ORIGINAL ARTICLE

Association between time to treatment failure and peripheral eosinophils in patients with non–small cell lung cancer treated with immune checkpoint inhibitors

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KEY WORDS

eosinophils, immune checkpoint inhibitor, non–small cell lung cancer, time to treatment failure

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ABSTRACT

INTRODUCTION There is an unmet clinical need to identify biomarkers predicting which patients with non–small cell lung cancer (NSCLC) would benefit from treatment with immune checkpoint inhibitors (ICPIs).

OBJECTIVES The purpose of this study was to draw a detailed time to treatment failure (TTF) curve with information on the changes in peripheral eosinophil expression during ICPI treatment for NSCLC, and to clarify whether eosinophil expression can predict prolonged TTF.

PATIENTS AND METHODS In 259 patients with NSCLC treated with ICPI therapy, peripheral eosinophil counts and percentages at the time of each ICPI administration were evaluated from the beginning of ICPI treatment up to TTF. Univariable and multivariable analyses were performed to identify clinical factors associated with TTF.

RESULTS Patients receiving ICPI monotherapy (n = 180) were divided into 3 groups (TTF ≤6 weeks, TTF >6 weeks and ≤24 weeks, and TTF >24 weeks) and the number of patients with an eosinophil percentage of 5% or more within 6 weeks of ICPI therapy initiation was significantly different among these groups. In univariable and multivariable analyses, performance status of 0 to 1, immune-related adverse event not requiring ICPI discontinuation as well as an eosinophil percentage of 5% or more and an eosinophil count of 330/μ or more within 6 weeks of ICPI therapy initiation were significant favorable factors for prolonged TTF. In patients treated with combination therapy of ICPI and chemotherapy (n = 79), the number of patients with an eosinophil percentage of 5% or more within 12 weeks of therapy initiation was significantly different between patients with a TTF of up to 12 weeks and those with a more prolonged TTF. However, the only significant favorable factor for TTF was female sex.

CONCLUSIONS In NSCLC patients treated with ICPI therapy, particularly ICPI monotherapy, eosinophil measurements during treatment might be useful for predicting prolonged TTF.

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INTRODUCTION Immune checkpoint inhibitors (ICPIs) have significantly changed the treatment of advanced non–small cell lung cancer (NSCLC).[1,2] In particular, the long plateau in the tail of the survival curve of patients treated with ICPI therapy is impressive, and the number of patients with advanced NSCLC who can be cured is astonishing.[1,2] However, not every patient will benefit from ICPI and be cured. When the results of progression-free survival in clinical trials of ICPI monotherapy were examined in detail, patients could be divided into 3 groups: no response group, short-term response group, and long-term response group.[3-8] However, in clinical

WHAT'S NEW?

With the advent of immune checkpoint inhibitors (ICPIs), the treatment of many carcinomas has made great strides. However, it is currently difficult to identify patients who would benefit from treatment with ICPIs. As a biomarker for ICPI therapy, programmed cell death ligand 1 (PD-L1) expression has been utilized. However, PD-L1 may show different immunostaining levels depending on where it was collected. In this study, we found that an eosinophil percentage of 5% or more as well as an eosinophil count of 330/μl or more within 6 weeks of ICPI therapy initiation were significant favorable factors associated with time to treatment failure in patients receiving ICPI monotherapy. In patients treated with combination therapy of ICPI and chemotherapy, eosinophil variability was further complicated by myelosuppression by antitumor drugs. However, fluctuations in the levels of peripheral eosinophils have been observed, and detailed analysis of this phenomenon might reveal the usefulness of eosinophils as biomarkers. Our study suggests that there is a possibility to predict response to ICPI therapy based on peripheral eosinophil expression.

trials of combination therapy involving ICPI and chemotherapy, the proportion of individuals included in the no response group was found to be very small, leaving 2 primary groups of patients with short- and long-term response.[9,10]

