THERAPEUTIC ADVANCES in
Hematology

Original Research

Monocyte or white blood cell counts and β_2 microglobulin predict the durable efficacy of daratumumab with lenalidomide

Ther Adv Hematol

2022, Vol. 13: 1–17

DOI: 10.1177/20406207221142487

Yutaka Shimazu, Junya Kanda, Hitomi Kaneko, Kazunori Imada, Ryosuke Yamamura, Satoru Kosugi, Yuji Shimura, Tomoki Ito, Shin-ichi Fuchida, Hitoji Uchiyama, Kentaro Fukushima, Satoshi Yoshihara, Hitoshi Hanamoto, Hirokazu Tanaka, Nobuhiko Uoshima, Kensuke Ohta, Hideo Yagi, Hirohiko Shibayama, Yoshiyuki Onda, Yasuhiro Tanaka, Yoko Adachi, Mitsuhiro Matsuda, Masato Iida, Takashi Miyoshi, Toshimitsu Matsui, Ryoichi Takahashi, Teruhito Takakuwa, Masayuki Hino, Naoki Hosen, Shosaku Nomura, Chihiro Shimazaki, Itaru Matsumura, Akifumi Takaori-Kondo, Junya Kuroda and The Kansai Myeloma Forum

Abstract

Background: Daratumumab is one of the most widely used treatments for relapsed/refractory multiple myeloma (MM) patients. However, not all patients achieve a lasting therapeutic response with daratumumab.

Objectives: We hypothesized that a durable response to daratumumab could be predicted by the balance between the MM tumor burden and host immune status.

Design: We conducted a retrospective study using the real-world data in the Kansai Myeloma Forum (KMF) database.

Methods: We retrospectively analyzed 324 relapsed/refractory MM patients who were treated with daratumumab in the KMF database.

Results: In this study, 196 patients were treated with daratumumab, lenalidomide, and dexamethasone (DLd) regimen and 128 patients were treated with daratumumab, bortezomib, and dexamethasone (DBd) regimen. The median age at treatment, number of prior treatment regimens and time-to-next-treatment (TTNT) were 68, 4 and 8.02 months, respectively. A multivariate analysis showed that the TTNT under the DLd regimen was longer with either higher monocyte counts (analysis 1), higher white blood cell (WBC) counts (analysis 2), lower β_2 microglobulin (B2MG <5.5 mg/L) or fewer prior regimens (<4). No parameters were correlated with TTNT under the DBd regimen.

Conclusion: We propose a simple scoring model to predict a durable effect of the DLd regimen by classifying patients into three categories based on either monocyte counts (0 points for $\geqslant$200/μl; 1 point for $<$200/μl) or WBC counts (0 points for $\geqslant$3500/μl; 1 point for $<$3500/μl) plus B2MG (0 points for <5.5 mg/L; 1 point for $\geqslant 5.5$ mg/L). Patients with a score of 0 showed significantly longer TTNT and significantly better survival compared to those with a score of 1 or 2 (both $p<0.001$). To confirm this concept, our results will need to be validated in other cohorts.

Keywords: β_2 microglobulin, daratumumab, monocyte, multiple myeloma, predictive markers

Received: 29 July 2022; revised manuscript accepted: 14 November 2022.

Correspondence to:
Junya Kanda
Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, 54 Kawaramachi, Shogoin, Sakyoku, Kyoto 606-8507, Japan.
jkanda16@kuhp.kyoto-u.ac.jp

Yutaka Shimazu
Akifumi Takaori-Kondo
Department of Hematology and Oncology, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Hitomi Kaneko
Kazunori Imada
Department of Hematology, Japanese Red Cross Osaka Hospital, Osaka, Japan

Ryosuke Yamamura
Department of Hematology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan

Satoru Kosugi
Department of Internal Medicine (Hematology), Toyonaka Municipal Hospital, Toyonaka, Japan

Yuji Shimura
Junya Kuroda
Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan

Tomoki Ito
Shosaku Nomura
First Department of Internal Medicine, Kansai Medical University, Moriguchi, Japan

Introduction

The prognosis of multiple myeloma (MM) patients has been dramatically improved by the introduction of immunomodulatory drugs (iMIDs) and proteasome inhibitors (PIs).[1] In addition to iMIDs and PIs, the anti-CD38 antibody daratumumab has shown a high response rate with superior prognosis both for

Shin-ichi Fuchida
Chihiro Shimazaki
Department of Hematology, Japan Community Health care Organization Kyoto Kuramaguchi Medical Center, Kyoto, Japan

Hitoji Uchiyama
Department of Hematology, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan

Kentaro Fukushima
Naoki Hosen
Department of Hematology and Oncology, Graduate School of Medicine, Osaka University, Osaka, Japan

Satoshi Yoshihara
Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan

Hitoshi Hanamoto
Department of Hematology, Kindai University Nara Hospital, Ikoma, Japan

Hirokazu Tanaka
Itaru Matsumura
Department of Hematology and Rheumatology, Faculty of Medicine, Kindai University, Osakasayama, Japan

Nobuhiko Uoshima
Department of Hematology, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan

Kensuke Ohta
Hematology Ohta Clinic, Osaka, Japan

Hideo Yagi
Department of Hematology and Oncology, Nara Prefecture General Medical Center, Nara, Japan

Hirohiko Shibayama
Department of Hematology, National Hospital Organization Osaka National Hospital, Osaka, Japan

Yoshiyuki Onda
Department of Hematology, Japanese Red Cross Takatsuki Hospital, Takatsuki, Japan

Yasuhiro Tanaka
Department of Hematology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan

Yoko Adachi
Department of Internal Medicine, Japan Community Health care Organization Kobe Central Hospital, Kobe, Japan

relapsed/refractory and treatment-naïve transplantation-ineligible MM patients when used in combination with iMIDs or PIs.[2–4] Regimens containing daratumumab were found to be among the most effective used in relapsed/refractory MM in two network meta-analyses.[5,6] However, although more than 90% of MM patients responded to daratumumab treatment in clinical trials,[2,3] a discrepancy in the response rate of daratumumab treatment between the clinical trials and real-world data has been reported, especially for relapsed/refractory cases.[7,8] Moreover, a substantial number of patients either did not obtain a therapeutic response with daratumumab, or obtained a therapeutic response but could not sustain it. Unfortunately, we do not have appropriate biomarkers to predict the response or the durable efficacy of daratumumab before administration.

To identify, prior to treatment, patients with a potentially durable response to daratumumab, we focused on the immunological aspect of daratumumab. The mechanisms of action of daratumumab are immune-mediated effects, such as complement- or antibody-dependent cell-mediated cytotoxic effects and depletion of CD38-positive regulatory immune cells.[9–16] Among the immune cells, natural killer (NK) cells and monocytes play important roles particularly in daratumumab-mediated myeloma cells killing.[13–16] Here, we hypothesized that the balance between the tumor burden of myeloma and immune conditions [represented by white blood cell (WBC) counts and other leukocyte counts] might predict the efficacy of daratumumab treatment. As a proof of concept, we conducted a retrospective observational analysis using real-world data from the Kansai Myeloma Forum (KMF) database in Japan.

Methods

Study design and participants

KMF is a study group consisting of 123 physicians at 46 facilities in Japan. The KMF database includes physician-reviewed, real-world clinical data on the diagnosis, treatment, and periodical follow-up of patients with plasma cell dyscrasias. This study was approved by the Data Management Committee of the Kyoto University Graduate School of Medicine Institutional Review Board (approval no. R2887).

In the KMF database, 4133 patients with plasma cell dyscrasias were registered in March 2021. All the patients were diagnosed as having MM or MM-related disorders based on institutional assessment. From the KMF database, we selected patients older than 20 years who were treated for symptomatic MM with active-disease status in relapse setting between November 2017 to March 2021 using a regimen including daratumumab, after its approval for clinical use. A total of 388 patients met the above inclusion criteria for this study (Supplement Figure 1). We conducted secondary research to collect the laboratory data 1 to 7 days before cycle 1 day 1 daratumumab treatment. Sixty-four patients were omitted due to a lack of data, leaving 324 relapsed MM patients whose data were included in the final analysis. These relapsed/refractory MM patients were followed until August 2021.

The serum free light chain κ/λ ratio was measured by latex coagulating nephelometry. The patients' responses to treatment were assessed based on the criteria of the international uniform response criteria[17] for MM. The patients' best responses against daratumumab were classified by institutional physicians into five categories: complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD).

For the high-risk cytogenetic abnormalities, we adopted the abnormalities reported in the International Myeloma Working group consensus statement,[18] such as deletion 17p, $t(4;14)$, and $t(14;16)$. Unfavorable cytogenetic abnormalities were categorized by a fluorescence *in situ* hybridization (FISH) analysis.

Statistical methods

We calculated the time to next treatment (TTNT) for first daratumumab treatment as the time from daratumumab treatment until the date of next treatment, death by any cause, or the date of last contact. We chose the TTNT as the primary endpoint instead of progression-free survival (PFS) for our retrospective analysis,[19,20] since the timing of PD was difficult to precisely determine in our cohort. The data were censored for the date of next treatment in cases where the cessation of daratumumab was planned in advance. To analyze the underlying factors affecting the TTNT

under daratumumab treatment, we first analyzed the TTNT in relation to the treatment regimen [daratumumab, lenalidomide, and dexamethasone (DLd) or daratumumab, bortezomib, and dexamethasone (DBd)]. Then, we analyzed the data regarding the parameters used to estimate the tumor burden of myeloma,[21–23] that is, the κ/λ ratio and β_2 microglobulin (B2MG), and the parameters which, based on the mechanism of action of daratumumab, appear to be correlated with the host immune status, that is, the WBC count and other leukocyte fractions. The κ/λ ratio and B2MG are recognized to reflect tumor burden.[21–23] We selected the leukocyte fractions (neutrophil, lymphocyte, or monocyte counts) that showed significant correlation with TTNT in the univariate analysis, and applied them to the following analysis.

To determine the cutoff values for the WBC counts, neutrophil counts, lymphocyte counts, monocyte counts, and κ/λ ratio, we first tested the 25th, 50th, and 75th percentile values as potential cut-off values (Supplement Figures 2–6). We determined the cut-off value of monocytes as 200/μl and that of the κ/λ ratio as 0.1/10 according to the difference from the reference arm [Supplement Figure 3(A) and (B)]. We used the median value as a cutoff value for WBCs, neutrophils, and lymphocyte counts (Supplement Figures 4 and 5(A)–(D). The cutoff value of B2MG was determined according to the International Staging system[21] for MM (Supplement Figure 6).

The survival curve according to TTNT and the overall survival (OS) curve were plotted using the Kaplan–Meier method, and the log-rank test was used for comparisons among groups. The Cox proportional hazard model was used to calculate the hazard ratio for each variable along with the 95% confidence interval (CI). Variables considered in the univariate analysis were age, gender, high-risk cytogenic abnormalities, WBC counts, neutrophil counts, lymphocyte counts, monocyte counts, κ/λ ratio, B2MG, number of daratumumab treatments, prior regimen number, and prior use of elotuzumab. A multivariate analysis was conducted for the variables which showed a p value of less than 0.1 in the univariate analysis. To establish a predictive model for the durability treatment of DLd, we first included all the factors which showed $p < 0.1$ in univariate analysis. Because we found a correlation among three factors related to immune tatus enhancement – namely, monocyte counts, lymphocyte counts, and WBC counts – we divided the cases into three different multivariate analyses, respectively, using one of these three factors. We also adjusted the survival curves by the significant factors in the multivariate analysis. We used the bootstrap method to validate the results of our multivariate analysis.[24,25] In each step, 1000 bootstrap samples with replacements were created from the dataset. We used C statistics (C-index) to evaluate the predictive accuracy of prediction models.[26,27] C-index is calculated by the area under the receiver operating characteristic (ROC) curve. The c-index of an ideal test became closer to 1.0. All statistical analyses were performed using the EZR (ver. 1.54) software package (Saitama Medical Center/Jichi Medical University, Saitama, Japan)[28] along with a graphical user interface for the R software package (version 4.0.3; The R Foundation for Statistical Computing) or SPSS software version 28 (IBM, USA). P values <0.05 were considered significant in all analyses.

Results

TTNT of daratumumab in relapsed MM

The characteristics of the patients undergoing each regimen are summarized in Table 1. In brief, a total of 324 patients incorporating daratumumab were analyzed. The median age at the time of daratumumab treatment was 68 years old. The numbers of patients treated with the DLd and DBd regimens were 196 (60.5%) and 128 (39.5%), respectively. The median number of prior regimens was 4. In most cases, both iMIDs and PIs were used before daratumumab treatment. Elotuzumab was used before daratumumab treatment in 35 cases (17.9%) treated with a DLd regimen and 9 cases (7.0%) treated with a DBd regimen. Autologous stem cell transplantations (auto-SCT) were performed prior to daratumumab treatment in 61 cases (31.1%) treated with a DLd regimen and 31 cases (24.2%) treated with a DBd regimen. The histogram of laboratory data is shown in Supplemental Figure S1. Patients with a CR, VGPR, or PR were regarded as having a therapeutic response to daratumumab; these included 130 patients (66.3%) treated with the DLd regimen and 79 cases (61.7%) treated with the DBd regimen (Supplement Figure 7).

The median TTNT under daratumumab treatment was 8.02 (95% CI: 6.48–9.20) months in this cohort [Figure 1(a)]. When we compared the

Mitsuhiro Matsuda
Department of Hematology, PL General Hospital, Osaka, Japan

Masato Iida
Department of Internal Medicine, Kawasaki Hospital, Kaizuka, Japan

Takashi Miyoshi
Department of Hematology, Uji Tokushukai Hospital, Uji, Japan

Toshimitsu Matsui
Department of Hematology, Nishiwaki Municipal Hospital, Nishiwaki, Japan

Ryoichi Takahashi
Department of Hematology, Omihachiman Community Medical Center, Omihachiman, Japan

Teruhito Takakuwa
Masayuki Hino
Department of Hematology, Graduate School of Medicine, Osaka City University, Suita, Japan

Table 1. Characteristics of the patients with multiple myeloma.

Number of patients		**DLd regimen**	**DBd regimen**
		196	128
Median age (years) at daratumumab treatment	Median (range)	71 (44–89)	70 (39–92)
Gender	Male	92 (46.9%)	70 (54.7%)
	Female	104 (53.1%)	58 (45.3%)
Type of heavy chain	IgG	118 (60.2%)	63 (49.2%)
	IgA	36 (18.4%)	33 (16.8%)
	IgM	3 (1.5%)	2 (1.6%)
	IgD	1 (0.5%)	1 (0.8%)
	Not detected	38 (19.4%)	29 (22.7%)
Type of light chain	λ	110 (56.1%)	80 (62.5%)
	κ	82 (41.8%)	48 (37.5%)
	NA	4 (2.0%)	0 (0%)
ISS stage at diagnosis	I	70 (35.7%)	39 (30.5%)
	II	69 (35.2%)	53 (41.4%)
	III	57 (29.1%)	36 (28.1%)
High risk cytogenic abnormalities	del (17)	21 (10.7%)	5 (3.9%)
	t(4;14)	30 (15.3%)	23 (18.0%)
	t(14;16)	5 (2.6%)	1 (0.6%)
	None of the above abnormalities	81 (41.3%)	54 (42.2%)
	NA	70 (35.7%)	45 (35.2%)
Laboratory data before daratumumab treatment			
White blood cell counts (/μl, median, range)		3650 (500–24,200)	3980 (1290–17,000)
Neutrophil counts (/μl, median, range)		2146 (68–21,538)	2304 (364–14,444)
Lymphocyte counts (/μl, median, range)		924 (106–3929)	962 (144–4880)
Monocyte counts (/μl, median, range)		300 (8–1694)	334 (3–1530)
Free light chain (mg/L, median, range)	κ	24.9 (0.3–9090)	44.9 (0.4–11,566)
	λ	14.70 (0.3–15,400)	12.70 (0.5–17,370)
	κ/λ ratio	1.69 (0–8260)	4.78 (0–11,566)

(Continued)

Table 1. (Continued)

Number of patients		DLd regimen	DBd regimen
B2MG (mg/L, median, range)		3.50 (0.35–121.9)	3.3.6 (0.34–37.8)
IgG (mg/dL, median, range)		1154 (15–11793)	732 (72–7379)
IgA (mg/dL, median, range)		30.5 (3–2205)	53 (3–6566)
IgM (mg/dL, median, range)		14 (5–89)	16 (3–3537)
Prior regimen numbers	Median (range)	4 (1–22)	3 (1–14)
Prior treatments	IMIDs	166 (84.7%)	98 (77.2%)
	PI	181 (92.3%)	112 (87.5%)
	Elotuzumab	35 (17.9%)	9 (7.0%)
Auto-SCT		61 (31.1%)	31 (24.2%)
Follow-up period of survivors (median days, range)		509 (2–1142)	515 (2–1228)

Auto-SCT, autologous stem cell transplantation; B2MG, β_2 microglobulin; DBd, dexamethasone; DLd, dexamethasone; IMIDs, immunomodulatory drugs; ISS, international staging system; NA, not available; PI, proteosome inhibitor.
The characteristics of multiple myeloma patients who were treated with a daratumumab, lenalidomide, and DLd regimen or daratumumab, bortezomib, and DBd regimen are shown in Table 1. Laboratory data were collected before the daratumumab treatment.

TTNTs by regimen, the TTNTs under the DLd and DBd regimens were 9.20 (7.85–11.93) and 5.98 (4.30–7.13) months, respectively [Figure 1(b); $p = 0.001$]. Because the mechanism of action differed between the DLd and DBd regimens, we performed the following analysis according to the type of regimen.

