Prognostic nutritional index of early post-pembrolizumab therapy predicts long-term survival in patients with advanced urothelial carcinoma

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Abstract. Pembrolizumab has been widely used to treat advanced urothelial carcinoma that has progressed after first-line platinum-based chemotherapy. Because its clinical benefits are limited, biomarkers that can predict a good response to pembrolizumab are required. The prognostic nutritional index (PNI), calculated using the serum albumin level and peripheral lymphocyte count, has been evaluated as a predictive biomarker in cancer immunotherapy. The present study investigated the application of PNI as a predictive biomarker for pembrolizumab response in patients with advanced urothelial cancer. A retrospective study was conducted on 34 patients treated with pembrolizumab at Shiga University of Medical Science Hospital between January 2018 and July 2022. The posttreatment PNI (post-PNI) was calculated within 2 months of starting pembrolizumab. The present study investigated the association between post-PNI and objective response, overall survival (OS) and progression-free survival (PFS). The patient cohort was stratified into two categories, high and low post-PNI groups, with a cutoff value of post-PNI at 40. The higher post-PNI group demonstrated a better disease control rate than the lower post-PNI group (complete response + partial response + stable disease, 75 vs. 21%, P=0.004). Regarding median OS, the higher post-PNI group exhibited a significantly longer survival time than the lower post-PNI group (23.1 vs. 2.9 months, P<0.001). Similarly, the higher post-PNI group exhibited a significantly longer PFS than the lower post-PNI group (10.2 vs.1.9 months, P<0.001). Multivariate analysis showed that a higher post-PNI value was an independent predictor for OS (hazard ratio, 0.04; 95% confidence interval, 0.01-0.14; P<0.001) and PFS (hazard ratio, 0.12; 95% confidence interval, 0.04-0.35; P<0.001). The present study indicated that the post-PNI was a predictor of favorable clinical outcomes in patients treated with pembrolizumab for advanced urothelial carcinoma.

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Introduction

Advanced urothelial carcinoma (aUC), consisting of locally progressive and metastatic disease, is generally considered incurable (1). Since the 1980s, cisplatin-based chemotherapy has been the standard of care for aUC. A landmark regimen in systemic chemotherapy was the development of a combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) (2). Patients on MVAC demonstrated a good response against aUC, but its toxicity has been known to be severe. A randomized control study on gemcitabine and cisplatin (GC) vs. MVAC revealed the lower toxicity of GC compared to standard MVAC, which resulted in GC becoming a new standard regimen (3). Although the majority of patients with metastatic UC initially respond to these chemotherapy regimens, most such cancers eventually progress. To establish systemic salvage therapy for patients who have progressed after first-line chemotherapy is one of the unmet needs in the field.

Pembrolizumab, a programmed death 1 inhibitor, was approved as second-line therapy for aUC that had progressed after chemotherapy. A randomized phase 3 KEYNOTE-045 trial showed a superior overall survival (OS) benefit of pembrolizumab vs. chemotherapy (paclitaxel, docetaxel or vinflunine) in patients with aUC that progressed on platinum-based chemotherapy (4). However, its survival benefit was relatively short (10.3 vs. 7.4 months). The objective response rate [complete response (CR)+ partial response (PR), 21.1%] was also unsatisfactory although it was significantly higher than that of the chemotherapy group (11.4%). Unfortunately, only a minority of patients benefits from pembrolizumab. Establishing biomarkers to predict the efficacy of this drug is therefore an important challenge (5).

Recently, the prognostic nutritional index (PNI) has been studied as a potential biomarker that predicts patients' response to immunotherapy for various cancers (6,7). These

works demonstrated that a low pretreatment PNI value was a candidate prognostic biomarker of a poor objective response and adverse prognosis in patients with advanced cancer treated with immune checkpoint inhibitors (ICIs). In the field of aUC, a small number of publications exist on PNI and pembrolizumab treatment outcomes (8,9). However, their findings on the predictive impact of a survival benefit were inconsistent. Therefore, we planned a retrospective observational study of PNI before and after the induction of pembrolizumab in our cohort. In the present study, we elucidated that early post-treatment PNI after the induction of pembrolizumab therapy predicts better clinical outcomes in patients with aUC.