In ICPI therapy, programmed death ligand 1 (PD-L1) is considered the most common biomarker predicting the response to treatment.[11,12] However, the expression of PD-L1 relies on immunostaining of pathological specimens, and the biopsy site may not fully represent the entire lung cancer.[12] What is more, the results of PD-L1 expression may differ depending on the place where the surgically excised specimen is stained and evaluated.[12] Therefore, better biomarkers are needed in the clinical setting. A biomarker that does not require a complicated system or costly equipment but, rather, is easy and inexpensive to evaluate, and, if possible, derived from standard clinical data, would be highly useful clinically. These factors are driving the search for new biomarkers other than PD-L1.[13-31] Studies have been investigating whether neutrophils, lymphocytes, and eosinophils could be useful in this regard.[18-31] Although the detailed biological mechanism, either direct or indirect, is unknown, it seems that changes in peripheral blood cell counts are associated with ICPI treatment, and this phenomenon has been the focus of several studies.[18,20,22,23,29,31] To the best of our knowledge, however, no investigation has been performed of the detailed changes of eosinophils during the clinical course of individual patients.

Recently, we reported the importance of eosinophil variability after the initiation of ICPI therapy.[32] Our study found that time to treatment failure (TTF) of ICPI therapy was longer in patients with a maximum eosinophil percentage greater than 5% and a maximum eosinophil count of 330/μl or more at 5 weeks since the initiation of therapy.[32] However, we did not separately analyze peripheral eosinophil expression in patients treated with ICPI monotherapy and those treated with combination therapy of ICPI and chemotherapy, although there were no significant differences in patient backgrounds between these 2 groups. Moreover, it was not possible to show in detail the changes in eosinophil expression during the clinical courses of individual patients. We believed that these data are important, and that an analysis visualizing detailed TTF including this information is absolutely necessary; therefore, we conducted the present study.

The purpose was to investigate whether peripheral eosinophil expression, as a convenient and inexpensive biomarker, could help predict whether or not ICPI treatment should be continued. In particular, we focused on findings that would be useful for selecting patients who could be treated with ICPIs for a long period of time, and for those who should switch from ICPIs to other therapeutic agents.

PATIENTS AND METHODS

Patients We analyzed the medical records of all patients diagnosed with NSCLC in 3 tertiary hospitals in Japan (Mito Medical Center, University of Tsukuba–Mito Kyodo General Hospital, Ryugasaki Saiseikai Hospital, and Tsukuba University Hospital) between February 2016 and March 2021. All patients with NSCLC treated with ICPI monotherapy or combination therapy of ICPI and chemotherapy during this period were included. NSCLC was diagnosed based on the World Health Organization classification. Tumor node metastasis staging (TNM Classification, 8th Edition) using computed tomography or magnetic resonance imaging of the head, bone scans, and ultrasonography and/or computed tomography of the abdomen was performed in all patients prior to ICPI therapy initiation. Patients with the following comorbidities or a history of treatment for these conditions were excluded: parasitic infestations, allergic diseases, autoimmune diseases, and hematologic malignancies. Patients with chronic obstructive pulmonary disease and those with bronchial asthma and chronic obstructive pulmonary disease overlap requiring systemic steroid use were also excluded. Particular attention was paid to adrenal insufficiency as an immune-related adverse event (irAE). Patients who developed eosinophilia associated with adrenal insufficiency as an irAE were excluded from this study. Demographic data of the patients, including age, sex, Eastern Cooperative Oncology Group score for performance status (PS), histopathology, disease stage, PD-L1 expression, objective tumor response, and survival, were obtained from the patients' medical records. Tumor response was evaluated as complete response, partial response, stable disease, or progressive disease according to the Response Evaluation Criteria in Solid Tumors (Version 1.1).

Measurement of peripheral eosinophil count and percentage Eosinophil counts and percentages were measured at the same time as complete

blood count before and during ICPI therapy. Results were obtained from the medical records of each patient. Counts for leukocyte subpopulations were measured by routine clinical laboratory analysis using a Sysmex XN 3000 analyzer (Sysmex Co, Ltd, Kobe, Japan).