The underlying factors affecting the TTNT under daratumumab treatment

When we analyzed the impact of tumor burden, B2MG and the κ/λ ratio against TTNT in patients undergoing the DLd regimen, the TTNT under daratumumab treatment was longer in the patients with a lower B2MG (<5.5 mg/L)

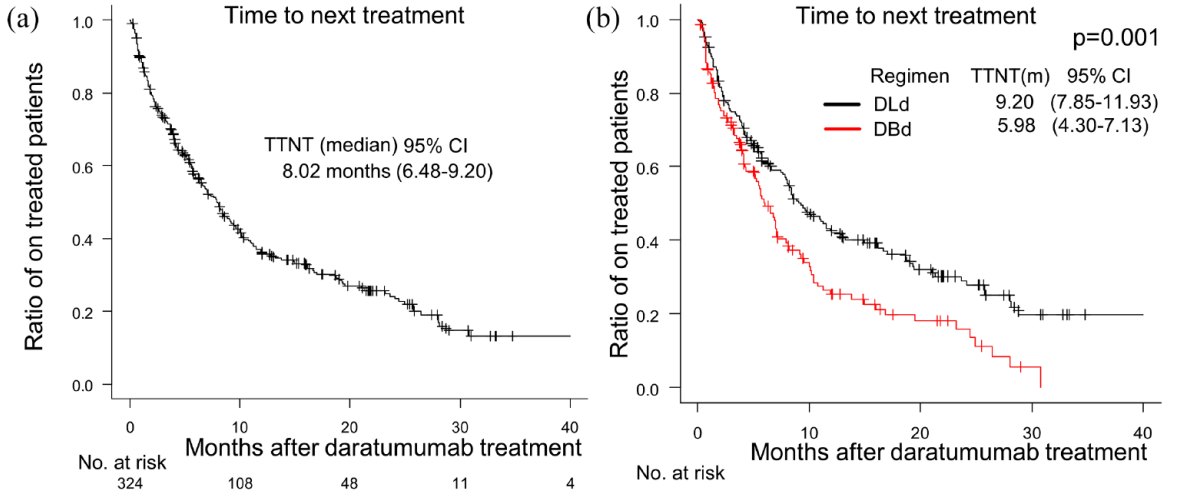


Figure 1. *(Continued)*

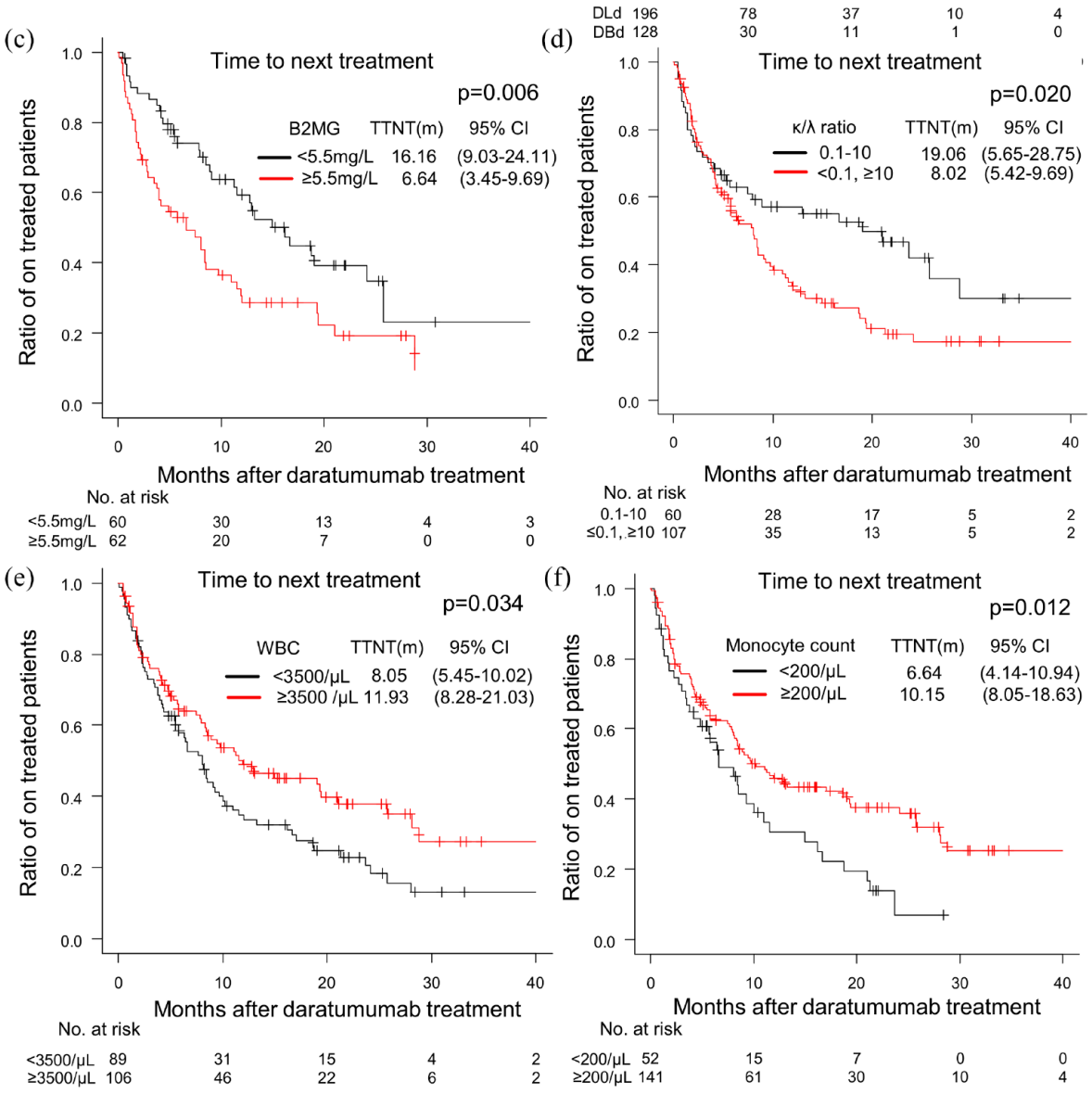


Figure 1. (a) The time-to-next treatment (TTNT) of the multiple myeloma (MM) patients treated with daratumumab. Median TTNT (months) values with the 95% CI (confidence interval) are shown. (b) The TTNT of the multiple myeloma (MM) patients according to the treatment regimen: daratumumab, lenalidomide, and dexamethasone (DLd, black) or daratumumab, bortezomib, and dexamethasone (DBd, red). Median TTNT (months) values with the 95% CI are shown. (c) The TTNT of the MM patients treated with the DLd regimen according to the β_2 microglobulin (B2MG) level: less than 5.5 mg/L (black) or 5.5 mg/L or more (red). Median TTNT (months) values with the 95% CI are shown. (d) The TTNT of the MM patients treated with the DLd regimen according to the κ/λ ratio: 0.1–10 (*black*) and less than 0.1 or 10 or more (red). Median TTNT (months) values with the 95% CI are shown. (e) The TTNT of the MM patients treated with the DLd regimen according to the white blood cell (WBC) counts: less than 3500/μl (black) and 3500/μl or more (red). The median TTNT (months) values with the 95% CI are shown. (f) The TTNT of the MM patients treated with the DLd regimen according to the monocyte counts: less than 200/μl (black) and 200/μl or more (red). The median TTNT (months) values with the 95% CI are shown. The number of patients at risk in each group is shown in the lower panel of each figure.

[$p = 0.006$; Figure 1(c), Table 2] or a non-deviated κ/λ ratio (κ/λ ratio of 0.1–10) [$p = 0.020$; Figure 1(d), Table 2]. We next analyzed TTNT according to the immune status, WBC counts and other leukocyte fractions. The patients with higher WBC counts (≥3500/μl) before daratumumab treatment showed longer TTNT than those with lower WBC counts [$p = 0.034$; Figure 1(e) and Table 2]. The patients with higher monocyte counts (≥200/μl) also showed longer TTNT [$p = 0.012$, Figure 1(f), Table 2]. Higher lymphocyte counts (≥1000/μl) were associated with slightly longer TTNT, but the neutrophil counts were not correlated with TTNT [Table 2 and Supplement Figure 5(B) and (D)]. Other factors which showed better TTNT in the univariate analysis in patients undergoing the DLd regimen were a prior regimen number < 4 and no prior use of elotuzumab [Table 2, Supplement Figure 8(A)–(D)]. In the analysis of TTNT under the DBd regimen, we could not find any factors which correlated to TTNT (Table 2).

Prediction model for daratumumab treatment

We performed a multivariate analysis regarding the TTNT in patients undergoing the DLd regimen by analyzing all the factors that showed *p* values of less than 0.1 in the univariate analysis. Because the lymphocyte counts and WBC counts were correlated, and the monocyte counts and WBC counts were also correlated [Supplement Figure 9(A)–(B)], we used either monocyte counts (analysis 1), WBC counts (analysis 2) or lymphocyte counts (analysis 3) for the multivariate analysis. In analysis 1, we found that higher monocyte counts (≥200/μl, $p = 0.009$), lower B2MG (<5.5 mg/L, $p = 0.011$), and prior regimen number <4 ($p = 0.005$) were each independently associated with superior TTNT under the DLd regimen. In analysis 2, higher WBC counts (≥3500/μl, $p = 0.048$), lower B2MG (<5.5 mg/L, $p = 0.010$) and prior regimen number <4 ($p = 0.018$) were associated with superior TTNT under the DLd regimen (Table 3). In analysis 3, lower B2MG (<5.5 mg/L, $p = 0.019$) and prior regimen numbers <4 ($p = 0.012$) were associated with superior TTNT under the DLd regimen. All these multivariate analysis results were confirmed by bootstrap methods (Table 3).

From these results, we proposed two new models to predict a durable effect (longer TTNT) under the DLd regimen by classifying the patients into three categories based on either (1) monocyte counts and B2MG (model 1) or (2) WBC counts and B2MG (model 2). We assigned 0 points to patients with monocyte counts of 200/μl or more, and 1 point to those with less than 200/μl. We also assigned 0 points to patients with a B2MG less than 5.5 mg/L and 1 point to those with a B2MG of 5.5 mg/L or more. Patients with a total score of 0 showed significantly longer TTNT compared to those with scores of 1 or 2 [$p = 0.001$, Figure 2(a)]. The c-index for this model was 0.675. We confirmed that this scoring system was significantly correlated with the TTNT under DLd treatment in multivariate analysis with bootstrap methods (Table 4). This model showed the same tendency regardless of the prior regimen numbers [Supplement Figure 10(A)–(B)]. When we analyzed the OS after the DLd treatment, we found that the patients with a total score of 0 showed significantly longer OS than the patients with total scores of 1 or 2 [$p < 0.001$, Figure 2(b)].

In model 2, we assigned 0 points to the patients with WBC counts of 3500/μl or more and 1 point to those with WBC counts of 3500/μl. We also scored the patients by B2MG in the same manner as in model 1. The patients with total scores of 0 or 1 showed significantly longer TTNT compared to those with a score of 2 [$p < 0.001$, Figure 2(c)]. The c-index for this model was 0.688. We confirmed that this scoring system was significantly correlated with the TTNT under DLd treatment in multivariate analysis with bootstrap methods (Table 4). This model showed the same tendency regardless of the number of prior regimens [Supplement Figure 11(A) and (B)]. When we analyzed the OS after the DLd treatment, we found that the patients with a total score of 0 showed significantly longer OS than the patients with total scores of 1 or 2 [$p < 0.001$, Figure 2(d)].

We conclude that by using this simple model, we could predict the patients who could obtain a durable response (longer TTNT) by the DLd regimen (Supplement Figure 12).

Discussion

It has been proposed that the therapeutic effects of novel anti-MM agents involve not only their

Table 2. Univariate analysis for TTNT.

Factors		DLd regimen			DBd regimen		
		TTNT (month)	95% CI	*p* value	TTNT (month)	95% CI	*p* value
Age at daratumumab treatment	<65 years	9.42	6.28–23.66	0.331	5.98	2.30–11.89	0.345
	⩾65 years	8.51	6.60–12.02		5.95	4.11–7.13	
Gender	Male	9.69	8.05–16.69	0.898	6.77	4.30–9.49	0.259
	Female	8.41	6.28–12.91		5.22	3.45–7.03	
High-risk cytogenic abnormalities	None	11.24	7.62–26.16	0.119	5.52	4.11–10.35	0.977
	At least one	8.51	4.24–17.05		6.51	5.65–9.13	
White blood cell counts	<3500/μl	8.05	5.45–10.02	0.034	5.49	3.68–7.13	0.546
	⩾3500/μl	11.93	8.27–21.03		6.87	4.21–9.20	
Neutrophil counts	<2000/μl	8.41	6.28–11.24	0.317	5.65	3.94–9.99	0.774
	⩾2000/μl	9.69	7.43–19.06		6.77	4.21–9.13	
Lymphocyte counts	<1000/μl	8.41	5.65–10.94	0.069	6.51	4.04–9.20	0.888
	⩾1000/μl	11.5	7.89–25.72		5.95	4.11–7.13	
Monocyte counts	<200/μl	6.64	4.14–10.94	0.012	6.51	3.91–10.35	0.769
	⩾200/μl	10.15	8.05–18.63		5.98	4.21–8.11	
κ/λ ratio	0.1-10	19.06	5.65–28.75	0.020	6.87	4.11–14.92	0.591
	⩽0.1, ⩾10	8.02	5.42–9.69		5.98	4.04–8.21	
B2MG	<5.5mg/L	16.16	9.03–24.11	0.006	7.03	4.11–9.20	0.567
	⩾5.5mg/L	6.64	3.45–9.69		4.3	1.22–10.12	
Prior regimen numbers	<4	19.06	14.98–NA	<0.001	7.03	3.91–9.20	0.798
	⩾4	7.85	5.45–8.90		5.65	4.11–7.00	
Prior use of elotuzumab	No	10.02	8.02–16.13	0.050	5.98	4.30–7.95	0.881
	Yes	6.44	3.98–10.15		5.65	0.13–NA	
Auto-SCT prior to daratumumab	No	8.41	5.65–11.04	0.061	6.47	4.21–7.95	0.726
	Yes	11.93	8.28–24.11		5.78	3.09–11.24	

Auto-SCT, autologous stem cell transplantation; B2MG, β_2 microglobulin; CI, confidence interval; NA, not available; TTNT, time to next treatment. TNT was calculated from the time of each daratumumab treatment to the time of the next treatment. Univariate analyses against TTNT in MM patients treated with the DLd regimen or DBd regimen were performed for each factor. The log-rank test was used for comparisons among groups. TTNT (months) is shown with the 95% confidence interval (CI) and *p* value.

Table 3. Multivariate analysis for TTNT.

Factors		Analysis 1				Analysis 2				Analysis 3			
		Hazard ratio	95% CI	*p* value	*p* value*	Hazard ratio	95% CI	*p* value	*p* value*	Hazard ratio	95% CI	*p* value	*p* value*
Monocyte counts	<200/μl	1		0.009	0.039								
	⩾200/μl	0.514	0.312–0.849										
White blood cell counts	<3500/μl					1		0.002	<0.001				
	⩾3500/μl					0.446	0.271–0.735						
Lymphocyte counts	<1000/μl									1		0.006	0.152
	⩾1000/μl									0.633	0.390–1.028		
κ/λ ratio	0.1–10	1		0.212	0.171	1		0.489	0.316	1		0.181	0.169
	⩽0.1, ⩾10	1.395	0.827–2.351			1.210	0.704–2.080			1.439	0.845–2.452		
B2MG	<5.5 mg/L	1		0.015	0.047	1		0.01	0.009	1		0.020	0.033
	⩾5.5 mg/L	1.800	1.121–2.892			2.282	1.375–3.789			1.746	1.088–2.801		
Number of prior regimens	<4	1		0.005	0.006	1		0.018	0.014	1		0.009	0.016
	⩾4	2.190	1.272–3.771			1.930	1.122–3.320			2.059	1.200–3.532		
Prior use of elotuzumab	No	1		0.270	0.439	1		0.451	0.343	1		0.237	0.340
	Yes	1.421	0.761–2.655			1.259	0.692–2.292			1.452	0.783–2.691		
Auto-SCT prior to daratumumab	No	1		0.653	0.243	1	0.093		0.105	1		0.120	0.195
Auto-SCT prior to daratumumab	Yes	0.653	0.368–1.159			0.613	0.347–1.084			0.640	0.364–1.124		

Auto-SCT, autologous stem cell transplantation; B2MG, β_2 microglobulin; CI, confidence interval; TTNT, time to next treatment.
Multivariate analyses against TTNT in MM patients treated with the DLd regimen were performed using the factors which showed $p < 0.1$ in univariate analysis. Because monocyte counts, lymphocyte counts and WBC counts were correlated, we adopted these factors as indexes of immune status as follows: monocyte counts in analysis 1, WBC counts in analysis 2 and lymphocyte counts in analysis 3. The Cox proportional hazard model was used to calculate the hazard ratio for each variable; the 95% CI and *p* value are shown.
**P* value indicates the *p* value after the bootstrapping process (1000 samples).

Table 4. Multivariate analysis for TTNT.

Factors		Model 1				Model 2			
		Hazard ratio	95% CI	*p* value	*p* value*	Hazard ratio	95% CI	*p* value	*p* value*
Monocyte B2MG score	0	1		0.003	0.009				
	1	2.093	1.196–3.661						
	2	3.391	1.613–7.127						
WBC B2MG score	0					1		<0.001	0.002
	1					1.200	0.656–2.196		
	2					4.727	2.297–9.724		
κ/λ ratio	0.1–10	1		0.320	0.252	1		0.517	0.501
	⩽0.1, ⩾10	1.313	0.768–2.244			1.195	0.697–2.052		
Prior regimen numbers	⩽4	1		0.004	0.013	1		0.027	0.012
	>4	2.189	1.276–3.755			1.853	1.074–3.196		
Prior use of elotuzumab	No	1		0.290	0.321	1		0.547	0.481
	Yes	1.398	0.751–2.602			1.202	0.661–2.185		
Auto-SCT prior to daratumumab	No	1		0.155	0.206	1		0.182	0.136
Auto-SCT prior to daratumumab	Yes	0.666	0.380–1.166			0.692	0.403–1.188		

Auto-SCT, autologous stem cell transplantation; B2MG, β_2 microglobulin; CI, confidence interval; TTNT, time to next treatment; WBC, white blood cell. Multivariate analyses against TTNT in MM patients treated with the DLd regimen were performed using the scoring system (model 1 and model 2) as factors. In model 1, we picked up the following factors: monocyte B2MG score, κ/λ ratio, number of prior regimens and prior use of elotuzumab. In model 2, we picked up the following factors: WBC B2MG score, κ/λ ratio, number of prior regimens and prior use of elotuzumab. The Cox proportional hazard model was used to calculate the hazard ratio for each variable; the 95% CI and *p* value are shown.
**P* value indicates the *p* value after the bootstrapping process (1000 samples).