Materials and methods

Patients. Thirty-four consecutive patients who underwent second-line or later pembrolizumab treatment for aUC from Jan 2018 to July 2022 at Shiga University of Medical Science Hospital were included in this observational study. Clinical and pathological data were collected from their medical records. Patients with non-UC, or concurrent active cancer other than UC, were excluded. This study was approved by the ethics committee of Shiga University of Medical Science (approval number R2018-189), and it conforms to the provisions of the Declaration of Helsinki. Information on the present study was outlined on the website of our hospital in order for patients to be able to opt-out as desired. The requirement for written informed consent was waived because of the nature of the study.

Treatment. Patients were intravenously administered 200 mg of pembrolizumab every three weeks or 400 mg every six weeks. In principle, treatment was continued until disease progression as determined by imaging. However, some patients continued receiving pembrolizumab after disease progression because no effective salvage therapy existed at the time, such as enfortumab-vedotin. When immune-related adverse events (irAE) occurred, pembrolizumab treatment was terminated or interrupted.

Assessments. Hematological and biochemical laboratory tests were performed every treatment cycle, and an imaging study (computed tomography, magnetic resonance imaging, or 18F-fluorodeoxyglucose-positron emission tomography) was performed every 2 to 3 months. The treatment response was determined according to Response Evaluation Criteria in Solid Tumors, version 1.1 (10). Performance status was determined in accordance with Eastern Cooperative Oncology Group performance-status scores. The PNI was calculated by a formula established by Onodera *et al* (11): PNI=[10 x serum albumin (g/dl)] + [0.005 x lymphocyte count (/mm^3)].

Pretreatment PNI values (pre-PNI) were determined by hematological data within four weeks prior to the initiation of pembrolizumab therapy; in most patients, data were obtained on the starting day or the day before. Posttreatment PNI values (post-PNI) were defined as the highest value within two months from the initiation of pembrolizumab therapy. Prognostic nutritional index values within one week after the start of treatment were excluded because the observation period was considered too short. We stratified our cohort into two categories (high and low PNI groups) with cutoff values of pre- and post-PNI at 36 and 40, respectively.

Preliminary analysis to determine the optimal cutoff value. As a preliminary study to determine the optimal PNI cutoff value, we applied several cutoff values (31 to 48) used in previous studies described in the systematic review by Ni *et al* (6). We selected the cutoff value with the most significant difference in median overall survival (OS) between the low and high groups and the smallest P-value by log-rank test. Then, we considered that 36 (pre-PNI) and 40 (post-PNI) were the best cutoff values to discriminate OS in our cohort (Table SI).

Statistical analysis. Statistical analyses were carried out using EZR software (12). We used Wilcoxon's signed rank test to assess continuous variables. Fisher's exact test was used to analyze the differences in categorical variables of the groups. OS and progression-free survival (PFS) were calculated using the Kaplan-Meier method and compared using the log-rank test. Survival periods were calculated from the date of initial administration of pembrolizumab to the events (death or disease progression). A Cox proportional hazards model was used to test the significance of predictive factors of OS and PFS. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Patients' demographics. Table I shows patients' demographics. The median age of patients was 72.5 years, and the male-to-female ratio was 62 vs. 38%. Twenty-two and twelve patients were diagnosed with bladder and upper tract cancers as primary lesions, respectively. With regard to the purpose of pembrolizumab treatment, seven patients (21%) were treated for early relapsing disease after the receipt of platinum-based perioperative chemotherapy, and the remaining 27 patients (79%) were administered pembrolizumab for the purpose of second-line or later salvage therapy. Most patients (98%) received prior cisplatin/carboplatin-containing chemotherapy. Liver metastasis was present in nine cases (26%).

Treatment results. The median number of pembrolizumab administrations was five (Table II). Thirty-two patients (94%) were terminated from further treatment by reason of disease progression (21), irAE (7), fatigue (2) or having a long-term CR (2). The remaining two cases continued with pembrolizumab treatment. The objective response rate was 29% (CR 3; PR 7), and the disease control rate was 53% [CR 3; PR 7; stable disease (SD) 8]. The irAEs that resulted in discontinuation of treatment were interstitial pneumonia (2), liver dysfunction (2), severe diarrhea (1), encephalitis (1), and a worsening of rheumatoid arthritis (1).