Measurements of eosinophils In a previous study, we established that an eosinophil percentage of 5% or more and an eosinophil count of 330/μl or more 5 weeks following the initiation of ICPI therapy were the optimal cutoff values for patients with controlled disease.[32] However, current administration methods for ICPIs are every 2, 3, and 6 weeks.[3-10] Therefore, in the present study, we used the thresholds of an eosinophil percentage of 5% or more and an eosinophil count of 330/μl or more within 6 weeks after the initiation of treatment in patients treated with ICPI monotherapy. In patients treated with combination therapy of ICPI and chemotherapy, we adopted the same cutoff values noted within 12 weeks after the initiation of treatment.

Time to treatment failure and changes in eosinophil levels during immune checkpoint inhibitor therapy Peripheral eosinophils were measured after each ICPI administration. Regarding the eosinophil percentage, a TTF curve was drawn by color-coding the period until the next administration according to whether the eosinophil percentage of 5% or more was reached or not. Similarly, for the peripheral eosinophil count, a TTF curve was created by color-coding the period until the next administration depending on the presence or absence of an eosinophil count of 330/μl or more. Next, we compared the groups, based on whether the threshold of an eosinophil percentage of 5% or more or the eosinophil count of 330/μl or more was reached or not, either within 6 or 12 weeks following the initiation of treatment (in patients treated with ICPI monotherapy and those treated with ICPI combination therapy of ICPI and chemotherapy, respectively).

For the purpose of determining the characteristics of individuals with long-term therapeutic efficacy of ICPI treatment, we also investigated data on changes in eosinophil expression in patients with a TTF of 120 weeks or longer (for patients treated with ICPI monotherapy) or 60 weeks or longer (for those treated with combination therapy of ICPI and chemotherapy).

Univariable and multivariable analyses We performed a univariable analysis to investigate the association between characteristics of the patients (sex, PS, age, pathology, cancer stage, driver genes, PD-L1 expression, and irAEs) and TTF. In patients treated with ICPI monotherapy, we looked for the association between TTF and an eosinophil rate of 5% or more and eosinophil count of 330/μl or more within 6 weeks of the start of treatment. Similarly, in patients treated with combination therapy of ICPI and chemotherapy, the association between TTF and an eosinophil rate of 5% or more and eosinophil count of 330/μl or more within 12 weeks of treatment initiation was examined. Factors that were statistically significant in a univariable analysis were entered into the multivariable model. The analyses were performed separately for patients receiving ICPIs alone and those receiving the ICPI and chemotherapy combination.

Statistical analysis The χ^2 test was used to compare nominal variables and the nonparametric Mann–Whitney test was used to compare values with unknown population variance. We adopted the definition of TTF that is commonly used in cancer treatment; that is, the interval from initiation of therapy with ICPIs to treatment discontinuation or the last follow-up visit. Time to treatment failure was estimated by the Kaplan–Meier method and compared using the log-rank test. We used the Cox proportional hazards model and forward-backward stepwise method to determine the independent variables used in the final model. In this study, multivariable analyses were performed using only the variables with a *P* value of less than 0.1 in a univariable analysis. Time to treatment failure was the dependent variable in that model. All statistical analyses were conducted using SPSS, version 23 (IBM Corporation, Armonk, New York, United States). A *P* value of less than 0.05 was considered significant.

Ethics This study conformed to the Ethical Guidelines for Clinical Studies issued by the Ministry of Health, Labor, and Welfare of Japan. Written informed consent for participation in a non-interventional retrospective study was obtained from each patient. The analysis of the medical records of patients with lung cancer was approved by the ethics committee of Mito Medical Center–University of Tsukuba Hospital (No. 20–57).

RESULTS

Patient characteristics We analyzed the clinical characteristics of 259 patients who met all inclusion criteria within the study period. Detailed data of the study patients are shown in TABLE 1. Of those 259 patients enrolled, 180 were treated with ICPI monotherapy and 79 were treated with combination therapy of ICPI and chemotherapy.

