



# Predicting marker for early progression in unresectable melanoma treated with nivolumab

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Received: 22 June 2018 / Accepted: 23 August 2018 / Published online: 30 August 2018  
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## Abstract

**Background** The objective of this study was to identify predictive markers, including inflammatory and nutritional status measures, of early progressive disease (EPD) in unresectable melanoma patients treated with nivolumab.

**Methods** A retrospective review was performed on 39 consecutive patients with unresectable melanoma treated with nivolumab. EPD was defined as progressive disease within 60 days after starting nivolumab according to Response Evaluation Criteria in Solid Tumors version 1.1. The predictive index model [melanoma inflammation index (MII)] was determined by the number of predictive factors.

**Results** Seventeen patients had cutaneous melanoma and 22 patients had mucosal melanoma. The overall response rate was 18.4%, and the response rates for cutaneous and mucosal melanoma were 29.4% and 9.5%, respectively. EPD was observed in 13 patients (34.2%). By multivariate analysis, body mass index (BMI) and C-reactive protein to albumin ratio (CAR) were independently and significantly associated with EPD, disease control rate, progression-free survival, and overall survival. Low BMI (cutoff 20) and high CAR (cutoff 0.0055) were predictive factors of EPD and were determined to be prognostic factors. MII, from 0 to 2, was determined by the number of these factors. The incidence of EPD was 0% in the low-risk group (MII = 0), 50% in the intermediate-risk group (MII = 1), and 83% in the high-risk group (MII = 2).

**Conclusions** An MII status of low BMI and high CAR may be used to predict EPD in unresectable melanoma patients treated with nivolumab.

**Keywords** Nivolumab · Predictive biomarker · Melanoma · Body mass index · C-reactive protein to albumin ratio

## Introduction

The prognosis of patients with unresectable melanoma has improved since the introduction of novel anti-cancer drugs in the past decade. Immune checkpoint inhibitors, such as programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors and cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors, and targeted therapies such as BRAF and MEK inhibitors, have been approved for patients with unresectable melanoma [1–4]. Nivolumab, a fully human IgG4 monoclonal antibody directed against PD-1, has demonstrated significantly prolonged overall survival (OS) in the first- and second-line unresectable melanoma settings [2, 5].

Two immune checkpoint inhibitors, nivolumab and the CTLA-4 inhibitor ipilimumab, were evaluated in the Check-Mate 067 trial, in which patients with previously untreated advanced melanoma were randomized to nivolumab plus ipilimumab (nivolumab 1 mg/kg plus ipilimumab 3 mg/kg

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every 3 weeks for four cycles, followed by nivolumab 3 mg/kg every 2 weeks), nivolumab (nivolumab 3 mg/kg every 2 weeks), or ipilimumab (ipilimumab 3 mg/kg every 3 weeks for four doses). Although the results suggested that 3-year OS and progression-free survival (PFS) tended to be better with combination therapy compared to nivolumab monotherapy, the sample size was not sufficient to demonstrate a significant difference [6, 7]. Thus, nivolumab monotherapy remains as a standard treatment for unresectable melanoma.

Optimal biomarkers for predicting response to nivolumab have not yet been identified. Inflammatory and nutritional status measures such as C-reactive protein (CRP) to albumin ratio (CAR), Glasgow Prognostic Score (GPS), prognostic nutritional index (PNI), neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR), performance status (PS), and advanced lung cancer inflammation index (ALI) have been evaluated in several clinical studies in various types of cancer [8–13]. A recent large retrospective study that combined six clinical cohorts of patients with metastatic melanoma revealed that obesity, which was classified by body mass index (BMI), was associated with improved PFS and OS [14]. However, no information about BMI as a biomarker for response to immune checkpoint inhibitors in melanoma patients has been reported. Identification of optimal biomarkers for nivolumab response is critically needed for clinical decision-making. The objective of this study was to identify predictive markers, including inflammatory and nutritional status indicators, of early progression (EPD) in patients with unresectable melanoma treated with nivolumab.