Prognostic nutritional index. Median pre- and post-PNI values were 40.0 (21.6-52.7) and 41.4 (22.6-57.3), respectively ($P=0.153$, Wilcoxon's signed rank test). Fig. 1 shows the objective response stratified by pre- and post-PNI values. In pretreatment, the higher PNI group showed a better disease

Table I. Patients' demographics

Demographic	Values (n=34)
Median age, years (range)	72.5 (49-84)
Sex	
Men	21 (62%)
Women	13 (38%)
Performance status (ECOG)	
0	18 (53%)
1	11 (32%)
2	5 (15%)
Primary site	
Bladder	22 (65%)
Upper tract	12 (35%)
Histology	
Pure urothelial carcinoma	32 (94%)
Urothelial carcinoma with sarcomatoid variant	2 (6%)
Purpose of pembrolizumab administration	
For early relapse after perioperative chemotherapy	7 (21%)
2nd-line	25 (73%)
3rd-line or later	2 (6%)
Prior systemic therapy	
Gemcitabine/cisplatin or gemcitabine/carboplatin	33 (98%)
Gemcitabine/paclitaxel	4 (15%)
Others	2 (6%)
Metastatic sites	
Local recurrence	6 (18%)
Lymph nodes	23 (68%)
Lung	13 (38%)
Liver	9 (26%)
Bone	6 (18%)
Others (peritoneal carcinomatosis, port-site recurrence)	3 (9%)

ECOG, Eastern Cooperative Oncology Group.

Table II. Treatment results.

Factor	Values (n=34)
Median cycles (range)	5 (1-33)
Objective response of pembrolizumab	
CR	3 (9%)
PR	7 (20%)
SD	8 (24%)
PD	16 (47%)
Reasons for termination of pembrolizumab therapy[a]	
Disease progression	21 (62%)
irAE	7 (21%)
Long-term complete response	2 (6%)
Treatment-related fatigue 9+21+	2 (6%)

[a]Two patients continued with pembrolizumab therapy. CR, complete response; irAE, immune-related adverse events; PD, progressive disease; PR, partial response; SD, stable disease.

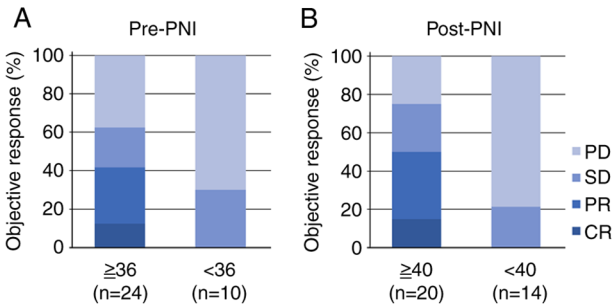

Figure 1. Objective response stratified by PNI value. (A) Pre-PNI and (B) post-PNI. CR, complete response; PD, progressive disease; PNI, prognostic nutritional index; PR, partial response; SD, stable disease.

control rate than the lower PNI group, but no significant difference was observed (63 vs. 30%, P=0.134, Fisher's exact test). Whereas, in posttreatment, the higher group demonstrated a significantly better disease control rate than the lower group (75 vs. 21%, P=0.004, Fisher's exact test).

Overall and progression-free survival rates stratified by PNI. The median overall survival (OS) and progression-free survival (PFS) of all patients were 10.2 and 3.5 months, respectively (Fig. 2). As for pre-PNI, patients with a higher PNI showed a longer median OS than the lower PNI group (12.2 vs. 3.0 months, P=0.003, log-rank; Fig. 3). With regard to PFS, no difference was observed between patients with higher and lower pre-PNI values (6.2 vs. 1.9 months, P=0.105). In terms of post-PNI, higher PNI patients showed both better OS and PFS than the lower post-PNI group; the median OS values for higher and lower PNI patients were 23.1 and 2.9 months (P<0.001); the median PFS values for higher and lower PNI patients were 10.2 and 1.9 months (P<0.001; Fig. 4). These results suggest that post-PNI has a better prognostic potential than the pre-PNI.

Table III shows univariate and multivariate analyses by a Cox hazard model regarding OS. In univariate analysis, the Eastern Cooperative Oncology Group performance status and post-PNI were revealed as significant predictors of OS. In multivariate analysis, a higher post-PNI value represented an independent prognostic factor for longer OS. Similarly, a higher post-PNI value indicated a predictive factor for better PFS (Table IV).