In the former group, the median TTF was 12 weeks (range, 3–217 weeks; 20 patients had ongoing treatment). A total of 71 patients (39.4%) had an eosinophil rate of 5% or more, with a median rate of 7.9% (range, 5%–53%). Eighty-five patients (47.2%) had an eosinophil count of 330/μl or more, with a median count of 598/μl (range, 330–6413/μl). Among the 180 patients treated with ICPI monotherapy, 8 had a TTF of 120 weeks or more, including 7 individuals with an eosinophil rate of 5% or more achieved several times over the course of treatment.

In the group of patients treated with combination therapy of ICPI and chemotherapy, the median TTF was 23 weeks (range, 9–93 weeks; 25

TABLE 1 Characteristics of patients with non–small cell lung cancer treated with immune checkpoint inhibitor monotherapy and combination therapy including immune checkpoint inhibitors and chemotherapy

Parameter		ICPI monotherapy (n = 180)	Combination therapy of ICPI and chemotherapy (n = 79)
Age, y, median (range)		69 (29–87)	69 (29–80)
Sex	Male	39	20
	Female	141	59
PS (ECOG)	0–1	152	77
	≥2	28	2
Pathology	Adenocarcinoma	114	49
	Other	66	30
Cancer stage	IIIA–C	49	15
	IVA–B	131	64
Driver genes	Absent	161	5
	Present	19	74
PD-L1 expression	≥25%	71	19
	<25%	109	60
ICPI	Pembrolizumab	55	61
	Atezolizumab	23	11
	Nivolumab	102	0
	Durvalumab	0	6
	Nivolumab + Ipilimumab	0	1
Response	Complete response	5	0
	Partial response	53	48
	Stable disease	66	25
	Progressive disease	55	6
irAE (not requiring discontinuation of ICPI)	Present	24	11
	Absent	156	68
TTF, w, median (range)		12 (3–217)	23 (9–93)
Ongoing treatment		20	25

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ICPI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD-L1, programmed death ligand 1; PS, performance status; TTF, time to treatment failure

patients had ongoing treatment). Thirty-seven patients (46.8%) had an eosinophil percentage of at least 5%, with a median rate of 8.2% (range, 5.2%–33%), whereas 33 individuals (41.8%) had an eosinophil count of 330/μl or more, with a median count of 616/μl (range, 381–5742/μl). Seven of the 79 patients in this group had a TTF of 60 weeks or more, with 4 of these individuals achieving an eosinophil rate of 5% or more several times.

Time to treatment failure curves and patient grouping by information on peripheral eosinophils The TTF curves of 180 patients who received ICPI monotherapy are shown in FIGURE 1A and 1B. Based on these curves, the patients were divided into 3 groups: no response group (group I: TTF ≤6 weeks), short-term response group (group II: TTF >6 weeks and ≤24 weeks), and long-term response group (group III: TTF >24 weeks). Characteristics of the patients (sex, PS, age, pathology, cancer stage, driver genes, and PD-L1 expression) were not different between these groups (TABLES 2 and 3).

The same analysis was performed for individuals treated with combination therapy of ICPI and chemotherapy. The TTF curves of these patients are shown in FIGURE 2A and 2B. On this basis, the patients were divided into 2 groups of short-term and long-term response (group IV: TTF ≤12 weeks and group V: TTF >12 weeks, respectively). No differences in patient characteristics were found between these groups (TABLES 2 and 3).

Data on peripheral eosinophils in particular groups are summarized in TABLE 4. In patients treated with ICPI monotherapy, the number of patients with an eosinophil rate of 5% or more within 6 weeks of treatment initiation was significantly different among the 3 groups ($P = 0.003$). A separate analysis was performed with an eosinophil count of 330/μl adopted as the cutoff, but there was no significant difference in the ratio of patients between the groups

