable lesions, for a total dose of 25 Gy in five fractions per week. The primary endpoint was the response rate of all lesions (overall response rate, ORR). The study was considered to have met its primary endpoint if at least 6 of the 17 patients had a response (ORR ≥35.3%). The secondary endpoints were the disease control rate, progression-free survival, overall survival, and toxicity.

Results: Eighteen patients were enrolled, and 17 were evaluable for efficacy. The ORR was 41.2%, with two patients showing complete response, five partial response, and four stable disease. The median progression-free and overall survival were 4.9 months [95% confidence interval (CI) 2.2-15.1 months] and 20.1 months (95% CI 7.5-31.5 months), respectively. Immune-related adverse events of grades 3 or 4 occurred in 35.2% (6/17) of the patients. The radiation-related adverse events were grade 3 radiation dermatitis in one patient and grade 3 radiation pneumonitis in one patient.

Conclusions: Concurrent radioimmunotherapy consisting of nivolumab and radiotherapy showed promising efficacy with a manageable safety profile in patients with metastatic mucosal melanoma, warranting further evaluation in large studies.

Key words: mucosal melanoma, immune checkpoint inhibitor, radiotherapy

INTRODUCTION

Immunotherapy and targeted therapies have improved the prognosis of patients with metastatic melanoma.[1-3] Combination treatment regimens have been evaluated to improve survival and treatment response compared with anti-programmed cell death protein 1 (PD-1) monotherapy. Combination treatment with nivolumab plus ipilimumab or nivolumab plus relatlimab resulted in longer overall survival (OS) compared with nivolumab alone, although the difference was not significant.[3] The incidence of grade 3 or 4 treatment-related adverse events was higher in patients who received a combination treatment compared with monotherapy (nivolumab plus ipilimumab versus nivolumab alone: 59% versus 21%; nivolumab plus relatlimab versus nivolumab alone: 22% versus 12%).[4] Therefore, anti-PD-1 monotherapy and combination regimens (nivolumab plus ipilimumab or nivolumab plus relatlimab) are considered standard treatment.[1-4]

Mucosal melanoma is a rare and aggressive melanoma subtype, accounting for 1% of all melanomas in the USA and 10% in Japan.[5,6] Although immune checkpoint inhibitors (ICIs) have demonstrated high response rates (RRs) and have improved survival outcomes in patients with cutaneous melanoma, the RR of ICIs for mucosal melanoma is significantly lower.[7]

Several studies have also explored the efficacy of radiotherapy as an immune adjuvant.[8-18] The immune system

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can be suppressed but also stimulated by irradiation at specific tumor volumes and dose fraction sizes.[13] Unfortunately, in previous reports of metastatic mucosal melanoma, most patients were treated with conventional palliative dose-fractionated radiotherapy.[14,15] ICI efficacy could be improved by exploring radiotherapy regimens that stimulate the immune system.

The aim of this phase II trial was to evaluate the efficacy and safety of nivolumab in combination with radiotherapy for unresectable or metastatic mucosal melanoma.

PATIENTS AND METHODS

Study design and patients

In this multicenter, open-label, phase II study, patients were recruited from three academic medical centers in Japan. Eligible patients were >20 years of age and had histologically confirmed unresectable or metastatic mucosal melanoma. All patients had measurable disease detected by computed tomography (CT) or magnetic resonance imaging (MRI) within 28 days before enrollment according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and had an Eastern Cooperative Oncology Group performance status of 0 or 1.

Patients with symptomatic brain metastasis, an autoimmune disease, a medical condition requiring systemic treatment with corticosteroids or other immunosuppressive drugs, or previous treatment with anti-PD-1, anti-programmed cell death-ligand 1, or anti-cytotoxic T-lymphocyte-associated antigen 4 antibodies were excluded. The study protocol was approved by the ethics committee and institutional review board of each institution and was conducted in accordance with the ethical principles outlined by the Declaration of Helsinki. This trial was registered at the Japan Registry of Clinical Trials with the number jRCTs 1051200028 (https://jrct.niph.go.jp/latest-detail/jRCT 1051200028).