## Patients and methods

### Patients

A retrospective review of 39 consecutive patients with unresectable melanoma treated with nivolumab at Kyoto University Hospital between September 2015 and October 2017 was performed. Inclusion criteria were (1) unresectable melanoma and (2) treatment with nivolumab. The study protocol was approved by the Ethics Committee and the Institutional Review Board of Kyoto University Hospital. Patients received 2 mg/kg nivolumab intravenously as a 60-min infusion every 3 weeks or 3 mg/kg nivolumab every 2 weeks.

### Data collection

The following information was acquired from medical records and radiological images: treatment initiation date, age, gender, height, weight, Eastern Cooperative Oncology Group (ECOG) PS, primary cancer site, number of metastatic sites, laboratory tests at the start of nivolumab

treatment, the sum of the longest diameters of each target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, prior treatment regimen before nivolumab, response, toxicity, and final date of survival assessment.

### Statistical analysis

The EPD was defined as progressive disease within 60 days after starting nivolumab according to RECIST v1.1 [15]. The predictive index model (melanoma inflammation index: MII) was determined by the number of predictive factors. The MII, from 0 to 2, was determined by the number of these factors, and was defined as low-, intermediate-, and high-risk groups. Objective response was assessed according to RECIST v1.1 [15]. PFS was defined as the interval between the date of initiation of nivolumab and the date of disease progression or death due to any cause. OS was defined as the interval between the date of initiation of nivolumab and the date of death due to any cause. Patients not experiencing disease progression or death were censored at the last follow-up visit. All patient characteristics were classified as categorical variables. The following cutoffs for categorical data were used: age  $\geq 65$  years, ECOG PS  $\geq 1$ , neutrophils  $\geq 3000/\mu\text{L}$ , lymphocytes  $\geq 1200/\mu\text{L}$ , platelets  $\geq 25.0 \times 10^4/\mu\text{L}$ , lactate dehydrogenase (LDH)  $\geq 227$  U/L, gamma-glutamyltransferase (GGT)  $\geq 30$  IU/L, albumin  $\geq 4.0$  g/dL, CRP  $\geq 0.2$  mg/dL, BMI  $\geq 20$  kg/m<sup>2</sup>, CAR  $\geq 0.057$ , NLR  $\geq 2.4$ , ALI  $\geq 35$ , PNI  $\geq 40$ , and GPS score  $\geq 770$ . Fisher's exact test was used for categorical data analysis. All factors with a *p* value  $< 0.10$  in univariate analysis were included as covariables in multivariate analysis. Multivariate analysis was performed using logistic regression. Median PFS was estimated using the Kaplan–Meier method. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated using Cox regression models. A *p* value  $< 0.05$  was considered statistically significant. Statistical analyses were performed using R version 3.4.1. (R Project for Statistical Computing, Vienna, Austria).

## Results

### Patient characteristics

Patient characteristics are summarized in Table 1. Thirty-nine patients with unresectable melanoma were evaluated. The median age was 65 years. Seventeen patients had cutaneous melanoma and 22 patients had mucosal melanoma. Of 39 patients, 28 patients had not received previous treatment, and 8 of the remaining 11 patients had received dacarbazine (DTIC)-based therapy as first-line treatment. The median follow-up period among survivors after administration of nivolumab was 11.9 months (range 5.0–36.1 months).

**Table 1** Patient characteristics

	<i>n</i> = 39
Age (years)	
Median	65
Range	28–84
< 65	18
≥ 65	21
Gender	
Male	24
Female	15
ECOG PS	
0	26
1	12
2	1
Primary cancer site	
Cutaneous	17
Mucosal	22
Head and neck	10
Genitourinary	7
Rectal	2
Bronchus	2
Choroid	1
Number of metastatic sites	
≥ 2	19
< 2	20
BRAF status	
Wild type	27
Mutant	9
Not evaluated	3
Dose of nivolumab	
2 mg/kg Q3W	29
3 mg/kg Q2W	10
Previous treatment	
None	28
DTIC based	8
Vemurafenib	2
Radiotherapy	1
LDH (U/L)	
Median	203
Range	127–1767
< ULN	27
≥ ULN	12
Body mass index (kg/m <sup>2</sup> )	
Median	23.0
Range	15.0–35.9
C-reactive protein (mg/dL)	
Median	0.20
Range	0.10–8.0
Serum albumin (g/dL)	
Median	3.8
Range	2.6–4.4