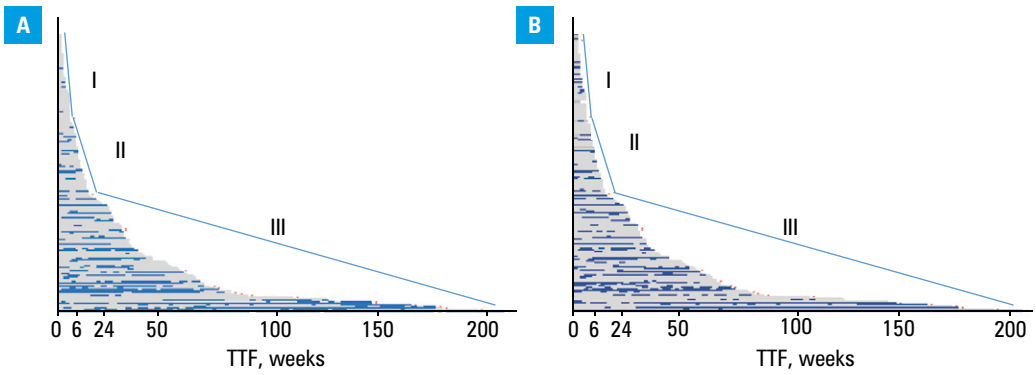

FIGURE 1 Time to treatment failure (TTF) curves of patients treated with immune checkpoint inhibitor monotherapy (n = 180); **A** – TTF curve with a cutoff peripheral blood eosinophil percentage of 5%; **B** – TTF curve with a cutoff eosinophil count of 330/μl. The curves were drawn by color-coding the period until the next administration of immune checkpoint inhibitor according to whether the specified cutoff values were achieved (dark blue) or not (gray). Patients were divided into 3 groups: no response group (group I, TTF ≤6 weeks), short-term response group (group II, TTF >6 weeks and ≤24 weeks), and long-term response group (group III, TTF >24 weeks).

TABLE 2 Comparison of patient characteristics by patient group[a]

Parameter		Patients treated with ICPI monotherapy (n = 180)				Patients treated with combination therapy of ICPI and chemotherapy (n = 79)		
		Group I (n = 58)	Group II (n = 54)	Group III (n = 68)	*P* value	Group IV (n = 19)	Group V (n = 60)	*P* value
Sex	Female	16	13	10	0.19	6	14	0.47
	Male	42	41	58		13	46	
PS (ECOG)	0–1	45	47	60	0.21	18	59	0.38
	≥2	13	7	8		1	1	
Age, y	<70	32	27	40	0.62	9	35	0.4
	≥70	26	27	28		10	25	
Pathology	Adenocarcinoma	43	31	41	0.14	11	38	0.67
	Other	15	23	27		8	22	
Cancer stage	IIIA–C	15	14	20	0.88	2	13	0.29
	IVA–B	43	40	48		17	47	
Driver genes	Absent	48	51	62	0.11	17	57	0.39
	Present	10	3	6		2	3	
PD-L1 expression	≥25%	20	18	33	0.15	7	12	0.13
	<25%	38	36	35		12	48	

a Stratification based on the therapeutic efficacy reflected by TTF: group I, TTF ≤6 weeks; group II, TTF >6 weeks and ≤24 weeks; group III, TTF >24 weeks; group IV, TTF ≤12 weeks; group V, TTF >12 weeks