Procedure

Patients received nivolumab at a dose of 240 mg every 2 weeks or 480 mg every 4 weeks together with concurrent radiotherapy for a symptomatic lesion or the largest asymptomatic lesion, with a total dose of 25 Gy in five fractions per week. Nivolumab treatment continued until disease progression, unacceptable toxicity, or withdrawal of consent. Patients were required to receive at least 3 consecutive days of radiation therapy to ensure treatment efficacy.

The lesions of all patients were evaluated by CT or MRI every 8 weeks. The tumor responses were assessed by the investigators at each institution according to the RECIST v1.1 for all lesions, lesions within the radiation field, and lesions outside the radiation field. An independent radiologic review for response assessment was not planned for this single-arm phase II study, and all responses were investigator-assessed. Adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0. The trial scheme and flow diagram are shown in Figure 1.

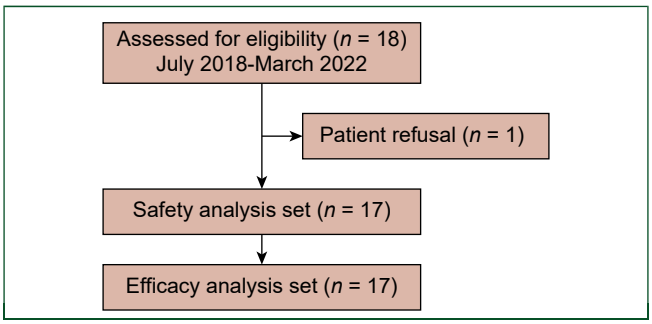

Figure 1. Patient selection flow chart.

Statistical analysis

The primary endpoint was the overall RR (ORR) as assessed by RECIST v1.1. The secondary endpoints were overall survival (OS), progression-free survival (PFS), disease control rate, RR within the radiation field, RR outside the radiation field, and adverse events. OS was defined as the time from enrollment to the date of death due to any cause. PFS was defined as the time from enrollment to the date of disease progression or death due to other causes. Patients with missing data for efficacy evaluation were excluded from the efficacy analysis. Time-to-event distributions were estimated using the Kaplan—Meier method, and confidence intervals (CI) were calculated using Greenwood's formula. Statistical analysis was carried out using STATA, version 17 (Stata Corp LP, College Station, TX).

A sample size of 16 was required to provide a power of 0.80 with a one-sided significance level of 0.05 and to detect an alternative ORR of 45% compared with the null hypothesis RR of 15% on a binomial distribution, according to calculations using PASS software (PASS 11; NCSS, Kaysville, UT). Accrual of 20 patients was planned, with allowance for a few dropouts. If the ORR was ≥ 35.3% (6/17 patients), we judged that the primary endpoint of this study met the decision criteria. All patients had at least 1 year of follow-up as of the cut-off of 30 April 2024.

An exploratory *post hoc* analysis was carried out based on previous studies that suggested a possible relationship between the irradiated tumor volume and treatment response.[17,18] This analysis evaluated whether the irradiated tumor volume correlated with the tumor response or the incidence of grade ≥3 adverse events. This analysis included only patients whose measurable lesions were treated with radiotherapy ($n = 10$). For each patient, we calculated the ratio of the sum of the diameters of the irradiated measurable lesions to the sum of the diameters of all measurable target lesions. This ratio was defined as the irradiated target lesion ratio. Following the cut-off used in a previous study,[18] patients were categorized into groups with an irradiated target lesion ratio of ≥50% or <50%. This analysis was not a prespecified endpoint and should be interpreted as descriptive.