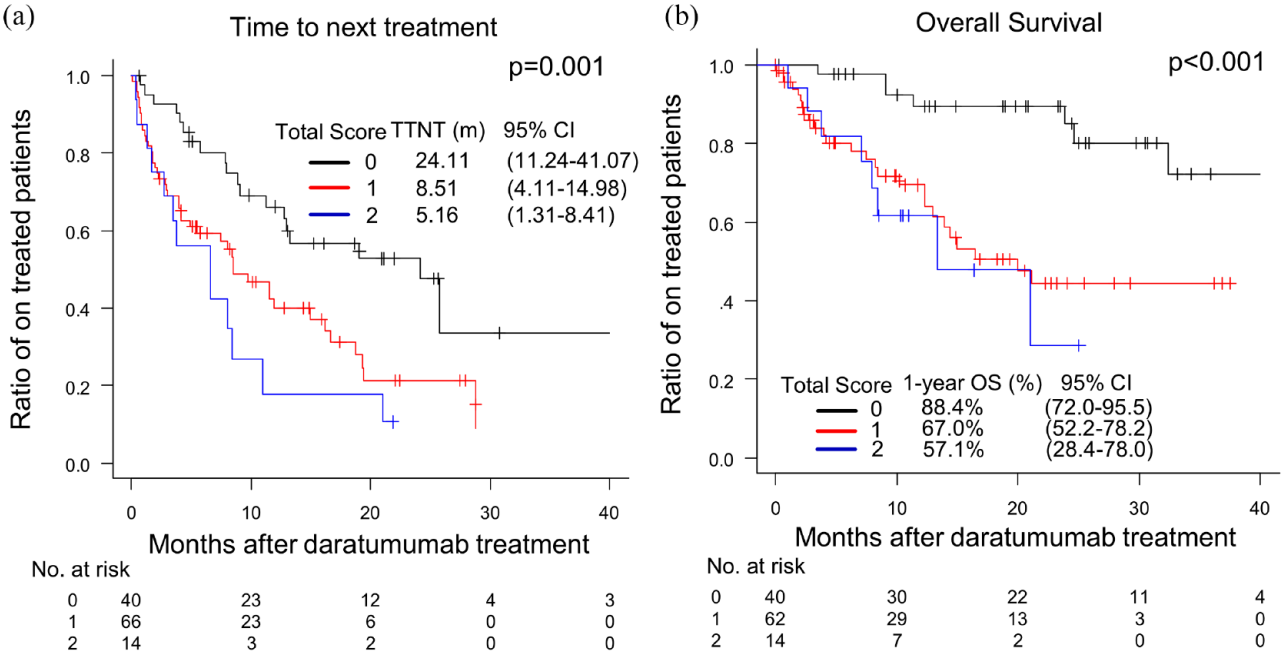
cytotoxicity against myeloma cells but also their immunomodulatory effects.[29] However, there is a lack of useful biomarkers related to immune status to predict the clinical response before treatment.[30] Recently, several studies have indicated that monocytes might predict the prognosis of MM patients[31–33] and also that monocytes are involved in daratumumab-mediated killing of myeloma cells.[13–16] We hypothesized that the efficacy of daratumumab could be predicted not only by the tumor burden of myeloma cells but also by the host immune status. As a proof of concept, we chose the κ/λ ratio and B2MG as candidate biomarkers representing the tumor burden. We also selected WBC and several subtypes of WBC which might reflect the host immune status. This study demonstrated that a simple model using B2MG plus either monocyte counts or WBC counts could easily predict the durable efficacy of the DLd regimen in relapsed/refractory MM patients. Patients with a total score of 0—namely, those with a low tumor burden (B2MG < 5.5 mg/L) and preserved host immune cells (monocyte counts ⩾ 200/μl or WBC counts ⩾ 3500/μl)—were determined to be those who could obtain the most benefit from a DLd regimen. In future

studies, we plan to use model 1 rather than model 2, because using the monocyte count is a more specific parameter than the WBC count.

Because previous reports have shown that the neutrophil-to-lymphocyte ratio or lymphocyte-to-monocyte ratio is correlated with the prognosis of MM,[33,34] we also analyzed neutrophil counts, lymphocyte counts, the neutrophil/lymphocyte ratio, and the monocyte/lymphocyte ratio as possible predictors of host immunity. However, these parameters were not significantly correlated with the TTNT under daratumumab treatment. Our study suggests that among leukocyte fractions, monocytes play the most important role in the DLd regimen, and this result was in keeping with previous reports.[16,31,32]

Another factor that was associated with a significantly longer TTNT under the DLd regimen in multivariate analysis was a lower number of prior regimens (<4 prior regimens). Because the use of daratumumab in prior regimens has been associated with better prognosis in a clinical study,[2] it is not surprising that the TTNT under the DLd regimen would be shorter in heavily treated patients with treatment-resistant MM. We demonstrated that patients with fewer than 4 prior treatment regimens showed significantly longer TTNT under the DLd regimen, but this difference was not observed in the patients treated with the DBd regimen. Because the median TTNT under the DBd regimen was shorter compared to that in clinical studies,[35,36] more treatment-resistant MM patients might have been included in our cohort treated with the DBd regimen.

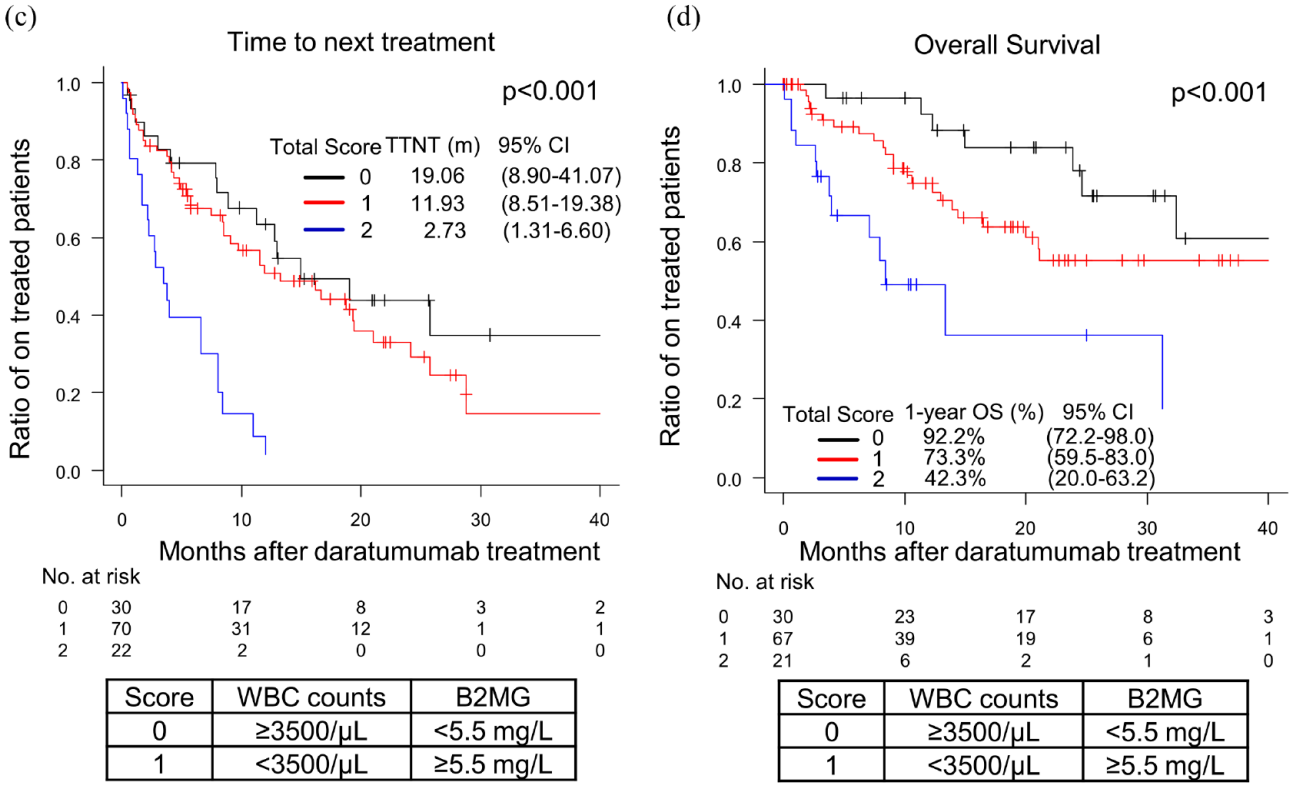
These findings notwithstanding, we must underscore that daratumumab treatment remains a high-priority treatment option for all MM patients due to its high response rate,[2–4] even for the relapsed/refractory MM patients with high tumor burden and suppressive immune status. However, our prediction model provides two important lessons. First, it is important to realize that the efficacy of daratumumab might not be sustained for patients with a high tumor burden and suppressive immune status. Second, it might be necessary for us to prepare for the next treatment after the DLd regimen in these patients.



Score	Monocyte counts	B2MG
0	≥200/μL	<5.5 mg/L
1	<200/μL	≥5.5 mg/L

Score	Monocyte counts	B2MG
0	≥200/μL	<5.5 mg/L
1	<200/μL	≥5.5 mg/L

Figure 2. *(Continued)*



Score	WBC counts	B2MG
0	≥3500/μL	<5.5 mg/L
1	<3500/μL	≥5.5 mg/L

Score	WBC counts	B2MG
0	≥3500/μL	<5.5 mg/L
1	<3500/μL	≥5.5 mg/L

Figure 2. (a) The TTNT of the MM patients treated with the DLd regimen according to the proposed scoring system: 0 points (black), 1 point (red), and 2 points (blue). Total scores were calculated according to the monocyte counts (0 points when ⩾200/μl and 1 point when <200/μl) and B2MG (0 points when <5.5 mg/L and 1 point when ⩾5.5 mg/L) before daratumumab treatment. The median TTNT (months) values with the 95% CI are shown in the figure. The TTNT values were corrected by the number of prior treatment regimens. (b) The overall survival (OS) of the MM patients treated with the DLd regimen according to the proposed scoring system: 0 points (black), 1 point (red), and 2 points (blue). The 1-year OS values of each group with the 95% CI are shown in the figure. The OS values are corrected by the number of prior treatment regimens. (c) The TTNT of the MM patients treated with the DLd regimen according to the proposed scoring system: 0 points (black), 1 point (red), and 2 points (blue). Total scores are calculated according to the WBC counts (0 points when ⩾3500/μl and 1 point when <3500/μl) and B2MG (0 points when <5.5 mg/L and 1 point when ⩾5.5 mg/L) before daratumumab treatment. Median TTNT (months) values with the 95% CI are shown in the figure. The TTNT values are corrected by the number of prior treatment regimens. (d) The overall survival (OS) of the MM patients treated with the DLd regimen according to the proposed scoring system: 0 points (black), 1 point (red), and 2 points (blue). The 1-year OS values of each group with the 95% CI are shown in the figure. The OS values are corrected by the number of prior treatment regimens. The number of patients at risk in each group are shown in the lower panel of each figure.

In our model 1, the TTNT of the patients with a total score of 0 was significantly longer than the TTNT of the patients with total scores of 1 or 2. In model 2, the TTNT of patients with a total score of 0 or 1 was significantly longer than the TTNT of those with a total score of 2. On the contrary, the OS after the DLd treatment was significantly superior in patients with a total score of 0 compared to the OS of the patients with a total score of 1 or 2 in both models. These results could be interpreted as follows. Because there are seldom better treatment options than daratumumab, once patients relapse or become refractory to daratumumab treatment, their prognosis can be quite poor. However, because this study was observational by design, we could not tell whether the prognosis would be changed by choosing another treatment, such as carfilzomib treatment, to debulk the tumor before starting DLd treatment. This might be one of the treatment options, but it needs to be confirmed in a future study. Our results also suggest that the DLd regimen might not be suitable for patients with a score of 2, not only because the TTNT

would likely be shorter, but also because the OS after DLd treatment would likely be poor.

Our predicting model works only for the DLd regimen, and this model could not be applied to the patients treated with the DBd regimen. This discrepancy might partly be explained by the different mechanisms of the DLd and DBd regimens. It has been reported that the DLd regimen works through the synergistic actions of its constituent agents, while the DBd regimen works through additive actions.[37] From an immunological point of view, this could be interpreted as meaning that the mechanism of the DLd regimen is more reliant on immune cells, particularly monocytes, compared to the DBd regimen. For this reason, our predictive model using monocyte counts (or WBC counts) as an index of immune status would be most suitable for patients treated with the DLd regimen. We could say that our model is not a prognostic model which fits all MM patients, but rather a predictive model for selecting the DLd regimen for relapsed/refractory MM patients. Our predictive model might also be applied to other regimens, such as a daratumumab, pomalidomide, and dexamethasone regimen, or an isatuximab, pomalidomide, and dexamethasone regimen, both of which preferentially rely on immune cells in the manner of the DLd regimen. We would like to address this issue in a future study.

This study also showed that the effectiveness of daratumumab was attenuated by the prior use of elotuzumab or daratumumab treatment. It has been reported that the expression of CD38 was downregulated and the number of immune cells such as NK cells and monocytes was decreased after daratumumab treatment.[13–16,38,39] Because the elimination of myeloma cells by daratumumab depends on a complement- or antibody-dependent cell-mediated cytotoxic effect[9–12] and NK cells and monocytes are the key player in DLd regimen,[13–16] the prior administration of antibody attenuates the effectiveness of daratumumab. Higher monocyte counts, or higher WBC counts may be a prerequisite along with a higher number of immune cells; this should also be confirmed in future studies.

There were several limitations in this study. First, this was a retrospective observational study in which the choice of treatment was made by the individual physicians. Thus, there may have been some bias for selecting daratumumab treatment that we could not include in the multivariate analysis. We will need to substantiate our results by means of analysis in other cohorts. Second, because the data regarding high-risk cytogenetic abnormalities were limited, we might not have sufficiently assessed the impact of high-risk cytogenic abnormalities. Third, we could not distinguish from the database whether patients were refractory to lenalidomide or bortezomib before daratumumab treatment, which could have affected the response to DLd or DBd treatment.

Despite these limitations, to the best of our knowledge, this is the first study to show that the efficacy of the DLd regimen can be predicted by the balance between tumor burden and host immune status.

In conclusion, we proposed a new scoring system using the combination of B2MG plus either monocyte counts or WBC counts to predict the TTNT in patients under the DLd regimen. These scoring systems would be useful for choosing patients who could obtain a benefit from DLd treatment.

Declarations

Ethical approval and consent to participate

All procedures performed in this study involving the patient were in accordance with the ethical standards of Kyoto University Graduate School and Faculty of Medicine, Ethics Committee institutional (approval no. R2887, approved date: 6 January 2022) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The informed consent requirement for this retrospective study was waived because the study was conducted retrospectively and the opportunity to refuse was guaranteed.

Consent for publication

Not applicable.

Author contributions

Yutaka Shimazu: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – original draft.

Junya Kanda: Conceptualization; Data curation; Formal analysis; Investigation; Project administration; Supervision; Writing – review & editing.

Hitomi Kaneko: Data curation; Investigation.

Kazunori Imada: Project administration; Supervision.

Ryosuke Yamamura: Data curation; Investigation.

Satoru Kosugi: Data curation; Investigation.

Yuji Shimura: Data curation; Investigation; Writing – review & editing.

Tomoki Ito: Data curation; Investigation; Supervision.

Shin-ichi Fuchida: Data curation; Investigation.

Hitoji Uchiyama: Data curation; Investigation.

Kentaro Fukushima: Data curation; Investigation.

Satoshi Yoshihara: Data curation; Investigation.

Hitoshi Hanamoto: Data curation; Investigation.

Hirokazu Tanaka: Data curation; Investigation.

Nobuhiko Uoshima: Project administration; Supervision.

Kensuke Ohta: Data curation; Investigation.

Hideo Yagi: Data curation; Investigation.

Hirohiko Shibayama: Project administration; Supervision; Writing – review & editing.

Yoshiyuki Onda: Data curation; Investigation.

Yasuhiro Tanaka: Data curation; Investigation.

Yoko Adachi: Data curation; Investigation.

Mitsuhiro Matsuda: Data curation; Investigation.

Masato Iida: Data curation; Investigation.

Takashi Miyoshi: Project administration; Supervision.

Toshimitsu Matsui: Data curation; Investigation.

Ryoichi Takahashi: Data curation; Investigation.

Teruhito Takakuwa: Data curation; Investigation.

Masayuki Hino: Project administration; Supervision.

Naoki Hosen: Project administration; Supervision.

Shosaku Nomura: Project administration; Supervision.

Chihiro Shimazaki: Project administration; Supervision; Writing – review & editing.

Itaru Matsumura: Project administration; Supervision.

Akifumi Takaori-Kondo: Project administration; Supervision; Writing – review & editing.

Junya Kuroda: Project administration; Supervision; Writing – review & editing.

The Kansai Myeloma Forum: Investigation; Project administration; Supervision.

Acknowledgements

This study was conducted by the support of the KMF.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare no conflicts of interest except JK received honorarium from Bristol-Myers Squibb Co, Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Sanofi K.K. and Ono Pharma Inc., and is an advisory role in Janssen Pharmaceutical K.K, and Novartis Pharma K.K. TI received honorarium from Bristol-Myers Squibb Co, Takeda Pharmaceutical Co., Ltd. and Sanofi K.K.; and research funding from Bristol-Myers Squibb Co. KI received honorarium from Bristol-Myers Squibb Co, Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Ono Pharma Inc., Novartis Pharma K.K., Kyowa Kirin Co., Ltd., Celgene K.K., Nippon Shinyaku Co., Ltd., Chugai Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co. Ltd., Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd. and Meiji Seika Pharma Co. Ltd. SF received honoraria from Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Sanofi K.K., Bristol-Myers Squibb Co., Ltd., and Celgene K.K. HT received personal fees from Bristol-Myers Squibb Co (Celgene K.K.), personal fees from Novartis Pharma K.K., grants from Kyowa Kirin Co., Ltd. HS reports

honoraria from Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Novartis Pharma K.K., Celgene K.K., Janssen Pharmaceutical K.K., Chugai Pharmaceutical Co., Ltd., Sanofi K.K., AstraZeneca K.K., AbbVie G.K., SymBio Pharmaceuticals Ltd., Eisai Co., Ltd., and Kyowa Kirin Co., Ltd.; and research funding from Pharma Essentia Japan K.K., Janssen Pharmaceutical K.K., Ono Pharmaceutical Co., Ltd., Celgene K.K., Novartis Pharma K.K., Sanofi K.K., AstraZeneca K.K., AbbVie G.K., Eisai Co., Ltd., HUYA Bioscience International, LLC., and Chugai Pharmaceutical Co., Ltd.; and scholarship endowment from Astellas Pharma Inc., Teijin Pharma Ltd., Shionogi & Co., Ltd., Eisai Co., Ltd., Sanofi K.K., Taiho Pharmaceutical Co., Ltd., and Nippon Shinyaku Co., Ltd. CS received honoraria from Bristol-Myers Squibb Co., Celgene K.K., Janssen Pharmaceutical K.K., and Sanofi K.K. IM received personal fees from Bristol-Myers Squibb Co. (Celgene K.K.), personal fees from Novartis Pharma K.K., grants and personal fees from Otsuka Pharmaceutical Co., Ltd., personal fees from Pfizer Japan Inc., during the conduct of the study; grants from Ono Pharmaceutical Co., Ltd., personal fees from Janssen Pharmaceutical K.K, grants from Nippon Shinyaku Co., Ltd., grants from Kyowa Kirin Co., Ltd., grants from Sumitomo Dainippon Pharma Co., Ltd., grants from Shionogi & Co., Ltd., grants from Teijin Pharma Ltd., grants from Boehringer Ingelheim Co., Ltd., grants from Sanofi K.K., grants from Chugai Pharmaceutical Co., Ltd., grants from Eisai Co., Ltd., grants from MSD K.K, grants from Asahi Kasei Pharma Corporation, grants and personal fees from Astellas Pharma Inc., grants and personal fees from Takeda Pharmaceutical Co., Ltd., grants from Japan Blood Products Organization, grants from Nihon Pharmaceutical Co., Ltd., grants and personal fees from AbbVie GK, grants from Taiho Pharmaceutical Co., Ltd., grants from Mitsubishi Tanabe Pharma Corporation, grants from Nippon Kayaku Co., Ltd., grants from CSL Behring LLC, grants from Mundipharma K.K, grants from Ayumi Pharmaceutical Corporation, grants from Eli Lilly Japan K.K., grants from Actelion Pharmaceuticals Japan Ltd., personal fees from Amgen BioPharma K.K., outside the submitted work. AT-K serves as an advisor for Megakaryon and receives research fundings from Ono Pharmaceutical Co., Ltd., DSK, and Cognano. JK received research funding from Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi K.K., Eisai Co., Ltd., Bristol-Myers Squibb Co., Sysmex, Dainippon Sumitomo Pharma Co., Ltd., Nippon Shinyaku Co., Ltd., AbbVie GK, Teijin Pharma Ltd. and Otsuka Pharmaceutical Co. Ltd., has received honoraria from Janssen Pharmaceutical K.K, Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi K.K., Eisai Co., Ltd., SymBio Pharmaceutical Limited, Bristol-Myers Squibb Co., Astellas Pharma Inc., Pfizer Japan Inc., Nippon Shinyaku Co., Ltd., Daiichi Sankyo Co. Ltd., Dainippon Sumitomo Pharma Co., Ltd., AbbVie G.K. and Otsuka Pharmaceutical Co. Ltd., and is a consultant for Janssen Pharmaceutical K.K, and Bristol-Myers Squibb Co.