Discussion

The era of cancer immunotherapy for the treatment of aUC commenced with the introduction of pembrolizumab (4). In the first report of the KEYNOTE-045 trial, median OS

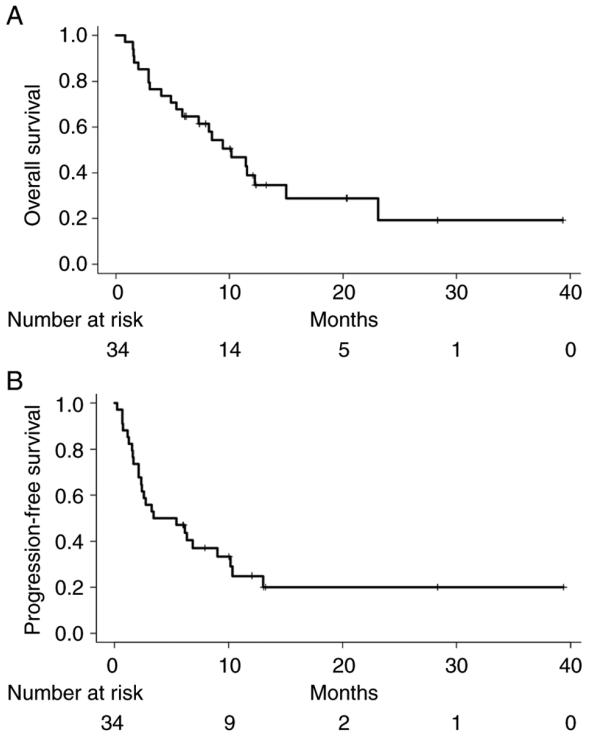

Figure 2. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival from the initiation of pembrolizumab treatment for all patients.

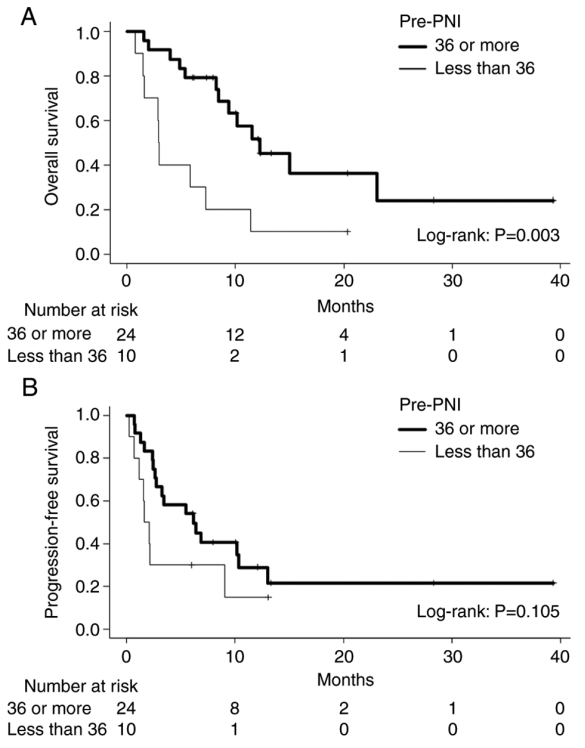

Figure 3. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival stratified by pretreatment PNI values. The cutoff value of PNI was 36. PNI, prognostic nutritional index.

and PFS were 10.3 and 2.1 months for a pembrolizumab treatment group compared with 7.4 and 3.3 months for a chemotherapy group, respectively. The trial revealed

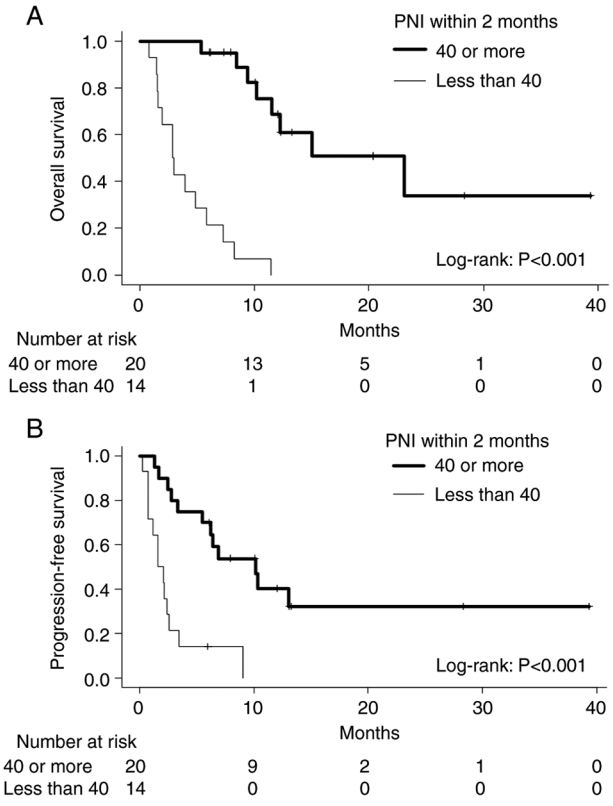

Figure 4. Kaplan-Meier curves for (A) overall survival and (B) progression-free survival stratified by posttreatment PNI values within 2 months after the induction of pembrolizumab therapy. The cutoff value of PNI was 40. PNI, prognostic nutritional index.