Table 1. Patient characteristics

Characteristics	Patients ($N = 17$)
Age, years	
Median (range)	77 (58-89)
Sex	
Male	5
Female	12
ECOG PS	
0	10
1	7
Primary cancer site	
Head and neck	7
Gastrointestinal	6
Genitourinary	2
Uveal	2
Disease status	
De novo metastatic	12
Recurrent	5
BRAF V600 status	
Mutant	0
Wild	14
Not evaluated	3
LDH (U/l)	
<Upper limit of normal	8
≥Upper limit of normal	9
Number of metastatic sites	
1	2
2	8
3	5
4	2
Follow-up period, years	
Median (range)	2.5 (1.2-3.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

RESULTS

Patient characteristics

Eighteen patients were enrolled between July 2018 and March 2022 (Table 1). The safety analysis involved only 17 patients because 1 patient was excluded due to refusal. The median age was 77 (range, 58-89) years. The primary cancer sites were the head and neck region, gastrointestinal tract, genitourinary system, and uveal tract. No *BRAF* mutations were observed in our patients. Six patients received radiotherapy to the primary site, seven to metastatic sites, and four to both (Supplementary Table S1, available at https://doi.org/10.1016/j.iotech.2025.101550). Six patients received radiotherapy at two sites, whereas the other patients received it at one site. The median follow-up period was 2.5 (range, 1.2-3.6) years.

Response and survival

The ORR was 41.2% (95% CI 18.4% to 67.1%), and the primary endpoint was met. The disease control rate (DCR) was 64.7% (95% CI 38.3% to 85.8%). Two patients achieved a complete response, five patients achieved a partial response, and four patients had stable disease (Table 2). Within the radiation field, the RR was 52.9% and the DCR 88.2%. Outside the radiation field, the RR was 35.3% and 52.9%, respectively.

The median PFS and OS were 4.9 months (95% CI 2.2-15.1 months) and 20.1 months (95% CI 7.5-31.5 months), respectively. The 1-year PFS and OS rates were 41.2% (95% CI 18.6% to 62.4%) and 70.6% (95% CI 43.2% to 86.6%), respectively (Figure 2). At the time of analysis, disease progression was observed in all patients.

After disease progression, 11 patients received subsequent systemic therapies, comprising nivolumab plus ipilimumab ($n = 4$), ipilimumab monotherapy ($n = 3$), and continued nivolumab monotherapy after disease progression ($n = 4$). Two patients of those (one who received nivolumab plus ipilimumab and one who continued to receive nivolumab alone) underwent radiation therapy concurrently.

Safety

The most frequently observed adverse event was a decreased lymphocyte count. Treatment-related adverse events were mostly grade 1. Nivolumab-related non-hematologic adverse events of grade 3 or 4 occurred in 17.6% (3/17) of the patients, while no grade 5 adverse events were observed (Table 3). Grade 3 fatigue and oral mucositis were observed in one patient, grade 3 maculopapular rash was observed in another patient, and grade 3 pneumonitis was observed in a third patient. Regarding radiotherapy-related adverse events, grade 3 dermatitis radiation was observed in one patient, and no grade 4 or 5 adverse events were observed.

Table 2. Objective response rate

	All lesions ($N = 17$)			Lesions within the radiation field ($N = 17$)		Lesions outside the radiation field ($N = 17$)	
	Patient, *n*	%	95% CI	Patient, *n*	%	Patient, *n*	%
Complete response	2	11.8		3	17.6	2	11.8
Partial response	5	29.4		6	35.3	4	23.5
Stable disease	4	23.5		4	23.5	4	23.5
Non-CR/non-PD	0	0		2	11.8	0	0
PD	6	35.3		2	11.8	7	41.2
ORR	7	41.2	18.4% to 67.1%	9	52.9	6	35.3
DCR	11	64.7	38.3% to 85.8%	15	88.2	9	52.9

CI, confidence interval; CR, complete response; PD, progressive disease; ORR, overall response rate; DCR, disease control rate.