Availability of data and materials

The data of this study are available from the corresponding author, JK, upon reasonable request.

ORCID iDs

Yutaka Shimazu https://orcid.org/0000-0002-1604-7220

Junya Kanda https://orcid.org/0000-0002-6704-3633

Yoshiyuki Onda https://orcid.org/0000-0003-3093-4974

Supplemental material

Supplemental material for this article is available online.

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Supplemental Materials

Monocyte or white blood cell counts and β2 microglobulin predict the durable efficacy of daratumumab with lenalidomide

Yutaka Shimazu[1], Junya Kanda[1*], Hitomi Kaneko[2], Kazunori Imada[2], Ryosuke Yamamura[3], Satoru Kosugi[4], Yuji Shimura[5], Tomoki Ito[6], Shin-ichi Fuchida[7], Hitoji Uchiyama[8], Kentaro Fukushima[9], Satoshi Yoshihara[10], Hitoshi Hanamoto[11], Hirokazu Tanaka[12], Nobuhiko Uoshima[13], Kensuke Ohta[14], Hideo Yagi[15], Hirohiko Shibayama[16], Yoshiyuki Onda[17], Yasuhiro Tanaka[18], Yoko Adachi[19], Mitsuhiro Matsuda[20], Masato Iida[21], Takashi Miyoshi[22], Toshimitsu Matsui[23], Ryoichi Takahashi[24], Teruhito Takakuwa[25], Masayuki Hino[25], Naoki Hosen[9], Shosaku Nomura[6], Chihiro Shimazaki[7], Itaru Matsumura[12], Akifumi Takaori-Kondo[1] and Junya Kuroda[5], The Kansai Myeloma Forum[26]

Inventory of Supplemental Information

Supplement Figure 6.

Supplement Figure 7.

Supplement Figure 8.

Supplement Figure 9.

Supplement Figure 10.

Supplement Figure 11.

Supplement Figure 12.

Supplemental Figure Legends

Supplement Figure 1. A consort diagram of this study.

Supplement Figure 2. (A-F) The histogram of white blood cell counts (/μL) **(A)**, neutrophil counts (/μL) **(B)**, lymphocyte counts (/μL) **(C)**, monocyte counts (/μL) **(D)**, β_2 microglobulin (B2MG; mg/L) **(E)** and κ/λ ratio **(F)**. The horizontal axis was plotted in log scale.

Supplement Figure 3. (A) The TTNT of the MM patients treated with daratumumab according to the monocyte counts: less than 200/μL (*black*), 200 to 300/μL (*red*), 300 to 400/μL (*blue*) and 400/μL or more (*green*). **(B)** The TTNT of the MM patients treated with a daratumumab regimen according to the κ/λ ratio: 0.1 to 10 (*black*), 0.01 to 0.1 or 10 to 100 (*red*) and less than 0.01 or 100 or more (*blue*). Median TTNT (months) values with the 95% CI are shown. Hazard ratios (HRs) with the 95% CI and p-values against the reference (*black*) are shown in the upper panel of each figure. The number of patients

at risk in each group is shown in the lower panel of each figure.

Supplement Figure 4. The TTNT of the MM patients treated with daratumumab according to the WBC counts: less than 2500/μL (*black*), 2500 to 3500/μL (*red*), 3500 to 5000/μL (*blue*) and 5000/μL or more (*green*). Median TTNT (months) values with the 95% CI are shown. Hazard ratios (HRs) with the 95% CI and p-value against the reference (*black*) are shown in the upper panel of each figure. The number of patients at risk in each group is shown in the lower panel of each figure.

Supplement Figure 5. (A) The TTNT of the MM patients treated with daratumumab according to the neutrophil counts: less than 1000/μL (*black*), 1000 to 2000/μL (*red*), 2000 to 3000/μL (*blue*) and 3000/μL or more (*green*). Median TTNT (months) values with the 95% CI are shown. Hazard ratios (HRs) with the 95% CI and p-value against the reference (*black*) are shown in the lower panel of the figure. **(B)** The TTNT of the MM patients treated with daratumumab according to the neutrophil counts: less than 2000/μL (*black*), and 2000/μL or more (*red*). **(C)** The TTNT of the MM patients treated with daratumumab according to the lymphocyte counts: less than 500/μL (*black*), 500 to 1000/μL (*red*), 1000 to 1500/μL (*blue*) and 1500/μL or more (*green*). Median TTNT (months) values with the 95% CI are shown. Hazard ratios (HRs) with the 95% CI and p-value against the reference (*black*) are shown in the lower panel of each figure. **(D)** The TTNT of the MM patients treated with daratumumab according to the lymphocyte counts: less than 1000/μL (*black*), and 1000/μL or more (*red*). The number of patients at risk in each group is shown in the lower panel of each figure.

Supplement Figure 6. The TTNT of the MM patients treated with daratumumab according to the B2MG: less than 3.5 mg/L (*black*), 3.5 to 5.5 mg/L (*red*) and 5.5 mg/L or more (*blue*). Median TTNT (months) values with the 95% CI are shown. Hazard ratios (HRs) with the 95% CI and p-value against the reference (*black*) are shown in the upper panel of the figure. The number of patients at risk in each group is shown in the lower panel of each figure.

Supplement Figure 7. The proportion of patients experiencing a best treatment response against daratumumab treatment (DLd regimen vs. DBd regimen). The overall response included cases with a CR, VGPR or PR. CR: complete remission; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; DLd: daratumumab, lenalidomide and dexamethasone; DBd: daratumumab, bortezomib and dexamethasone.

Supplement Figure 8. (A) The TTNT of the MM patients treated with the DLd regimen according to the number of prior treatment regimens: 2 or fewer (*black*), 3 (*red*) and 4 or more (*blue*) prior regimens. Median TTNT (months) values with the 95% CI are shown. NA indicates not applicable. **(B)** The TTNT of the MM patients treated with the DBd regimen according to the number of prior treatment regimens: 2 (*black*), 3 (*red*) and 4 or more (*blue*) prior regimens. Median TTNT (months) values with the 95% CI are shown. **(C-D)** The TTNT of the MM patients treated with the DLd **(C)** or DBd **(D)** regimen according to the prior elotuzumab use: no use of elotuzumab (*black*) or prior use of elotuzumab (*red*). Median TTNT (months) values with the 95% CI are shown. The number of patients at risk in each group is shown in the lower panel of each figure.

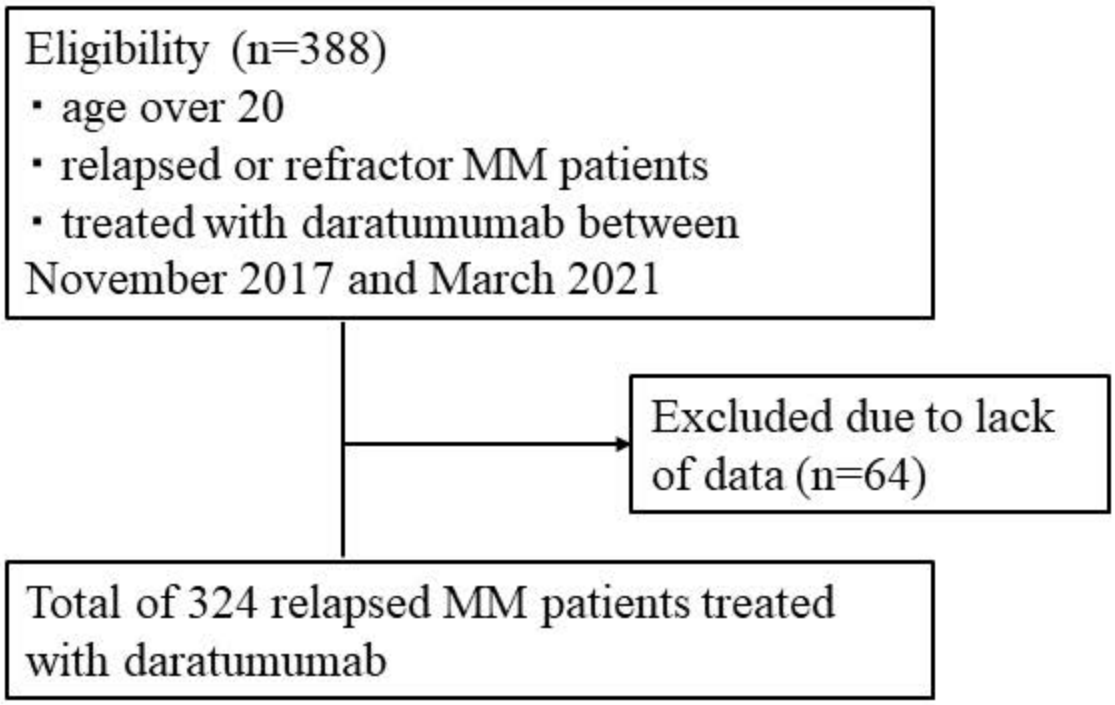
Supplement Figure 9. (A-B) The correlation between monocyte counts and white blood cell counts **(A)** or monocyte counts and white blood cell counts **(B)** was analyzed by Person's correlation coefficient.

Supplement Figure 10. (A-B) The TTNT of the MM patients treated with the DLd regimen and with fewer than 4 prior treatment regimens **(A)** or with 4 or more prior treatment regimens **(B)** according to the proposed scoring system: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). The total scores were calculated according to the monocyte counts (0 points when ≥200/μL and 1 point when <200/μL) and B2MG (0 points when＜5.5 mg/L and 1 point when ≥5.5 mg/L) before daratumumab treatment. Median TTNT (months) values with the 95% CI are shown in each figure. The number of patients at risk in each group is shown in the lower panel of each figure. NA indicates not applicable.

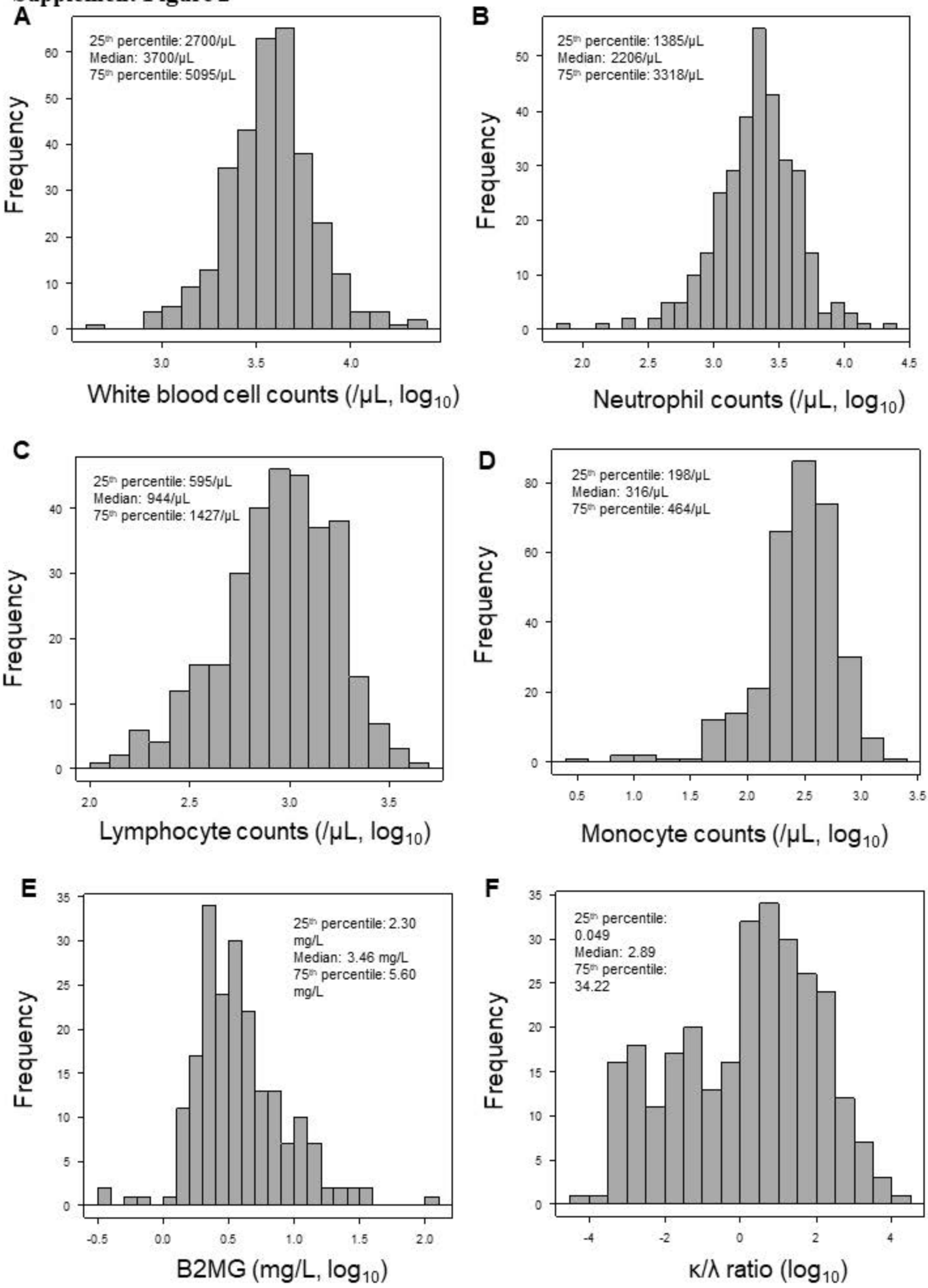
Supplement Figure 11. (A-B) The TTNT of the MM patients treated with the DLd regimen and having fewer than 4 prior treatment regimens **(A)** or having 4 or more prior treatment regimens **(B)** according to the proposed scoring system: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). Total scores were calculated according to the WBC counts (0 point when ≥3500/μL and 1 point when <3500/μL) and B2MG (0 point when＜5.5 mg/L and 1 point when ≥5.5 mg/L) before daratumumab treatment. Median TTNT (months) values with the 95% CI are shown in the figure. The number of patients at risk in each group is shown in the lower panel of each figure. NA indicates not applicable.

Supplement Figure 12. The algorithm for choosing an MM treatment based on the proposed scoring system.