longer OS for the pembrolizumab group compared to the chemotherapy group (hazard ratio = 0.73). After >2 years of follow-up, the long-term results were consistent with those of previously reported analyses, which showed that median OS and PFS were 10.1 and 2.1 months, respectively (13). Our cohort yielded similar results to those of the KEYNOTE-045 trial; the median OS and PFS were 10.2 and 3.5 months, respectively. Although our sample size was very small, the clinical outcome of our cohort is considered standard quality of care.

Not all patients benefit from cancer immunotherapy. Therefore, many researchers have made efforts to identify biomarkers to predict the therapeutic benefit of pembrolizumab. Histological markers, such as programmed death-ligand 1 (PD-L1), are generally used to predict the response during immunotherapy for some types of cancer (14). Bellmunt *et al* have shown that multiple biomarkers that characterize the tumor microenvironment, such as PD-L1, tumor mutational burden, and the T-cell-inflamed gene expression profile ($Tcell_{inf}GEP$), may be clinically useful in better selecting patients with UC in KEYNOTE-045 and 052 cohorts for treatment with pembrolizumab (15). However, the role of PD-L1 expression as second-line immunotherapy for aUC is uncertain. In a subgroup analysis of KEYNOTE-045, a survival benefit was observed in patients who had a tumor PD-L1 combined positive score of less than 1% as well as 1% or more (4). PD-L1 thresholds vary due to tumor types and the use of different assays. PD-L1 expression was also measured

Table III. Cox hazard model with regard to OS.

	Univariate		Multivariate	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years				
≤72	1			
>72	0.66 (0.28-1.55)	0.340		
Sex				
Men	1			
Women	0.83 (0.34-2.02)	0.688		
ECOG performance status				
0, 1	1		1	
2	3.69 (1.31-10.44)	0.014	2.03 (0.59-6.97)	0.262
Primary lesion				
Bladder	1			
Upper tract	0.87 (0.35-2.13)	0.757		
Purpose of pembrolizumab administration				
For early relapsing after perioperative chemotherapy	1			
2nd-line or later	1.11 (0.37-3.33)	0.859		
Liver metastasis				
No	1			
Yes	1.62 (0.61-4.30)	0.334		
Post-PNI (within 2 months)				
Less than 40	1		1	
40 or more	0.06 (0.02-0.20)	<0.001	0.04 (0.01-0.14)	<0.001

Multivariate analysis was performed on variables with P-values less than 0.25 in univariate analysis. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PNI, prognostic nutritional index.

in a variable fashion either on tumor cells, tumor-infiltrating immune cells, or both. To date, PD-L1 expression as a predictive biomarker appears to have limitations (14).

Along with the search for histological biomarkers, hematological biomarkers have also been explored (5). Pretreatment baseline hematological parameters, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and lymphocyte-to-monocyte ratio (LMR), have been studied (16-19). Such prior works described how low NLR and PLR were associated with a favorable outcome of pembrolizumab therapy. With regard to the correlation between pretreatment PNI and the outcome of pembrolizumab treatment in aUC, several studies have been reported (8,9). Ishiyama *et al* described how a low PNI group showed significant shorter OS and PFS; they concluded that PNI is a useful predictor of prognosis in patients with aUC treated with pembrolizumab (9). Ni *et al* performed a meta-analysis of several types of cancers (gastric, lung, esophageal, urothelial, among others) and reported that low PNI might be an effective biomarker of poor outcome in patients with advanced cancer administered ICIs (6). Chemotherapy suppresses the numbers of neutrophils, platelets, and monocytes severely, and the use of granulocyte colony-stimulating factor and platelet transfusion may influence NLR/PLR/LMR before the start of salvage pembrolizumab. In comparison, serum albumin levels and lymphocyte counts change moderately. Therefore, we considered that PNI to be suitable as a prognostic biomarker after chemotherapy.