Abbreviations: see **TABLE 1**

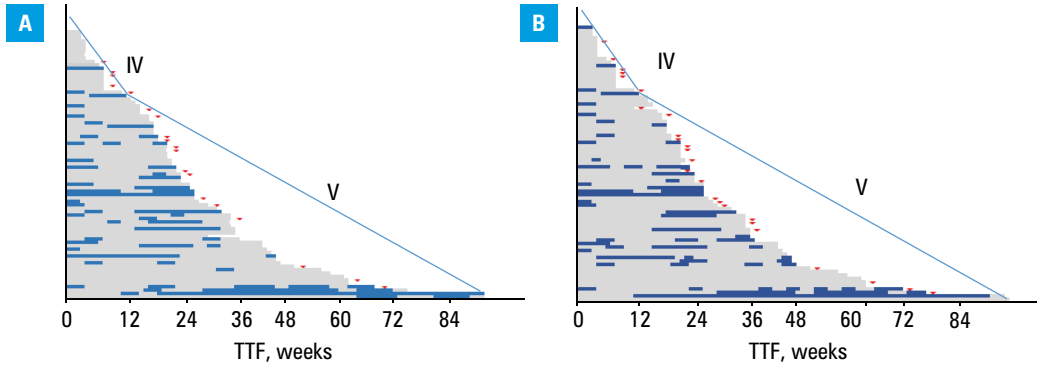

FIGURE 2 Time to treatment failure (TTF) curves of patients treated with combination therapy of immune checkpoint inhibitors and chemotherapy (n = 79); **A** – TTF curve with a cutoff peripheral blood eosinophil percentage of 5%; **B** – TTF curve with a cutoff eosinophil count of 330/μl. The curves were drawn by color-coding the period until the next administration of immune checkpoint inhibitor according to whether the specified cutoff values were achieved (dark blue) or not (gray). Patients were divided into 2 groups: short-term response group (group IV, TTF ≤12 weeks) and long--term response group (group V, TTF >12 weeks).

(*P* = 0.099). Similarly, in patients treated with combination therapy of ICPI and chemotherapy, the number of patients with an eosinophil rate of 5% or more within 12 weeks of the start of treatment was significantly different between the 2 groups (*P* = 0.023). With regard to the number of patients with an eosinophil count of 330/μl, there was no difference between the groups (*P* = 0.268).

Univariable and multivariable analyses As mentioned earlier, the groups did not differ in terms of patient characteristics (**TABLES 2** and **3**). The results of univariable and multivariable analyses are shown in **TABLE 5**. In patients treated with ICPI monotherapy, PS of 0 to 1, IrAE not requiring ICPI discontinuation, and an eosinophil percentage of 5% or more within 6 weeks of treatment initiation were significant favorable factors for prolonged therapeutic efficacy in a multivariable analysis. An eosinophil count of 330/μl or more within 6 weeks of ICPI therapy initiation was associated with a prolonged TTF in both univariable and multivariable analyses, whereas a PD-L1 expression exceeding 25% was not.

In patients treated with combination therapy of ICPI and chemotherapy, female sex was the only significant favorable factor for prolonged therapeutic efficacy in a univariable analysis (*P* = 0.019).

TABLE 3 Comparison of patient characteristics by peripheral eosinophil expression

Parameter		Patients treated with ICPI monotherapy (n = 180)			Patients treated with combination therapy of ICPI and chemotherapy (n = 79)		
		Eo ≥5% within 6 weeks			Eo ≥5% within 12 weeks		
		Present (n = 40)	Absent (n = 140)	*P* value	Present (n = 25)	Absent (n = 54)	*P* value
Sex	Female	8	31	0.77	4	16	0.2
	Male	32	109		21	38	
PS (ECOG)	0–1	36	116	0.27	25	52	0.99
	≥2	4	24		0	2	
Age, y	<70	25	74	0.28	15	29	0.63
	70≥	15	66		10	25	
Pathology	Adenocarcinoma	21	94	0.09	14	35	0.47
	Other	19	46		11	19	
Cancer stage	IIIA–C	11	38	0.96	6	9	0.54
	IVA–B	29	102		19	45	
Driver genes	Present	3	16	0.48	0	5	0.17
	Absent	37	124		25	49	
PD-L1 expression	≥25%	18	53	0.42	8	11	0.27
	<25%	22	87		17	43	
irAE (not requiring discontinuation of ICPI)	Present	7	17	0.38	2	9	0.3
	Absent	33	123		23	45	
Parameter		Eo ≥330/μl within 6 weeks			Eo ≥330/μl within 12 weeks		
		Present (n = 53)	Absent (n = 127)	*P* value	Present (n = 23)	Absent (n = 56)	*P* value
Sex	Female	8	31	0.23	3	17	0.11
	Male	45	96		20	39	
PS (ECOG)	0–1	45	107	0.99	23	51	0.99
	≥2	8	20		0	2	
Age, y	<70	35	64	0.06	13	31	0.99
	≥70	18	63		10	25	
Pathology	Adenocarcinoma	31	84	0.33	13	36	0.61
	Others	22	43		10	20	
Stage	IIIA-C	12	37	0.46	5	10	0.76
	IVA-B	41	90		18	46	
Driver genes	Present	3	16	0.2	0	5	0.31
	Absent	50	111		23	51	
PD-L1 expression	≥25%	24	47	0.32	9	10	0.08
	<25%	29	80		14	46	
irAE (not requiring discontinuation of ICPI)	Present	9	15	0.35	3	8	0.85
	Absent	44	112		20	48	