Supplement Figure 1

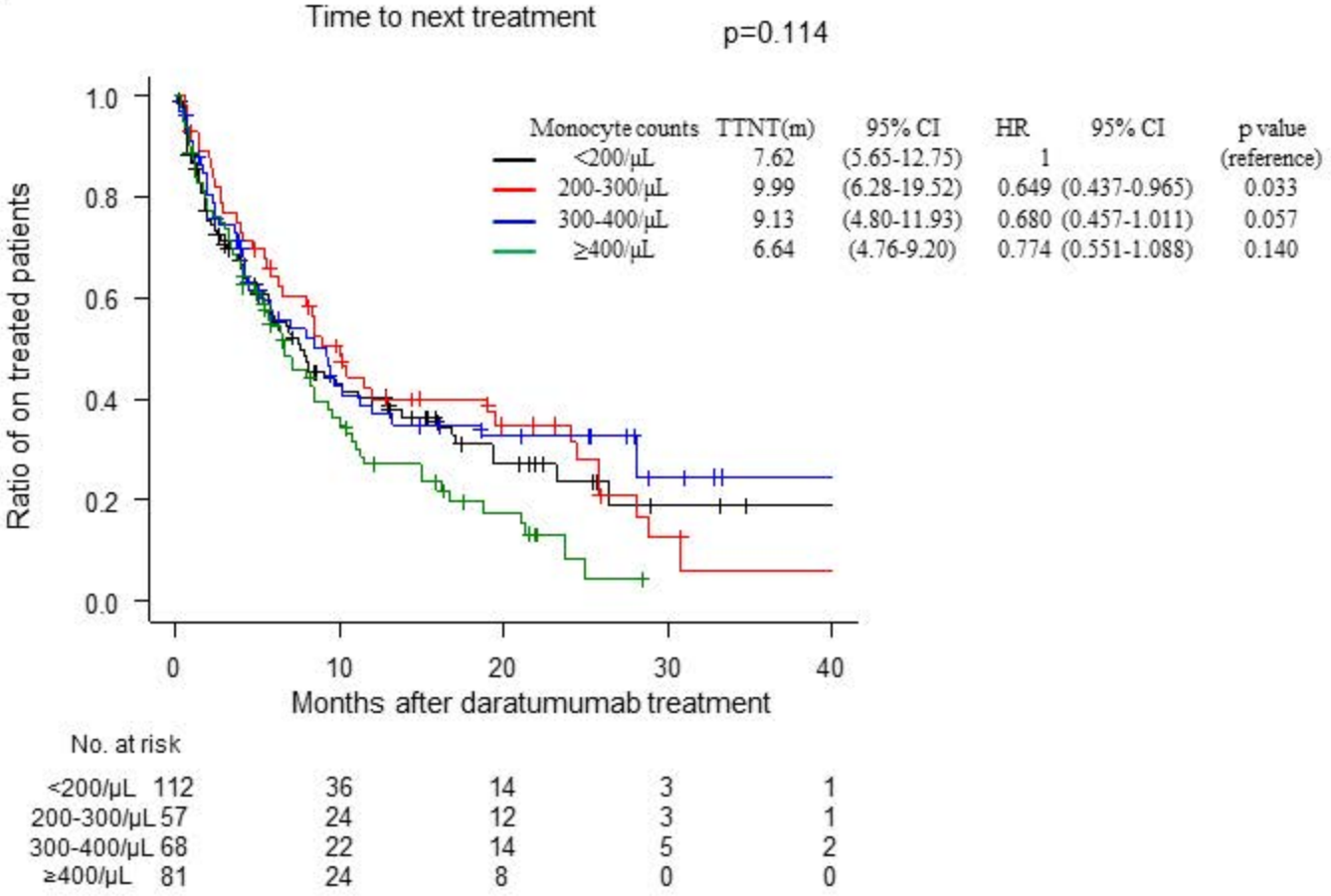


Supplement Figure 2



Supplement Figure 3

A



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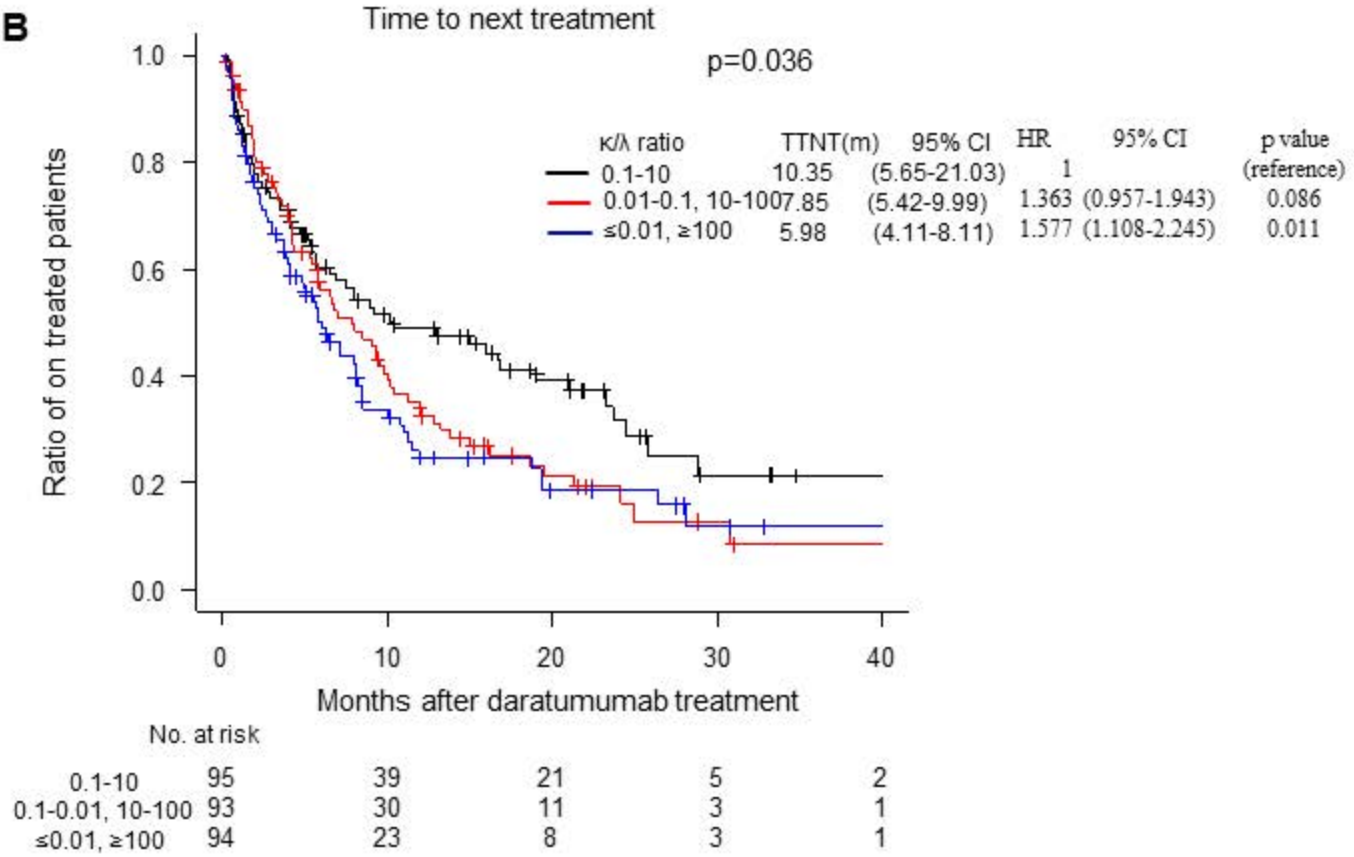
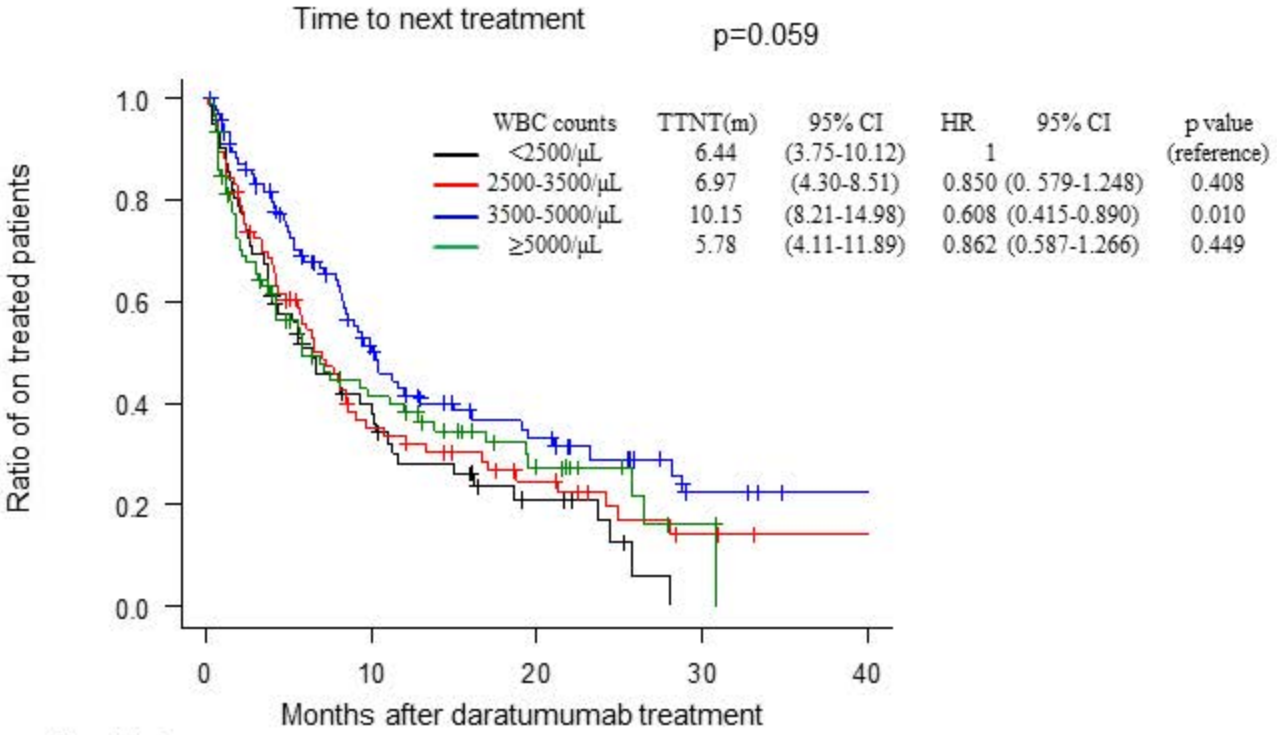


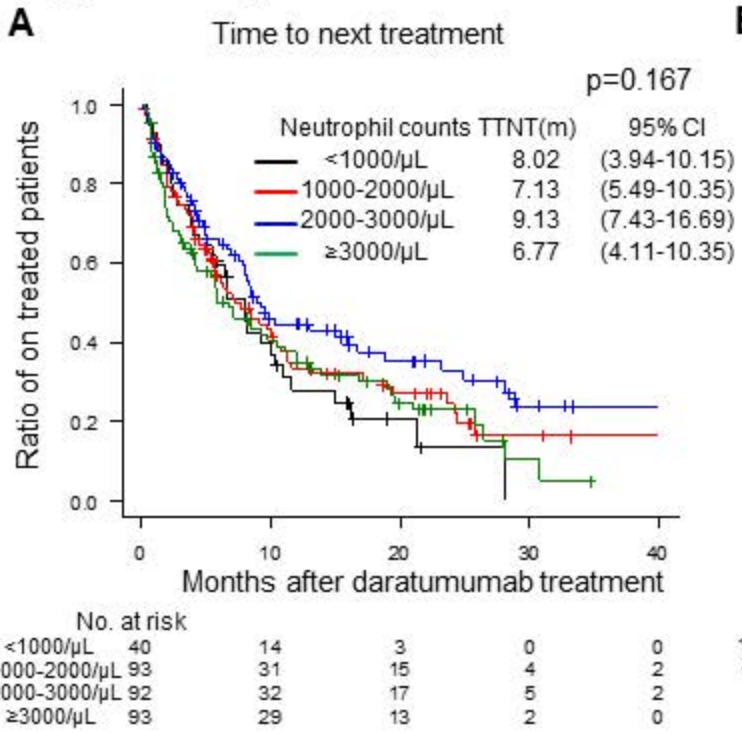
Supplement Figure 4

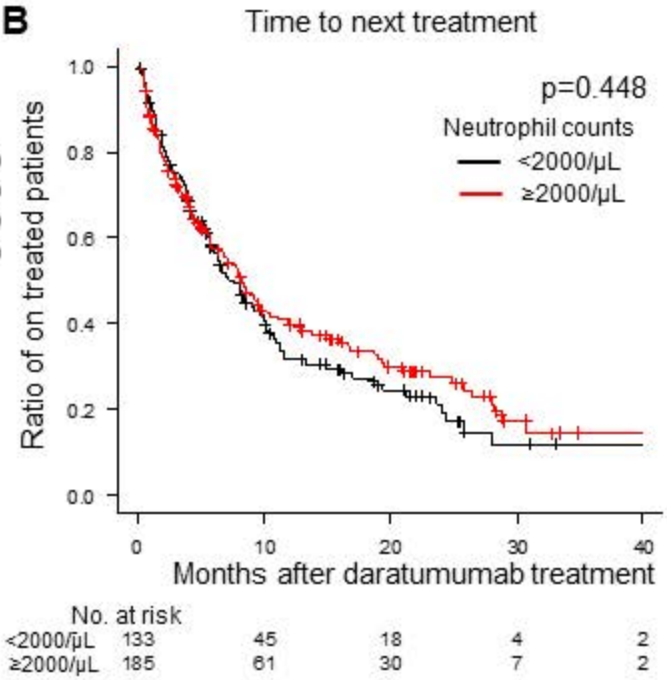


No. at risk

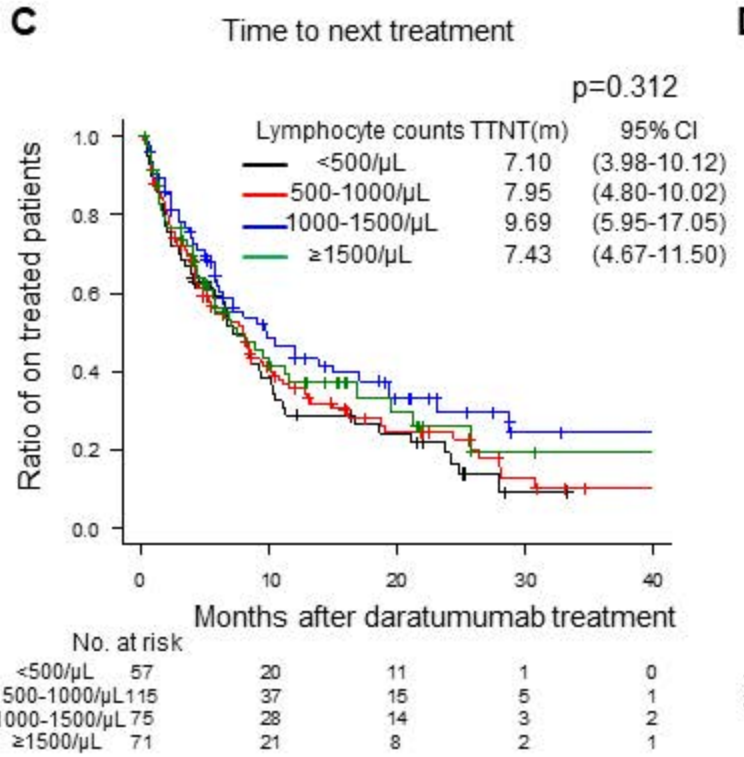
<2500/μL	62	21	7	0	0
2500-3500/μL	77	23	12	4	2
3500-5000/μL	97	37	19	5	2
≥5000/μL	86	26	10	2	0

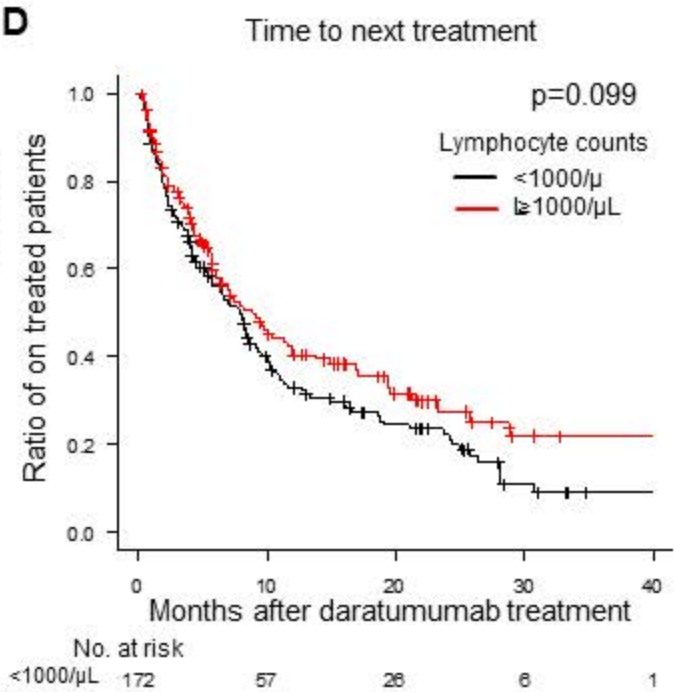
Supplement Figure 5





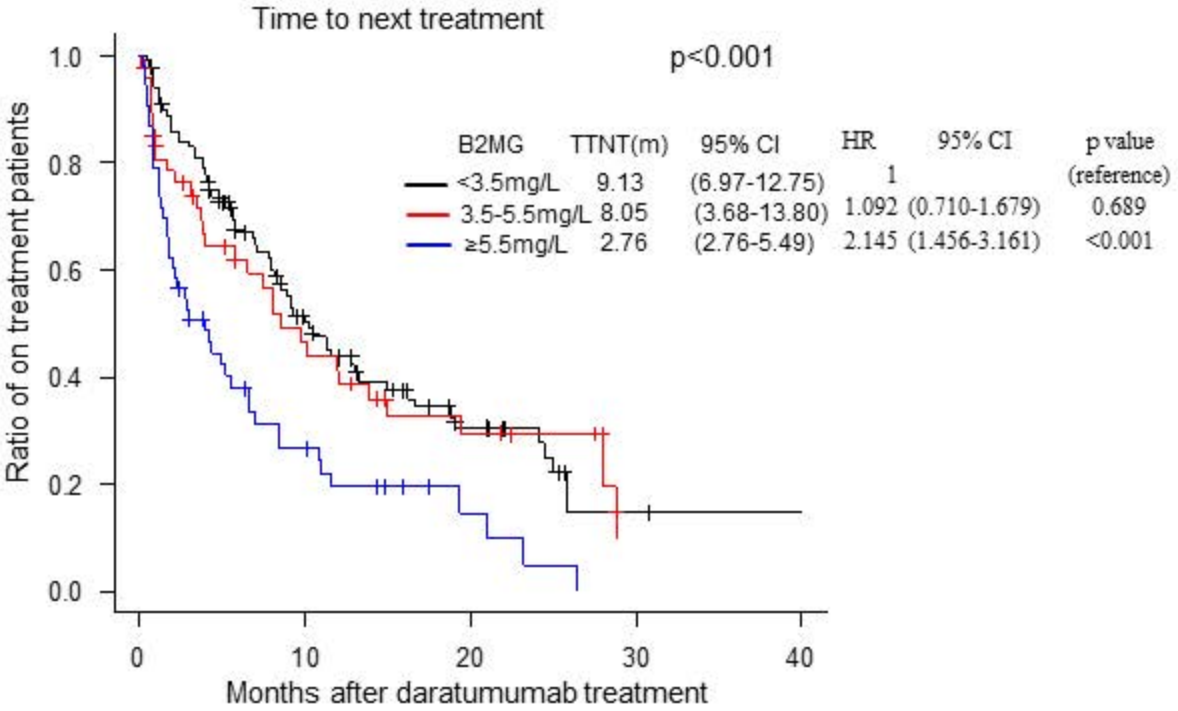
Neutrophil counts	HR	95% CI	p value
<1000/μL	1		(reference)
1000-2000/μL	0837	(0.544-1.287)	0.417
2000-3000/μL	0.665	(0.428-1.035)	0. 070
≥3000/μL	0.955	(0.622-1.464)	0.831