**Table 1** (continued)

	<i>n</i> = 39
C-reactive protein-to-albumin ratio	
Median	0.054
Range	0.022–2.70
Neutrophil-to-lymphocyte ratio	
Median	2.40
Range	0.92–11.0

*ECOG PS* Eastern Cooperative Oncology Group performance status, *LDH* lactate dehydrogenase, *DTIC* dacarbazine, *ULN* upper limit of normal

### Objective response rate and early progression

The overall response rate was 18.4%, and the response rates for cutaneous and mucosal melanoma were 29.4% and 9.5%, respectively. EPD was observed in 64.1% of patients (25/39). In univariate analysis, BMI < 20 kg/m<sup>2</sup>, CAR ≥ 0.057, CRP ≥ 0.2 mg/dL, LDH ≥ 227 IU/L, platelets ≥ 25 × 10<sup>4</sup>/μL, and ECOG PS ≥ 1 were associated with EPD. Multivariate analysis with logistic regression revealed BMI < 20 kg/m<sup>2</sup> and CAR ≥ 0.057 to be independently and significantly associated with EPD (Table 2). The incidence of EPD was 0% in the low-risk group (MII = 0), 50% in the intermediate-risk group (MII = 1), and 83% in the high-risk group (MII = 2).

### Progression-free survival

At the time of data cutoff, progressive disease was observed in 33 of 39 patients (84.6%). Median PFS was 3.22 months (95% CI 1.71–5.45 months). Patients with a CAR ≥ 0.057 experienced significantly shorter PFS compared with patients with a CAR < 0.057 (1.67 months vs 5.45 months, HR 3.32, 95% CI 1.60–6.90, *p* = 0.001). Patients with a BMI < 20 also experienced significantly shorter PFS than patients with a BMI ≥ 20 (1.38 months vs 5.45 months, HR 4.12, 95% CI 1.84–9.22, *p* = 0.001). The MII clearly distinguished the PFS of each risk group (MII 2 vs MII 1 vs MII 0: 0.45 vs 1.87 vs 8.51 months, HR 16.0 vs 4.25 vs reference, respectively); significant differences were observed between each MII risk group (*p* < 0.01 for each).

### Overall survival

At the time of data cutoff, 23 of 39 patients (59.0%) had died. Median OS was 17.1 months (range 12.9–26.8 months). Patients in the high-risk group (MII = 2) experienced significantly shorter OS than patients in the low- (MII = 0) or intermediate-risk (MII = 1) groups (MII 2 vs MII 1 vs MII 0: 2.9 vs 18.0 vs 27.6 months, HR 21.0 vs 1.76 vs reference, respectively). There were no significant differences in OS