Recently, several reports have focused on the early hematological response after the induction of pembrolizumab therapy (19-22). These studies demonstrated that changes between pre- and posttreatment NLR, or the absolute value of NLR after treatment, were significantly associated with patient outcomes. We observed trends in PNI values for our patients, before and during pembrolizumab treatment. In cases with a good prognosis, PNI values increased soon after the start of treatment, even when the pre-PNI value was low. Thus, we speculated that the PNI value after pembrolizumab initiation was a good prognostic indicator. In previous reports regarding posttreatment NLR, observation points varied according to investigator: Three weeks, six weeks, and two cycles (approximately 4 weeks) after the start of pembrolizumab (18-21). Although the timing of a rise in post-PNI values in our patients with good outcomes showed a wide distribution, most were observed within two months (8-58 days, median 25.5 days).

Table IV. Cox hazard model with regard to PFS.

	Univariate		Multivariate	
Variable	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, years				
≤72	1			
>72	0.76 (0.34-1.67)	0.492		
Sex				
Men	1			
Women	1.17 (0.51-2.65)	0.711		
ECOG performance status				
0, 1	1		1	
2	1.94 (0.66-5.75)	0.231	2.36 (0.67-8.32)	0.183
Primary lesion				
Bladder	1			
Upper tract	1.01 (0.48-2.54)	0.821		
Purpose of pembrolizumab administration				
For early relapsing after perioperative chemotherapy	1			
2nd-line or later	0.99 (0.37-2.68)	0.991		
Liver metastasis				
No	1			
Yes	1.38 (0.57-3.34)	0.475		
Post-PNI (within 2 months)				
Less than 40	1		1	
40 or more	0.18 (0.07-0.44)	<0.001	0.12 (0.04-0.35)	<0.001

Multivariate analysis was performed on variables with P-values less than 0.25 in univariate analysis. CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; PFS, progression-free survival; PNI, prognostic nutritional index.

Therefore, we designated the observation point as within two months after the initiation of pembrolizumab. To our knowledge, the present study is the first report regarding post-PNI in patients with aUC treated with pembrolizumab.

The exact reason why a low PNI value was associated with a poor outcome in cancer immunotherapy has not been fully elucidated (6). Ryman and Meibohm stated that the increased catabolism associated with malnutrition might accelerate the clearance of monoclonal antibodies, which are eliminated primarily by catabolic degradation (23). Turner *et al* also reported that patients showing high clearance of pembrolizumab were associated with cachexia and increased protein turnover secondary to chronic inflammation; they showed a shorter OS (24). In our patients, the rapid increase in absolute lymphocyte counts mainly contributed to the increase in post-PNI values. Elevation of absolute lymphocyte counts after the induction of ICIs has been reported in several cancers, including melanoma, non-small cell lung cancer, and renal cell carcinoma (25-29). These studies demonstrated that higher absolute lymphocyte counts after the start of ICI (3-6 weeks) led to longer survival. We speculated that the induction of an immune response with pembrolizumab leads to an early increase in lymphocyte count. Moreover, an improvement in the patient's nutritional condition results in an increase in albumin levels, which may cause an increase in the post-PNI level.

Several limitations existed in the present study. First, this was a single-institutional retrospective study with a small patient number, and thus may have been prone to selection bias. Further study with a larger and more diverse cohort is required to validate our results. In fact, we are currently planning a multi-institutional validation study using a larger number of patients. Second, the timing of blood tests was not strictly defined, since it varied from physician to physician. The optimal sampling time to determine the best post-PNI value should be validated in future studies. Third, the PNI does not reflect the inflammatory state of the host, although cancer-related inflammation is considered to indicate a worsened prognosis. A comparison in future of PNI with inflammation-based markers, such as NLR, PLR, LMR and c-reactive protein, should be performed in terms of their ability to discriminate prognosis.

In conclusion, higher post-PNI values within two months predict both longer OS and PFS. Our findings may help identify good responders with aUC to salvage pembrolizumab therapy in an early phase of treatment.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SKa and TY designed the study, analyzed the data and drafted the manuscript. SKa and TY confirm the authenticity of all the raw data. KK, AW, MaN, SKu, TK, FJ and SN acquired clinical data. KJ and MiN analyzed the data and reviewed the manuscript. AK interpreted data and supervised the study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics committee of Shiga University of Medical Science (approval no. R2018-189). This study was undertaken according to the provisions of The Declaration of Helsinki. The requirement for written informed consent was waived because of the nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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