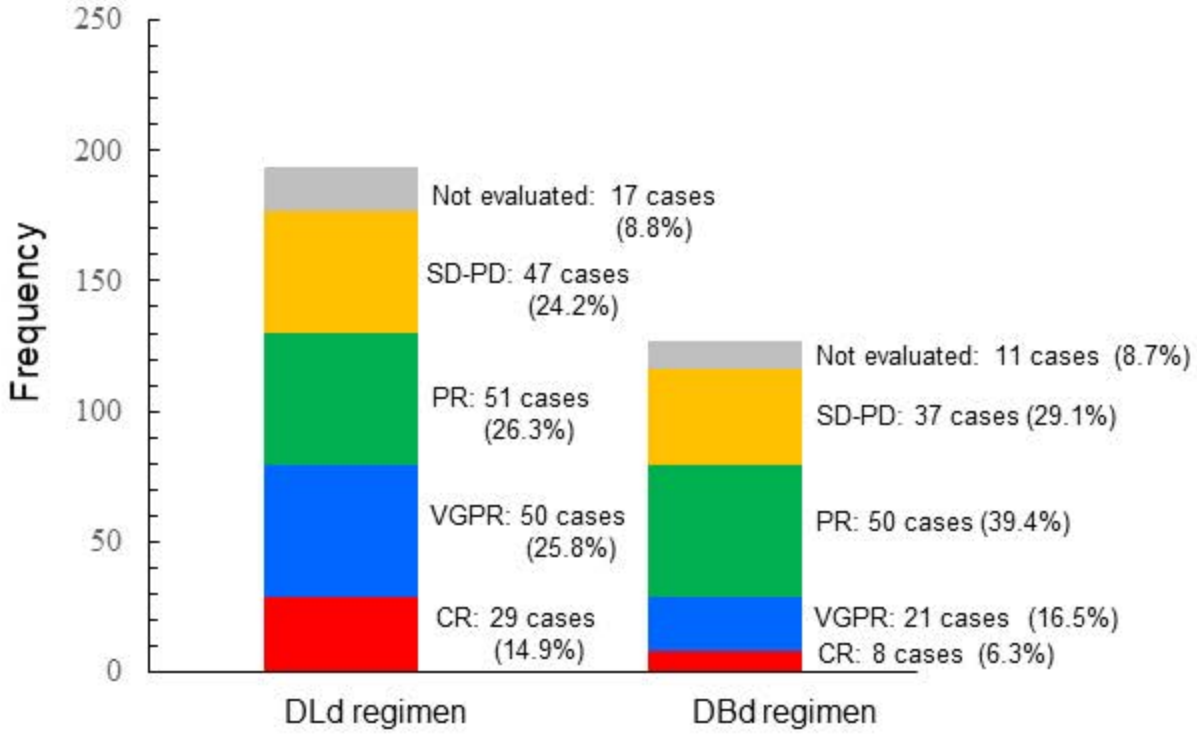
Lymphocyte counts	HR	95% CI	p value
<500/μL	1		(reference)
500-1000/μL	0.911	(0.635-1.307)	0.612
1000-1500/μL	0.693	(0.460-1.044)	0.079
≥1500/μL	0.822	(0.541-1.250)	0.360

Supplement Figure 6

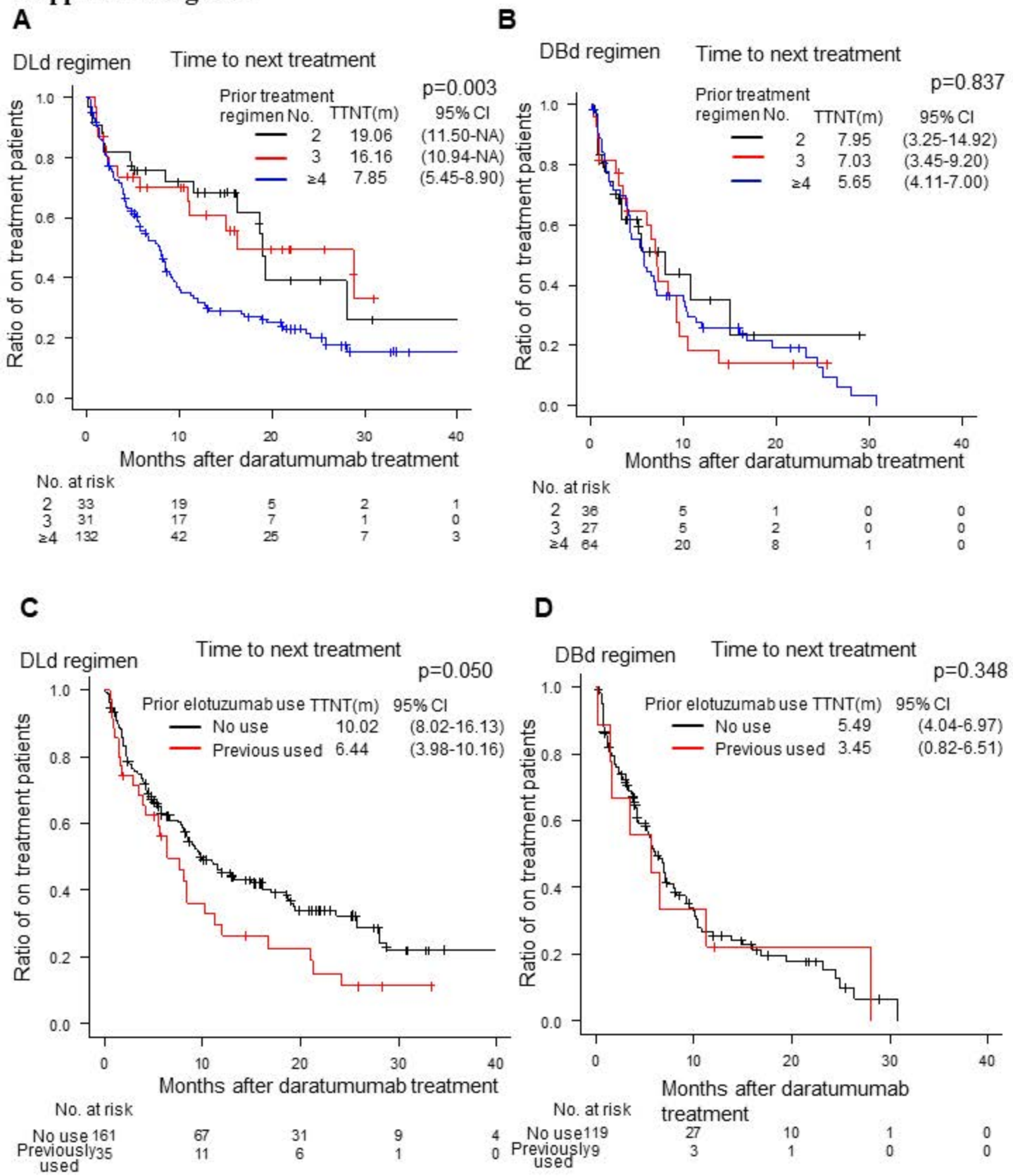


No. at risk					
<3.5mg/L	101	39	15	4	3
3.5-5.5mg/L	48	18	9	0	0
≥5.5mg/L	53	12	3	0	0

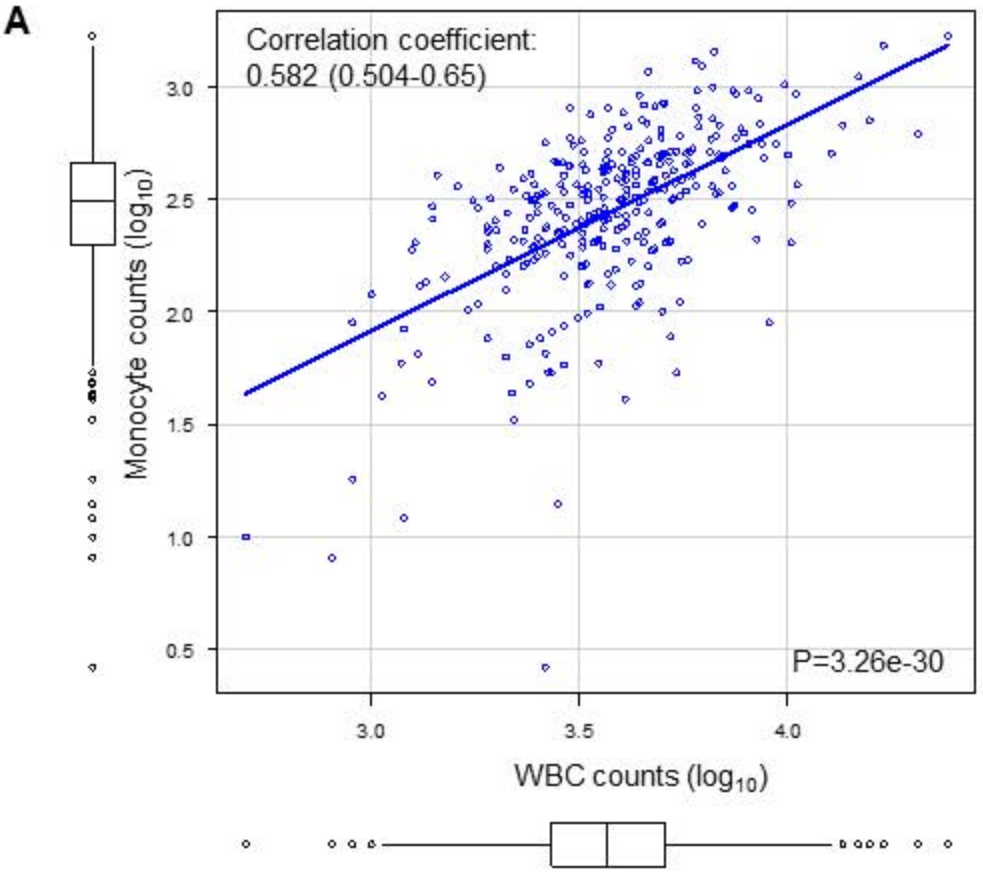
Supplement Figure 7

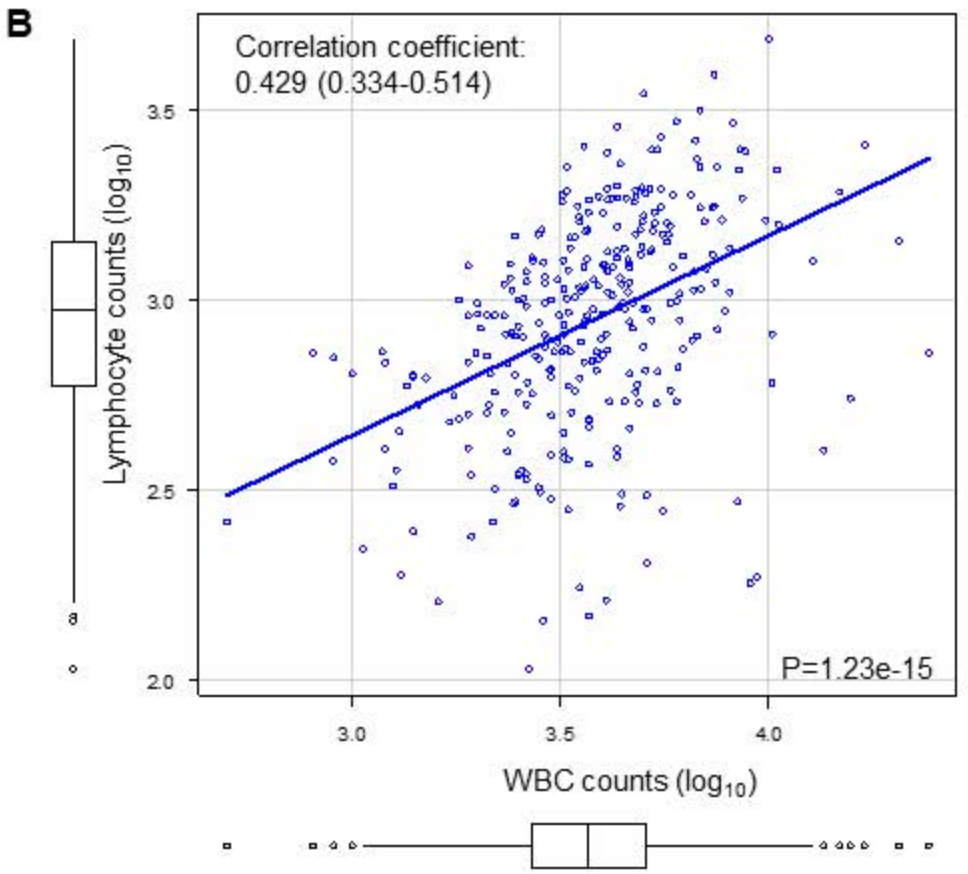


Supplement Figure 8



Supplement Figure 9

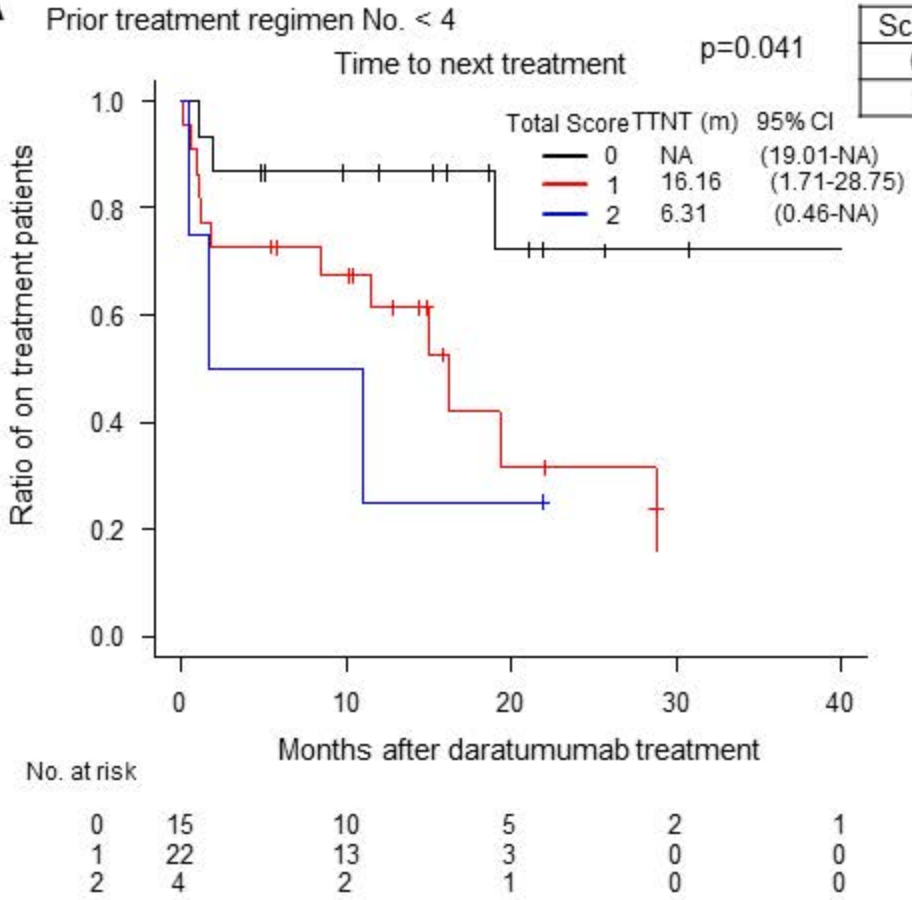




Supplement Figure 10

A

Prior treatment regimen No. < 4



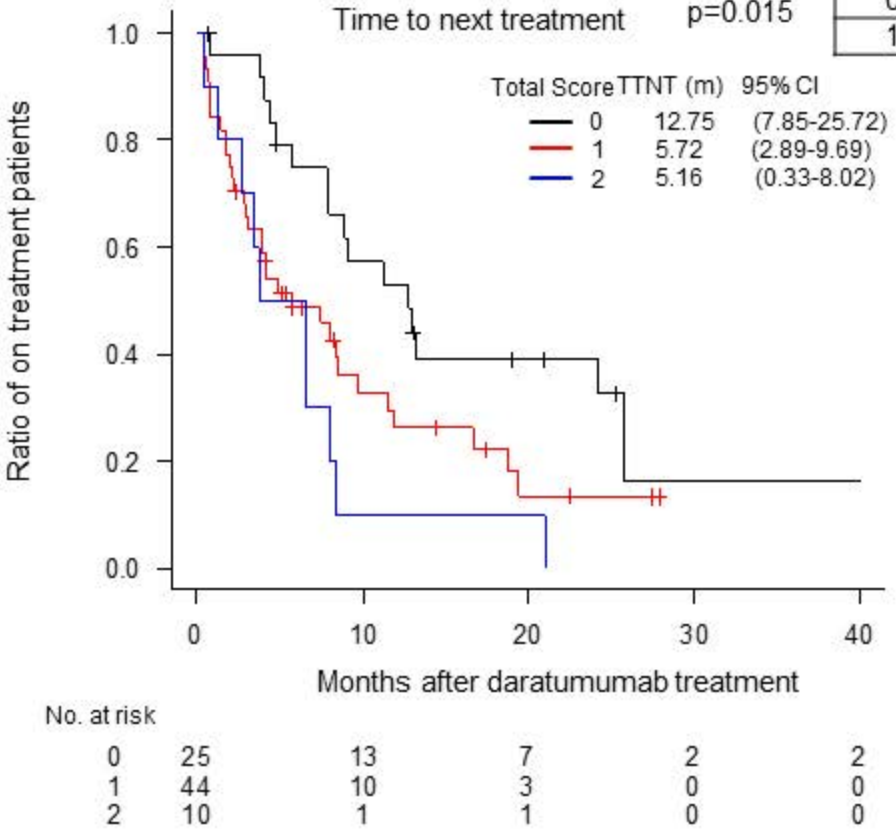
Score	Monocyte counts	B2MG
0	≥200/μL	<5.5 mg/L
1	<200/μL	≥5.5 mg/L

No. at risk

0	15	10	5	2	1
1	22	13	3	0	0
2	4	2	1	0	0

B

Prior treatment regimen No. ≥ 4



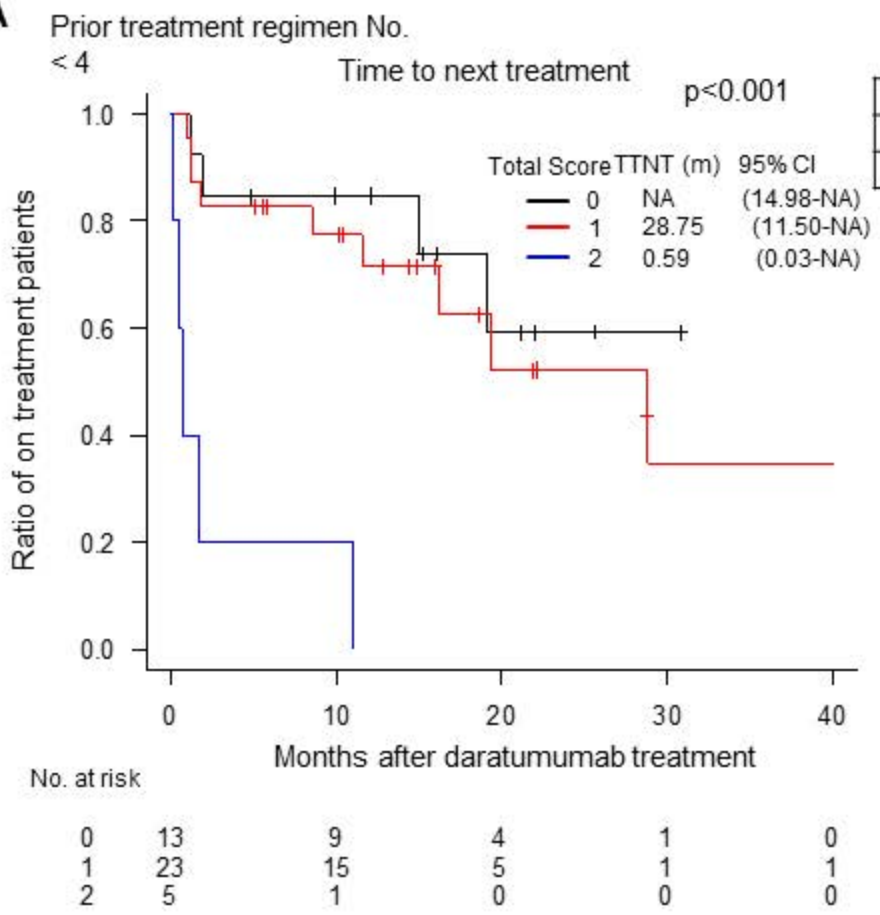
Score	Monocyte counts	B2MG
0	≥200/μL	<5.5 mg/L
1	<200/μL	≥5.5 mg/L