Abbreviations: Eo, eosinophils; others, see TABLE 1

DISCUSSION Based on the Kaplan–Meier curves of progression-free survival in several clinical trials of ICPI monotherapy for NSCLC, patients could be stratified into 3 groups: no response group, short-term response group, and long--term response group.[3-8] On the other hand, patients who received combination therapy of ICPI and chemotherapy could be divided into 2 groups of short-term and long-term response.[9, 10] On the basis of these stratifications, the relationship between the count and percentage of peripheral eosinophils and TTF was investigated. First, we created the Kaplan–Meier curves for TTF with eosinophil expression measured at the time of each ICPI administration during the clinical course of every patient. These data showed that the 3 groups of patients treated with ICPI monotherapy (group I: TTF ≤6 weeks; group II: TTF >6 weeks and ≤24 weeks; group III: TTF >24 weeks) differed significantly in terms of the number of patients with an eosinophil percentage of 5% or more achieved within 6 weeks of therapy initiation. In both univariable and multivariable analyses, not only a PS of 0 to 1 and IrAEs not

TABLE 4 Peripheral eosinophil expression in groups of patients with different time to treatment failure[a]

Parameter[b]		Patients treated with ICPI monotherapy (n = 180)				Patients treated with combination therapy of ICPI and chemotherapy (n = 79)		
		Group I (n = 58)	Group II (n = 54)	Group III (n = 68)	*P* value	Group IV (n = 19)	Group V (n = 60)	*P* value
Eosinophil percentage ≥5%	Present	4	15	21	0.003	2	23	0.023
	Absent	54	39	47		17	37	
Eosinophil count ≥330/μl	Present	12	15	26	0.099	3	20	0.268
	Absent	46	39	42		16	40	

a Stratification based on the therapeutic efficacy reflected by TTF: group I, TTF ≤6 weeks; group II, TTF >6 weeks and ≤24 weeks; group III, TTF >24 weeks; group IV, TTF ≤12 weeks; group V, TTF >12 weeks

b Threshold for achieving the specified counts and percentages of eosinophils was set at 6 weeks for patients treated with ICPI monotherapy and 12 weeks for those treated with combination therapy of ICPI and chemotherapy.

Abbreviations: see **TABLE 1**

requiring ICPI discontinuation, but also an eosinophil percentage of 5% or more and an eosinophil count of 330/μl or more within 6 weeks of ICPI treatment initiation were significant favorable factors for prolonged therapeutic efficacy. In patients treated with combination therapy of ICPI and chemotherapy, the number of patients with an eosinophil percentage of 5% or more within 12 weeks of therapy initiation was significantly different between groups IV and V ($P = 0.0231$). However, in a univariable analysis, the only significant favorable factor for prolonged TTF was female sex. Therefore, in this study, factors predicting a prolonged therapeutic efficacy in patients treated with combination therapy of ICPI and chemotherapy could not be determined.

We adopted cutoffs of 6 and 12 weeks for achieving an eosinophil percentage of 5% or more and an eosinophil count of 330/μl or more for patients receiving ICPI monotherapy and combination therapy of ICPI and chemotherapy, respectively. This was to reflect as much patient information as possible in terms of the therapeutic efficacy of ICPI treatment, but it remains arguable whether these grouping thresholds were optimal.