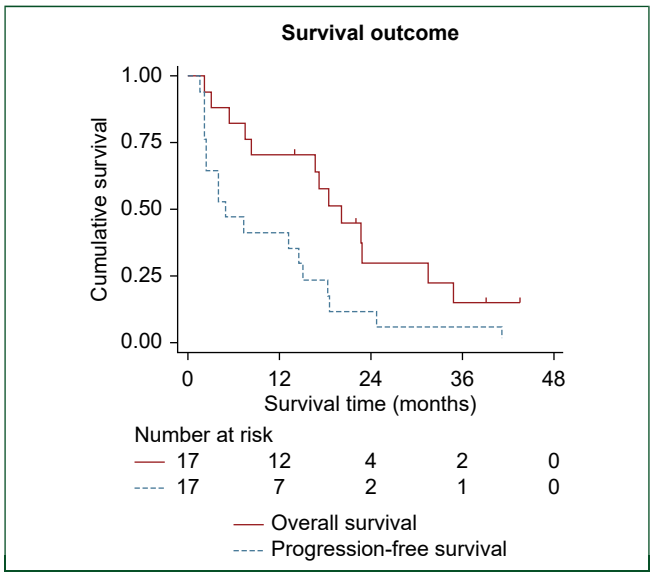

Figure 2. **Progression-free survival and overall survival of all patients.**

Exploratory post hoc analysis

In the exploratory *post hoc* analysis ($n = 10$), patients with an irradiated target lesion ratio of at least 50% had a substantially higher RR than those with a ratio of <50% [100% (4/4) versus 17% (1/6)]. Conversely, grade ≥3 adverse events occurred less frequently in patients with an irradiated target lesion ratio of at least 50% than in those with a ratio of <50% [25% (1/4) versus 66% (4/6)].

DISCUSSION

This is the first prospective, multicenter phase II trial to evaluate the efficacy and safety of nivolumab combined with concurrent radiotherapy in patients with unresectable or metastatic mucosal melanoma. We report an ORR of 41.2% (95% CI 18.4% to 67.1%), meeting our pre-defined primary endpoint. This result is noteworthy, as the overall RR of ICIs reported for mucosal melanoma is often ranging from 10%-25%.

Since the development of ICIs, no randomized controlled trials specifically for metastatic mucosal melanoma have been conducted. Several retrospective studies have reported no significant differences in the ORR, PFS, or OS between anti-PD-1 monotherapy and nivolumab plus ipilimumab in patients with metastatic mucosal melanoma.[19,20] Therefore, anti-PD-1 monotherapy remains the standard treatment.

The rationale for concurrent radiotherapy as an immune adjuvant is based on its potential to stimulate the immune system by inducing immunogenic cell death and enhancing antigen presentation.[21] Although adding radiotherapy to anti-PD-1 therapy was expected to enhance efficacy, previous reports did not show a clear synergistic effect.[14,15] The lack of a clear benefit in earlier studies may be attributed to the specific characteristics of the radiotherapy employed, including the dose fractionation, total number of fractions, and target lesions selected.

Table 3. **Treatment-related adverse events**

Adverse events related to nivolumab	Grade 1	Grade 2	Grade 3	Grade 4
White blood cell count decreased	3	2	0	0
Lymphocyte count decreased	3	3	8	0
Neutrophil count decreased	1	2	0	0
Platelet count decreased	0	1	0	0
Anemia	1	2	2	0
Hypokalemia	3	0	0	0
Hypoalbuminemia	1	2	1	0
Creatinine increased	2	0	0	0
Aspartate aminotransferase increased	8	0	0	1
Alanine aminotransferase increased	3	1	0	1
Creatine phosphokinase increased	0	1	0	0
Fatigue	1	1	1	0
Nausea	2	1	0	0
Anorexia	3	3	0	0
Diarrhea	1	1	0	0
Mucositis oral	2	2	1	0
Dysgeusia	1	1	0	0
Pruritus	5	1	0	0
Rash maculopapular	2	0	1	0
Dry skin	0	1	0	0
Generalized edema	1	1	0	0
Pneumonitis	1	0	1	0
Dyspnea	0	1	0	0
Palmar-plantar erythrodysesthesia syndrome	0	1	0	0
Tumor hemorrhage	0	1	0	0
Vision decreased	0	1	0	0
Proteinuria	0	1	0	0
Adverse events related to radiotherapy	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Dermatitis radiation	2	0	1	0
Nausea	3	2	0	0
Vomiting	0	1	0	0
Anorexia	2	0	0	0
Diarrhea	2	1	0	0
Enterocolitis	0	1	0	0
Gastritis	1	0	0	0
Pruritus	2	0	0	0
Rash maculopapular	1	0	0	0