**Table 2** Factors associated with early progressive disease in uni- and multivariate analyses

		Univariate analysis (Fisher's exact test)		Multivariate analysis		
		OR	95% CI	OR	95% CI	<i>p</i> value
Age (years)	≥ 65 (vs < 66)	2.00	0.53–7.54			
Gender	Male (vs female)	0.75	0.20–2.86			
Primary site	Cutaneous (vs mucosal)	0.95	0.25–3.58			
Number of metastatic sites	(≥ 2 vs < 2)	0.37	0.10–1.44			
BRAF status	Wild type or not evaluated (vs mutant)	1.60	0.35–7.30			
Dose of nivo	Q2W vs Q3W	1.42	0.30–6.69			
Previous Tx	None (vs treated)	0.56	0.13–2.36			
Neut (/ $\mu$ L)	≥ 3000 (vs < 3000)	0.43	0.11–1.68			
Lymph (/ $\mu$ L)	≥ 1200 (vs < 1200)	0.50	0.13–1.88			
PLT (x 10 <sup>4</sup> / $\mu$ L)	≥ 25 (vs < 25)	0.29	0.07–1.15			
Alb (mg/dL)	< 4.0 (vs ≥ 4.0)	2.30	0.56–9.35			
LDH (IU/L)	≥ 227 (vs < 227)	0.25	0.05–1.04			
CRP (mg/dL)	≥ 0.2 (vs < 0.2)	0.18	0.04–0.82			
ECOG PS	≥ 1 (vs < 1)	0.31	0.07–1.27			
BMI (kg/m <sup>2</sup> )	< 20 (vs ≥ 20)	0.10	0.02–0.50	0.048	0.0047–0.49	0.011
CAR	≥ 0.057 (vs < 0.057)	0.11	0.02–0.50	0.053	0.0057–0.49	0.010
PNI	< 45 (vs ≥ 45)	1.04	0.27–3.92			
NLR	< 2.4 (vs ≥ 2.4)	0.51	0.13–1.96			
PLR	< 185 (vs ≥ 185)	0.92	0.24–3.41			
ALI	< 35 (vs ≥ 35)	3.19	0.81–12.5			
GPS	< 770 (vs ≥ 770)	Inf	3.14–Inf			

OR odds ratio, CI confidence interval, HR hazard ratio, Neut neutrophil, Lymph lymphocyte, PLT platelet, Alb albumin, LDH lactate dehydrogenase, CRP C-reactive protein, ECOG PS Eastern Cooperative Oncology Group performance status, BMI body mass index, CAR C-reactive protein to albumin ratio, PNI prognostic nutritional index, NLR neutrophil–lymphocyte ratio, PLR platelet–lymphocyte ratio, ALI advanced lung cancer inflammation index, GPS Glasgow Prognostic Score, Inf infinite, Tx treatment, nivo nivolumab

between low- and intermediate-risk groups (HR 1.76, 95% CI 0.62–4.98).

## Discussion

This is the first report of predictive factors for EPD in patients with metastatic melanoma. The MII, including factors such as low BMI and high CAR, could predict the incidence of EPD and the efficacy of nivolumab in unresectable melanoma. Several biomarkers, including BMI, GPS, PNI, NLR, PLR, PS, CAR, and ALI, have been reported for various cancers [8–13]. Among these, BMI was reported to be associated with PFS and OS in patients with unresectable melanoma treated with immunotherapy in a recent study that combined six patient cohorts. In a pooled analysis, obesity (compared to normal BMI) was associated with improved survival among patients with metastatic melanoma who received immunotherapy [14]. Although the CAR had been reported to have value as a prognostic factor in solid tumors,

its prognostic value in patients with unresectable melanoma has not been previously reported. CRP level, a component of the CAR, has been demonstrated to be a predictive factor of objective response as well as a prognostic factor among melanoma patients in several studies [16–19]. The results of a multicenter retrospective study that included 81 patients with metastatic melanoma indicated that patients with high pretreatment serum CRP levels were unlikely to respond to IL-2 therapy [19]. Additionally, a low serum albumin level has been reported to be a prognostic factor in patients with unresectable melanoma, although it has not been reported to be a predictive factor of objective response or EPD [20]. These data support the idea that a high CAR and low BMI could be negative predictive factors of EPD in unresectable melanoma patients treated with nivolumab.

The present results showed that MII risk group, especially the low- and high-risk groups, could be useful as a clinical decision-making tool. However, the predictive power of the intermediate-risk group remains insufficient. Limitations of the present study include a limited sample size and the

retrospective study design. In addition, we were not able to evaluate other biomarkers, such as PD-L2, tumor mutation burden, and indicators of mismatch repair [21–23].

In summary, an MII status of low BMI and high CAR was associated with EPD in unresectable melanoma patients treated with nivolumab. Further studies, including larger retrospective studies and prospective studies, are required to validate the present findings.

**Funding** None of the authors have financial disclosures or funding support.

## Compliance with ethical standards

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Conflict of interest** None of the authors have conflicts of interest to declare.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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