A few reports suggested the involvement of eosinophils in cancer immunity.[33-38] However, it is unlikely that the increased number of eosinophils in the peripheral blood directly reflects the immune status of cancerous lesions. Indeed, some study patients in the long-term response group had an increase in the absolute eosinophil count up to 1000/μl and a high percentage of eosinophils, exceeding 20%. However, in the majority of patients, no such high eosinophil count or percentage was observed. Based on these results, the relative variability of eosinophil count in peripheral blood linked to the fluctuation of other blood cells might be more important. It might also be consistent with the observation that the percentage of eosinophils was a more useful prognostic factor than the absolute eosinophil count.

Elucidation of the biological role of eosinophils in cancer immunity is likely to be an area of future research. At the same time, our understanding of the changes in peripheral blood cells during ICPI therapy will increase. Such advances will clarify the role of eosinophil expression as a biomarker for response to ICPI therapy. In this study, we did not find a clear association between eosinophil variability and TTF in patients treated with combination therapy of ICPI and chemotherapy. Myelosuppression by antitumor drugs causes neutropenia, which is presumed to further complicate the movement of peripheral blood cells. As such, this area will also benefit from future research.

This study has several limitations. Firstly, we did not elucidate the relationship between changes in eosinophils following ICPI therapy and the biological role of eosinophils. Secondly, it was a retrospective study that included patients with various baseline characteristics. Thirdly, it involved a limited number of patients with a short follow-up period, and the number of patients required was not prespecified based on the power calculation. Among the 79 patients treated with combination therapy of ICPI and chemotherapy, 25 were on treatment during the study, and this might have influenced the results. Fourthly, we focused on the indications for patients who should switch from ICPI to other treatment and those who can continue ICPI therapy for a long period of time. Therefore, the analysis was conducted with the intention of providing useful information as to whether the treatment could be continued at 2 to 3 courses of ICPI monotherapy and at 3 to 4 courses of combination therapy of ICPI and chemotherapy.

Although the contribution of ICPI therapy to prolonging survival in many patients with carcinoma is significant, ICPIs can cause irAEs in different organs throughout the body, and these irAEs range from controllable to life-threatening.[39] Therefore, as clinicians, we should be on the alert for the onset of irAEs. On the other hand, however, an association between controllable irAEs and prolonged survival has been reported.[40,41] Therefore, in the event of an irAE, it should first be determined whether it is controllable. Subsequently, the decision

TABLE 5 Results of univariable and multivariable analyses in patients treated with immune checkpoint inhibitor monotherapy

Parameter	Univariable analysis		Multivariable analysis	
	P value	Hazard ratio	95% CI	*P* value
Eosinophil percentage ≥5% within 6 weeks				
Female sex	0.17	–	–	–
PS (ECOG), 0–1	0.077	1.559	1.007–2.412	0.047
Age, ≤70 years	0.56	–	–	–
Pathology, adenocarcinoma	0.42	–	–	–
Cancer stage, IIIA–C	0.41	–	–	–
Driver genes, absent	0.12	–	–	–
PD-L1 expression, ≥25%	0.043	1.234	0.930–1.831	0.12
irAE not requiring ICPI discontinuation, present	<0.001	2.826	1.680–4.754	<0.001
Eosinophil percentage ≥5% within 6 weeks of ICPI therapy initiation, present	0.003	1.837	1.242–2.717	0.002
Eosinophil count ≥330/μl within 6 weeks				
Female sex	0.17	–	–	–
PS (ECOG), 0–1	0.077	1.722	1.115–2.660	0.014
Age, ≤70 years	0.56	–	–	–
Pathology, adenocarcinoma	0.42	–	–	–
Cancer stage, IIIA–C	0.41	–	–	–
Driver genes, absent	0.12	–	–	–
PD-L1 expression, ≥25%	0.04	1.303	0.929–1.826	0.125
irAE not requiring ICPI discontinuation, present	<0.001	2.784	1.653–4.690	<0.001
Eosinophil count ≥330/μl within 6 weeks of ICPI therapy initiation, present	0.061	1.471	1.038–2.085	0.03

Abbreviations: see **TABLE 1**

whether to continue ICPI therapy can be made in consideration of the changes in peripheral eosinophils associated with ICPI treatment.

ARTICLE INFORMATION

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