NOTE: no grade 5 adverse events were observed.

Immunogenic death of tumor cells is more likely to occur with larger single doses of radiotherapy. However, the immune-activating effect from immunogenic cell death appears to plateau after ∼8 Gy, as the expression of DNA-degrading enzymes within the tumor cell cytoplasm increases responsively around this peak.[12] Conversely, a greater number of irradiation fractions also enhances the immune-activating effect associated with immunogenic cell death.[8] Considering these insights, our study design specifically incorporated a total dose of 25 Gy delivered in five fractions per week, a hypofractionated regimen that has been hypothesized to promote immune activation, rather than the conventional palliative dose-fractionated radiotherapy often used in previous reports for metastatic mucosal melanoma.

In our previous research,[17] we explored factors that trigger the abscopal effect caused by combination therapy with anti-PD-1 and radiotherapy, and found that a larger irradiated tumor volume was associated with a higher combined effect. This finding is also supported by a

retrospective study.[18] Consistent with earlier observations, our exploratory *post hoc* analysis of the present study showed that patients who had ≥50% of their measurable tumor burden irradiated had higher RRs and lower rates of grade ≥3 adverse events than those who had <50% irradiated. However, these findings were not derived from a prespecified endpoint and should be interpreted cautiously due to the small sample size. Nevertheless, these findings support the hypothesis that the extent of the irradiated tumor burden may influence the effects of systemic treatment. In the current study, although we had hoped to observe a clear abscopal effect, it was not directly confirmed. Nevertheless, compared with nivolumab monotherapy, the improved RR and DCR in lesions outside the radiation field suggest a potential contribution from the abscopal effect.

Although our study did not directly compare the effects of radiotherapy with nivolumab versus without nivolumab, nor different radiotherapy fractionation schemes, the favorable ORR observed warrants further investigation into the optimal integration of radiotherapy with ICI for mucosal melanoma. The median PFS and OS of 4.9 and 20.1 months and 1-year PFS and OS rates of 41.2% and 70.6%, respectively, also appear promising. When compared with our previous phase II trial, which demonstrated an ORR of 23.5%, median PFS of 1.4 months, and 1-year OS rate of 50.0% after nivolumab monotherapy,[22] the current results suggest an improved outcome with the combination therapy.

The present study has several limitations. This was a single-arm, phase II trial with a relatively small sample size. The lack of a control arm makes it difficult to definitively attribute the observed efficacy directly to the combination of nivolumab and radiotherapy, or to differentiate the contribution of radiotherapy itself. Furthermore, the patient population was heterogeneous regarding the primary cancer sites and radiation sites, which might have influenced outcomes. In the future, larger randomized controlled trials are needed to confirm these findings and to optimize the dose and fractionation of radiotherapy, as well as to compare nivolumab monotherapy with versus without concurrent radiotherapy in patients with unresectable or metastatic mucosal melanoma.

In conclusion, this phase II trial met its primary endpoint, suggesting that nivolumab combined with concurrent hypofractionated radiotherapy demonstrates encouraging efficacy in patients with unresectable or metastatic mucosal melanoma. These findings support further investigation into this therapeutic strategy for this aggressive and hard-to-treat malignancy.

FUNDING

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DISCLOSURE

The authors have declared no conflicts of interest.

DATA SHARING

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request. The data are not publicly available due to restrictions on the inclusion of information that could compromise the privacy of research participants.

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