No. at risk

0	25	13	7	2	2
1	44	10	3	0	0
2	10	1	1	0	0

Supplement Figure 11

A

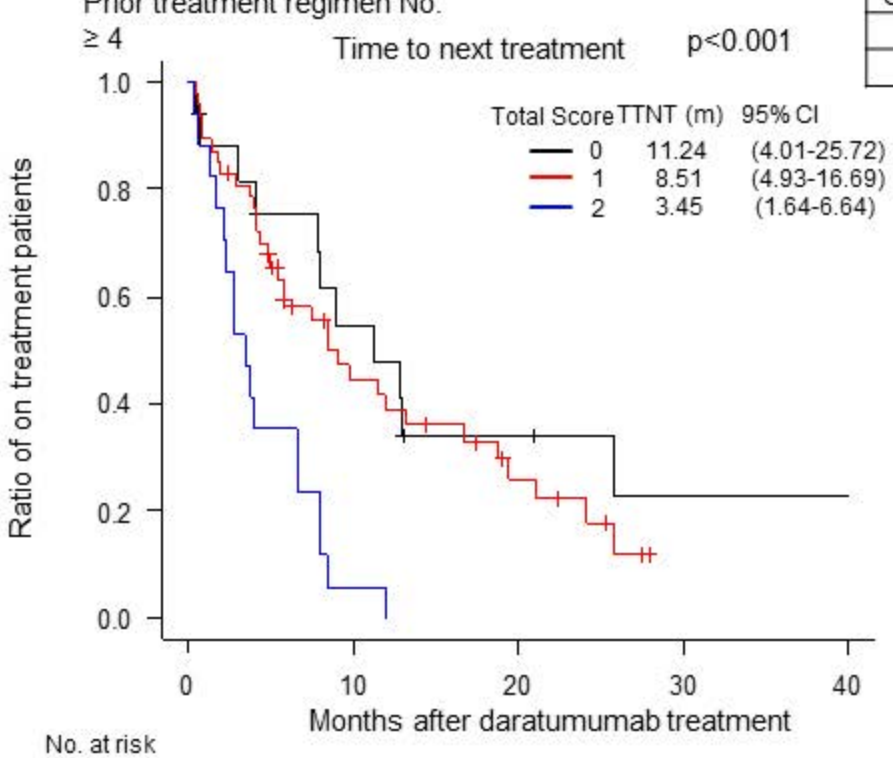


No. at risk

0	13	9	4	1	0
1	23	15	5	1	1
2	5	1	0	0	0

Score	WBC counts	B2MG
0	≥3500/μL	<5.5 mg/L
1	<3500/μL	≥5.5 mg/L

B

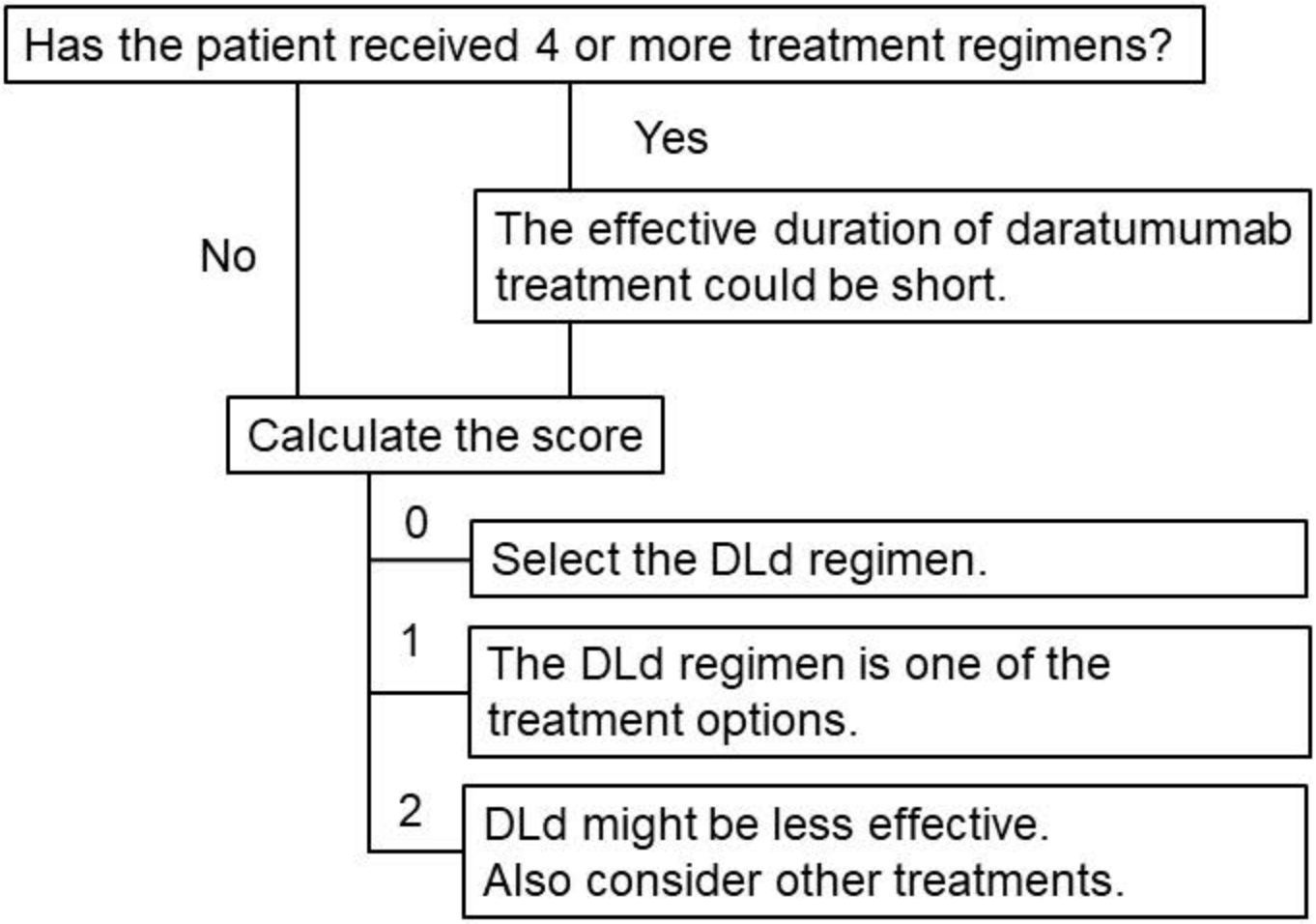


No. at risk

0	17	8	4	2	2
1	47	16	7	0	0
2	17	1	0	0	0

Score	WBC counts	B2MG
0	≥3500/μL	<5.5 mg/L
1	<3500/μL	≥5.5 mg/L

Supplement Figure 12



Supplement Table 1 only for reviewer.

The cases with auto-SCT prior to daratumumab treatment among each score in model 1 and in model 2

Model 1	Score 0	Score 1	Score 2	p-value
Auto-SCT prior to daratumumab +	23 (57.5%)	48 (72.7%)	12 (85.7%)	0.093
Auto-SCT prior to daratumumab -	17 (42.5%)	18 (27.3%)	2 (14.2%)	

Model 2	Score 0	Score 1	Score 2	p-value
Auto-SCT prior to daratumumab +	21 (70.0%)	46 (65.7%)	17 (77.3%)	0.586
Auto-SCT prior to daratumumab -	9 (30.0%)	24 (34.3%)	5 (22.7%)	

The number of cases who had received auto-SCT prior to daratumumab treatment among each score in model 1 and in model 2 were described.

Supplement Table 2 only for reviewer.

Multivariate analysis for TTNT including both lymphocyte counts and monocyte counts

		Analysis 4		
Factors		**Hazard ratio**	**95% CI**	**p-value**
Lymphocyte counts	<1000/μl	1		0.395
	≥1000/μl	0.782	0.444-1.379	
Monocyte counts	<200/μl	1		0.009
	≥200/μl	0.514	0.312-0.849	
κ/λ ratio	0.1-10	1		0.212
	≤0.1, ≥10	1.395	0.827-2.351	
B2MG	<5.5mg/L	1		0.015
	≥5.5mg/L	1.800	1.121-2.892	
Prior regimen numbers	<4	1		0.005
	≥4	2.190	1.272-3.771	
Prior use of elotuzumab	no	1		0.270
	yes	1.421	0.761-2.655	
Auto-SCT prior to daratumumab	no	1		0.145
	yes	0.653	0.368-1.159	

Multivariate analyses against TTNT in MM patients treated with the DLd regimen were performed using the following factors: lymphocyte counts, monocyte counts, κ/λ ratio, B2MG, prior regimen numbers, prior use of elotuzumab and auto-SCT prior to daratumumab. The Cox proportional hazard model was used to calculate the hazard ratio for each variable; the 95% CI and p-value are shown. TTNT: time to next treatment; CI: confidence interval; B2MG: β_2 microglobulin; autologous stem cell transplantation: auto-SCT.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6,7,8
Bias	9	Describe any efforts to address potential sources of bias	6,7,8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6,7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7,8
		(*b*) Describe any methods used to examine subgroups and interactions	6,7,8
		(*c*) Explain how missing data were addressed	6,7
		(*d*) If applicable, explain how loss to follow-up was addressed	6,7
		(*e*) Describe any sensitivity analyses	6,7,8
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	6,9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6,9
		(b) Indicate number of participants with missing data for each variable of interest	6,9
		(c) Summarise follow-up time (eg, average and total amount)	6, 9
Outcome data	15*	Report numbers of outcome events or summary measures over time	9

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9,10
		(*b*) Report category boundaries when continuous variables were categorized	9,10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9,10
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	9,10,11
Discussion			
Key results	18	Summarise key results with reference to study objectives	12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12,13,14
Generalisability	21	Discuss the generalisability (external validity) of the study results	12,13,14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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Efficacy of elotuzumab for multiple myeloma in reference to lymphocyte counts and kappa/lambda ratio or B2 microglobulin

Yutaka Shimazu[1], Junya Kanda[1]✉, Satoru Kosugi[2], Tomoki Ito[3], Hitomi Kaneko[4], Kazunori Imada[4], Yuji Shimura[5], Shin-ichi Fuchida[6], Kentaro Fukushima[7], Hirokazu Tanaka[8], Satoshi Yoshihara[9], Kensuke Ohta[10], Nobuhiko Uoshima[11], Hideo Yagi[12], Hirohiko Shibayama[13], Ryosuke Yamamura[14], Yasuhiro Tanaka[15], Hitoji Uchiyama[16], Yoshiyuki Onda[17], Yoko Adachi[18], Hitoshi Hanamoto[19], Ryoichi Takahashi[20], Mitsuhiro Matsuda[21], Takashi Miyoshi[22], Teruhito Takakuwa[23], Masayuki Hino[23], Naoki Hosen[7], Shosaku Nomura[3], Chihiro Shimazaki[6], Itaru Matsumura[8], Akifumi Takaori-Kondo[1] & Junya Kuroda[5]

Novel therapeutic drugs have dramatically improved the overall survival of patients with multiple myeloma. We sought to identify the characteristics of patients likely to exhibit a durable response to one such drug, elotuzumab, by analyzing a real-world database in Japan. We analyzed 179 patients who underwent 201 elotuzumab treatments. The median time to next treatment (TTNT) with the 95% confidence interval was 6.29 months (5.18–9.20) in this cohort. Univariate analysis showed that patients with any of the following had longer TTNT: no high risk cytogenic abnormalities, more white blood cells, more lymphocytes, non-deviated κ/λ ratio, lower β_2 microglobulin levels (B2MG), fewer prior drug regimens, no prior daratumumab use and better response after elotuzumab treatment. A multivariate analysis showed that TTNT was longer in patients with more lymphocytes (≥ 1400/μL), non-deviated κ/λ ratio (0.1–10), lower B2MG (< 5.5 mg/L) and no prior daratumumab use. We proposed a simple scoring system to predict the durability of the elotuzumab treatment effect by classifying the patients into three categories based on their lymphocyte counts (0 points for ≥ 1400/μL and 1 point for < 1400/μL) and κ/λ ratio (0 points for 0.1–10 and 1 point for < 0.1 or ≥ 10) or B2MG (0 points

[1]Department of Hematology and Oncology Graduate School of Medicine, Kyoto University, 54, Kawaramachi, Shogoin, Sakyoku, Kyoto 606-8507, Japan. [2]Department of Internal Medicine (Hematology), Toyonaka Municipal Hospital, Toyonaka, Japan. [3]First Department of Internal Medicine, Kansai Medical University, Hirakata, Japan. [4]Department of Hematology, Japanese Red Cross Osaka Hospital, Osaka, Japan. [5]Division of Hematology and Oncology, Department of Medicine, Kyoto Prefectural University of Medicine, Kyoto, Japan. [6]Department of Hematology, Japan Community Health Care Organization Kyoto Kuramaguchi Medical Center, Kyoto, Japan. [7]Department of Hematology and Oncology, Osaka University Graduate School of Medicine, Suita, Japan. [8]Department of Hematology and Rheumatology, Kindai University Faculty of Medicine, Higashiōsaka, Japan. [9]Division of Hematology, Department of Internal Medicine, Hyogo College of Medicine, Nishinomiya, Japan. [10]Hematology Ohta Clinic, Shinsaibashi, Japan. [11]Department of Hematology, Japanese Red Cross Kyoto Daini Hospital, Kyoto, Japan. [12]Department of Hematology and Oncology, Nara Prefecture General Medical Center, Nara, Japan. [13]Department of Hematology, National Hospital Organization Osaka National Hospital, Osaka, Japan. [14]Department of Hematology, Osaka Saiseikai Nakatsu Hospital, Osaka, Japan. [15]Department of Hematology, Japanese Red Cross Wakayama Medical Center, Wakayama, Japan. [16]Department of Hematology, Japanese Red Cross Kyoto Daiichi Hospital, Kyoto, Japan. [17]Department of Hematology, Japanese Red Cross Takatsuki Hospital, Takatsuki, Japan. [18]Department of Internal Medicine, Japan Community Health Care Organization Kobe Central Hospital, Kobe, Japan. [19]Department of Hematology, Kindai University Nara Hospital, Ikoma, Japan. [20]Department of Hematology, Omihachiman Community Medical Center, Omihachiman, Japan. [21]Department of Hematology, PL General Hospital, Tondabayashi, Japan. [22]Department of Hematology, Uji Tokushukai Hospital, Uji, Japan. [23]Department of Hematology, Osaka Metropolitan University Graduate School of Medicine, Osaka, Japan. ✉email: jkanda16@kuhp.kyoto-u.ac.jp

for < 5.5 mg/L and 1 point for ≥ 5.5 mg/L). The patients with a score of 0 showed significantly longer TTNT ($p < 0.001$) and better survival ($p < 0.001$) compared to those with a score of 1 or 2. Prospective cohort studies of elotuzumab treatment may be needed to validate the usefulness of our new scoring system.

The introduction of new drugs, particularly the monoclonal antibodies (mAbs) elotuzumab, daratumumab, and isatuximab, has dramatically improved the prognosis of patients with multiple myeloma (MM)[1–4]. Patients with relapsed MM currently receive dexamethasone, proteosome inhibitors, immunomodulatory drugs, mAbs or a combination of these drugs. Among the mAbs, the anti-CD38 antibodies daratumumab[1] and isatuximab[3] are widely used for relapsed MM patients and are associated with a high response rate and superior prognosis. There is another mAb called elotuzumab, which is an antibody against signaling lymphocytic activation molecule F7 (SLAMF7)[5]. Elotuzumab is used with the combination of lenalidomide or pomalidomide in a relapsed setting[2,5,6]. Elotuzumab is effective against SLAMF7-expressing myeloma via active immune cells, particularly natural killer cells[7,8]. Although previous studies reported that elotuzumab showed a high response rate in relapsed MM patients, durable efficacy was achieved in only one fourth of the patients[2,6]. In addition, there are no appropriate biomarkers to predict the durable efficacy of elotuzumab before administration. Because non-responders might benefit from alternative treatments, it is important to select suitable patients for elotuzumab treatment beforehand.

In this study, we attempted to identify biomarkers of the suitability of patients for elotuzumab treatment by focusing on the immunological mechanism of elotuzumab. Elotuzumab is not a cytotoxic drug but rather an immunotherapeutic that works with the help of host immune cells. Therefore, it is important to take into account the host's immune status. Here, we hypothesized that the balance between the tumor burden and the immune status of the host before treatment may determine the efficacy of elotuzumab treatment. To examine this hypothesis, we conducted a retrospective observational analysis using the real-world database collected by the Kansai Myeloma Forum (KMF) in Japan.

Patients and methods

Data source and patients. The KMF is a study group consisting of 123 physicians from 46 facilities in Japan. The KMF database includes the physician-reviewed real-world clinical data of patients with plasma cell dyscrasias and their periodic follow-ups. This study was approved by the Data Management Committee of the Graduate School of Medicine, Kyoto University, and by the institutional review board (approval no. R2887).

A total of 4,095 patients with plasma cell dyscrasias were registered in the KMF database as of February 2021. All the patients were diagnosed as having MM or MM-related disorders based on institutional assessment. From the KMF database, we selected patients who fulfilled the following inclusion criteria: symptomatic MM, age over 20, treatment for relapsed or refractory MM, and treatment with elotuzumab between November 2016 and February 2021 (after its approval for clinical use). Because elotuzumab was approved only for the treatment of relapsed or refractory MM in Japan, elotuzumab was used as a second-or later-line treatment in all cases. A total of 201 patients met the above inclusion criteria for this study. We conducted secondary research to collect the laboratory data 1–7 days before cycle 1 day 1 elotuzumab treatment (after the previous treatment). After excluding 22 patients for lack of data, we finally analyzed 179 relapsed MM patients who underwent a total of 201 treatments with elotuzumab.

The patient responses to treatment were assessed based on the criteria of the international uniform response criteria[9] for multiple myeloma. The best responses against elotuzumab were classified by institutional physicians into five categories: complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), and progressive disease (PD).

We included the data related to high risk cytogenetic abnormalities based on the physicians' input data by referring to the consensus of the International Myeloma Working group[10], which includes the deletions 17p, t(4;14) and t(14;16). Unfavorable cytogenetic abnormalities were categorized by a fluorescence in situ hybridization analysis.

Statistical analyses. The histogram of white blood cell (WBC) counts, neutrophil counts, monocyte counts, lymphocyte counts, β_2 microglobulin (B2MG) and κ/λ ratio were shown in Fig. S1. To determine the cutoff value, we applied the cutoff value of β_2 microglobulin (B2MG) according to the International Staging system for MM[11] as it has been widely accepted (Fig. S2A). As there were no fixed cut off values for other laboratory parameters, we tested the 25th, 50th and 75th percentile value as potential cut-off values (Fig. S2B–E).We referred to prior studies analyzing the overall survival (OS) of immune therapies which reported lymphocyte counts of 500–1500/μL as the threshold[12–15]. We also took into account that only one fourth of the patients were able to obtain durable efficacy by elotuzumab treatment[2,6] and determined the cut off values for WBC counts, neutrophile counts, lymphocyte counts, monocyte counts and κ/λ ratio as 3500/μl, 3000/μl, 1400/μl, 300/μl and 0.1–10, respectively.

We chose the time to the next treatment (TTNT) as primary endpoint instead of progression free survival (PFS) for our retrospective analysis[16,17], since the timing of progressive disease is difficult to precisely determine in our cohort. We included the TTNT for elotuzumab treatment, which was calculated from the time of elotuzumab treatment until the date of next treatment, death by any cause or the date of last contact. The data were censored for the date of next treatment when the cessation of elotuzumab treatment was planned advance. We calculated TTNT depending on each treatment. To analyze the underlying factors affecting the TTNT of elotuzumab treatment, we selected the following parameters. First, we selected the type of treatment regimen:

elotuzumab plus lenalidomide (ERd) regimen and/or elotuzumab plus pomalidomide (EPd) regimen. Next, we adapted two parameters to estimate the tumor burden of myeloma: the κ/λ ratio and B2MG. These two parameters are recognized to reflect tumor burden[11,18,19]. And finally, we adopted several parameters which, based on our clinical experience, appear to be correlated with the host immune status: white blood cell counts and other leukocyte fractions. We selected the leukocyte fractions (neutrophil, lymphocyte, or monocyte counts) which showed significant correlation with TTNT on univariate analysis and used them in the subsequent analysis.

To calculate the OS, only the data for the patients with first elotuzumab treatment were analyzed. The survival curves of TTNT and OS were plotted using the Kaplan–Meier method, and the log-rank test was used for comparisons among groups. The Cox proportional hazard model was used to calculate the hazard ratios (HRs) for each variable along with the 95% confidence interval (CI). Variables considered in the univariate analysis were age, gender, type of treatment regimen, high risk cytogenic abnormalities, WBC counts, neutrophil counts, lymphocyte counts, monocyte counts, κ/λ ratio, B2MG, number of elotuzumab treatments, number of prior regimens and prior use of daratumumab. A multivariate analysis was conducted for all the variables except the high-risk cytogenic abnormalities that showed p values of less than 0.1 in a univariate analysis. Presence of high-risk cytogenetic abnormality was excluded from the multivariate analysis because more than 40% of cases lacked the requisite data. We also adjusted the OS by the significant factors in multivariate analysis.

To establish a predictive model for the durability of elotuzumab treatment, we used two different sets of multivariate analyses. We used two different parameters to estimate the tumor burden of myeloma: the κ/λ ratio and B2MG. In model 1, we adapted the type of treatment regimen, the κ/λ ratio and the lymphocyte counts which showed significant correlation with TTNT on univariate analysis as parameters. In model 2, we adapted the type of treatment regimen, the B2MG and the leukocyte fractions which showed significant correlation with TTNT on univariate analysis as parameters. As we found weak correlation between WBC counts and lymphocyte counts (correlation coefficient: 0.585) and very weak correlation between monocyte counts and WBC counts (correlation coefficient: 0.468) or lymphocyte counts (correlation coefficient: 0.339), we selected lymphocyte counts in our models. We used C statistics (C-index) to evaluate the predictive accuracy of the models[20,21]. The c-index of an ideal test became closer to 1.0. We used the bootstrap method to validate our results of the scoring system[22,23]. In each step, 1000 bootstrap samples with replacements were created from the dataset. All statistical analyses were performed using the EZR (ver. 1.54) software package (Saitama Medical Center/Jichi Medical University, Saitama, Japan)[24] along with a graphical user interface for the R software package (ver. 4.0.3; The R Foundation for Statistical Computing) or SPSS software (ver. 28; IBM, USA). *P*-values < 0.05 were considered significant in all analyses.

Ethical approval. All procedures performed in this study involving the patient were in accordance with the ethical standards of Kyoto University Graduate School and Faculty of Medicine, Ethics Committee institutional (approval no. R2887, approved date: January 6th, 2022) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The informed consent requirement for this retrospective study was waived by Kyoto University Graduate School and Faculty of Medicine, Ethics Committee institutional because the study was conducted retrospectively and the opportunity to refuse was guaranteed.

Results

TTNT of elotuzumab in relapsed MM. The characteristics of patients are summarized in Table 1. A total of 201 elotuzumab treatments in 179 patients were analyzed. The median age at the elotuzumab treatment was 71 years. The numbers of patients treated with ERd regimen and EPd regimen were 146 (72.6%) and 55 (27.4%), respectively. The median number of prior regimens was 4, and about 90% of cases were treated with immunomodulatory drugs and/or proteasome inhibitors prior to elotuzumab treatment. Daratumumab was used in 53 (26.4%) cases. Elotuzumab was administered for a second time in 22 (10.9%) cases: 16 cases received ERd followed by EPd regimen, 5 cases received ERd followed by ERd regimen and 1 case received EPd followed by EPd regimen. A histogram of the laboratory data is shown in Suppl. Fig. S1. The number of patients showing a response to elotuzumab, which included those with a CR, VGPR or PR, was 83 (41.3%) in this cohort (Fig. S3).

TTNT of elotuzumab was 6.29 months (with a 95% CI of 5.18–9.20: Fig. 1A). When we compared the TTNT according to the regimen, the TTNTs of the ERd regimen and EPd regimen were 7.10 (5.49–9.99) and 4.86 (2.99–9.92) months, respectively (Fig. S4A; $p = 0.076$). The TTNTs of the first and second administrations of elotuzumab were 7.00 (5.36–9.89) and 4.86 (1.38–9.93) months, respectively (Fig. S4B, $p = 0.149$).

The underlying factors affecting the TTNT of elotuzumab. To analyze the underlying factors affecting the TTNT of elotuzumab treatment, we analyzed two parameters: the κ/λ ratio and B2MG. The TTNT of elotuzumab treatment was longer in the patients with a non-deviated κ/λ ratio (κ/λ ratio of 0.1–10) ($p < 0.001$; Fig. 1B and Table 2) and in patients with a lower B2MG (< 5.5 mg/L) ($p = 0.001$; Fig. 1C, Table 2 and Fig. S2B) before elotuzumab treatment. When we analyzed the TTNT according to WBC and lymphocyte counts, the patients with higher WBC counts (≥ 3500/μl) before elotuzumab treatment showed longer TTNT than the patients with lower WBC counts ($p = 0.004$; Fig. 1D and Table 2). The patients with higher lymphocyte counts (≥ 1400/μl) showed longer TTNT ($p = 0.011$, Fig. 1E, Table 2 and Fig. S2A). There was no correlation between TTNT and neutrophil or monocyte counts (Table 2 and Fig. S5A-B).

We performed a univariate analysis to clarify other factors correlated with TTNT and found that patients with the following showed better TTNT: no high risk cytogenic abnormalities, fewer than 4 prior regimens, and no prior daratumumab use (Table 2 and Fig. S6A,B). The TTNT of the patients with prior use of daratumumab was shorter (8.97 months vs 3.65 months), and this relation was independent of the period from the last daratumumab

		Elotuzumab treatment
Number of patients		179
Total number of treatments		201
Median age (years) at elotuzumab treatment	Median (range)	71 (20–87)
Gender	Male	100 (55.9%)
	Female	79 (44.1%)
Type of treatment regimen	ERd	146 (72.6%)
	EPd	55 (27.4%)
Type of heavy chain	IgG	115 (64.2%)
	IgA	31 (17.3%)
	IgM	2 (1.1%)
	Not detected	31 (17.3%)
Type of light chain	λ	73 (40.8%)
	κ	105 (58.7%)
	NA	1 (0.6%)
ISS stage at diagnosis	I	53 (29.6%)
	II	64 (35.8%)
	III	48 (26.8%)
	NA	14 (7.8%)
High risk cytogenic abnormality	del (17)	12 (6.7%)
	t(4;14)	12 (6.7%)
	t(14;16)	3 (1.7%)
	None of above abnormalities	78 (43.6%)
	NA	74 (41.3%)
Laboratory data before elotuzumab treatment		
White blood cell count (/μL, median, range)		3600 (900–11,900)
Neutrophil count (/μL, median, range)		2019 (216–8888)
Lymphocyte count (/μL, median, range)		1065 (39–4403)
Monocyte count (/μL, median, range)		284 (13–1420)
Free light chain (mg/L, median, range)	κ	17.8 (0–6010)
	λ	13.6 (0–10,900)
	κ/λ ratio	1.1 (0.001–3320)
B2MG (mg/L, median, range)		2.9 (0.15–30.7)
IgG (mg/dL, median, range)		788 (45–10,500)
IgA (mg/dL, median, range)		42 (1–4813)
IgM (mg/dL, median, range)		14 (1–2286)
Bone marrow infiltration of plasma cell (%)	Median (range)	4.6 (0.0–78.7)
Prior regimen numbers	Median (range)	4 (1–20)
Prior treatments	IMIDs	181 (90.0%)
	PI	184 (91.5%)
	Daratumumab	53 (26.4%)
	Elotuzumab	22 (10.9%)
	Autologous SCT	64 (35.8%)
	Allogenic SCT	3 (1.7%)
Follow-up period of survivors (median days, range)		553 (14–1726)

Table 1. Characteristics of multiple myeloma patients. The characteristics of multiple myeloma patients who were treated with elotuzumab are shown in Table 1. Laboratory data were collected before the elotuzumab treatment. ERd, EPd, NA, IMIDs, PI and B2MG. ERd: elotuzumab, lenalidomide and dexamethasone regimen; EPd: elotuzumab, pomalidomide and dexamethasone regimen; NA: not available; IMIDs: immunomodulatory drugs; PI: proteosome inhibitor; B2MG: β_2 microglobulin; SCT: stem cell transplantation.

administration to the elotuzumab treatment (Fig. S6C). Also, the patients with prior use of daratumumab had lower lymphocyte counts (Fig. S7).

Prediction model for elotuzumab treatment. Next, we performed a multivariate analysis to determine factors related to the TTNT of elotuzumab; we included all factors that showed p values of less than 0.1 in the univariate analysis. The factors independently associated with superior TTNT were lymphocyte counts ≥ 1400/

μL ($p = 0.009$), non-deviated κ/λ ratio ($p = 0.050$), B2MG < 5.5 mg/L ($p = 0.008$) and nonuse of daratumumab before elotuzumab treatment ($p < 0.001$; Table 3).

From these results, we proposed a new model to predict the durability of the effect (longer TTNT) of elotuzumab treatment. We first made a model using three factors: lymphocyte counts, κ/λ ratio and B2MG. Although we did not observe a strong correlation between the κ/λ ratio and B2MG, when we categorized the cases by all three factors, we found a strong correlation between the cases categorized by the κ/λ ratio and B2MG. Therefore, we divided the cases into two different multivariate models (model 1 and model 2) using one of these two factors (κ/λ ratio and B2MG) reflecting the tumor burden. We then classified the patients into three categories based on (1) the lymphocyte counts and κ/λ ratio (model 1) or (2) the lymphocyte counts and B2MG (model 2). We assigned 0 points to patients with lymphocyte counts of 1400/μl or more and 1 point to those with lymphocyte counts of less than 1400/μl. We also scored 0 points to patients having a κ/λ ratio of 0.1–10 and 1 point to those having a κ/λ ratio of less than 0.1 or 10 or more. We confirmed that the scoring system (model 1) was significantly correlated with the TTNT of elotuzumab treatment in multivariate analysis (Table 4). We also corrected the TTNT of our models with the prior regimen numbers and the prior use of daratumumab (Fig. 2A). The patients with a total score of 0 showed significantly longer TTNT compared to those with scores of 1 or 2 ($p < 0.001$, Fig. 2A). This result was confirmed by bootstrap methods (Table 4). Moreover, when we analyzed the OS after the elotuzumab treatment only for the patients with first elotuzumab treatment, we found that the patients with a total score of 0 or 1 showed significantly superior OS than the patients with a total score of 2 ($p < 0.001$, Fig. 2B). The c-index of model 1 was 0.728.

Next, we assigned the patients scores according to their lymphocyte counts in the same way as in model 1. We also scored the patients with a B2MG of less than 5.5 mg/L with 0 points and those with a B2MG of 5.5 mg/L or more with 1 point. The patients with a total score of 0 or 1 showed significantly longer TTNT compared to those with a score of 2 ($p < 0.001$, Fig. 2C). The scoring system (model 2) was significantly correlated with the TTNT of elotuzumab treatment in multivariate analysis, and this result was also confirmed by bootstrap methods (Table 4). The TTNT of model 2 was also corrected with prior use of daratumumab (Fig. 2C). When we analyzed the OS after elotuzumab treatment only for the patients with first elotuzumab treatment, we also found that the patients with total scores of 0 and 1 showed significantly superior OS compared to the patients with a total score of 2 ($p < 0.001$, Fig. 2D). The c-index for model 2 was 0.641. We applied these models to each treatment regimen and confirmed that both models fit both regimens (Figs. S8A,B and S9A,B).

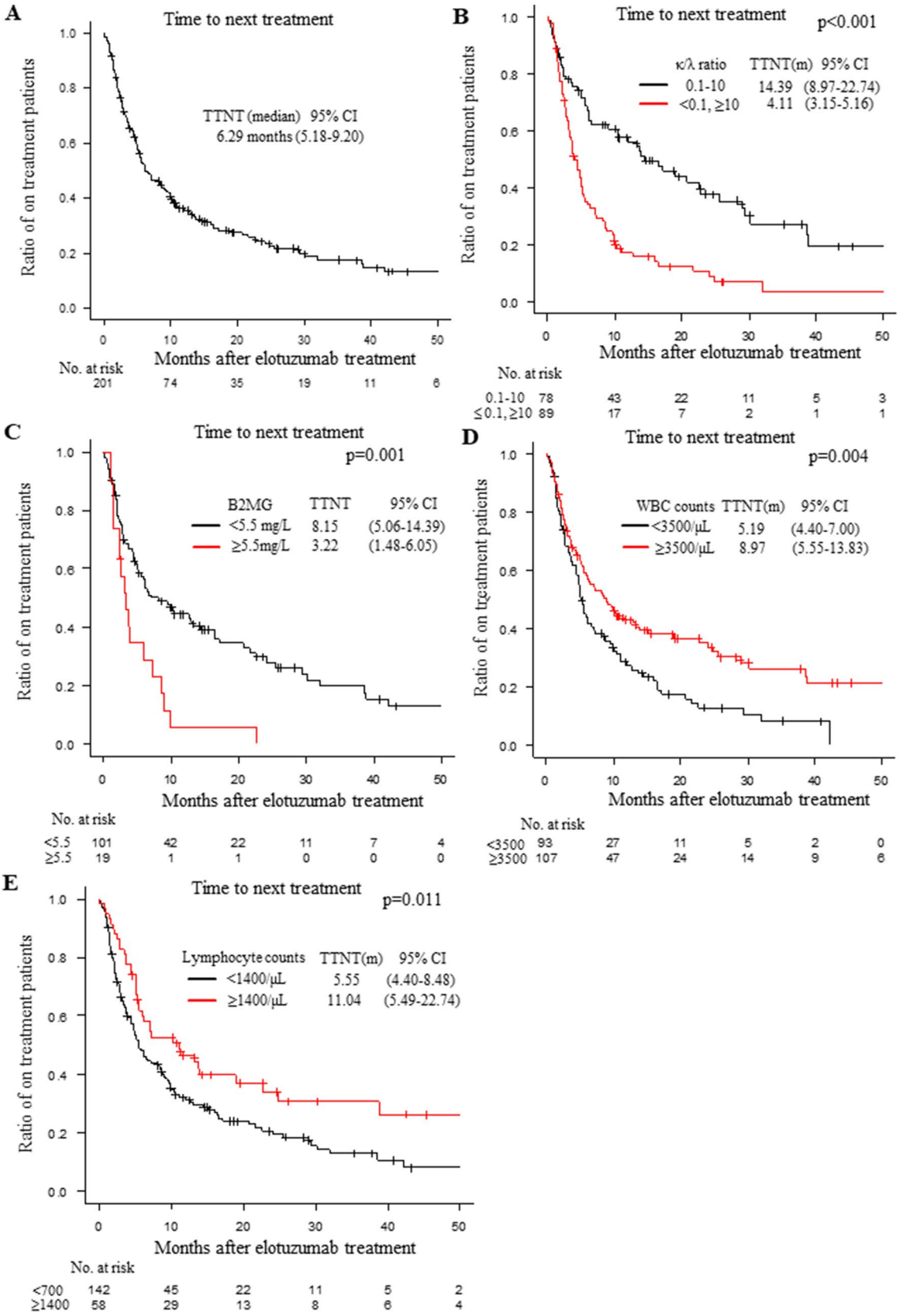
Therefore, we conclude that by using this simple model, we could predict the patients who would exhibit a durable response (longer TTNT) to elotuzumab treatment (Fig. S10).

Discussion

Repeated chemotherapy against cancer and hematological malignancy frequently leads to severe lymphopenia. Moreover, lymphopenia has long been associated with poor prognosis not only in lymphoma but also other cancers[13–15]. Recently, an association between the pretreatment lymphocyte count and the efficacy of immune checkpoint inhibitors was reported in patients with head and neck squamous cell carcinoma[25]. Also there is a report that the similarity of a patient's immune cell composition to that of healthy donors may have prognostic relevance at diagnosis and after ERd treatment in high risk smoldering myeloma[26]. We hypothesized that the efficacy of elotuzumab could be predicted by the balance between the tumor burden of myeloma and host immune cells. To prove our concept, we chose the κ/λ ratio and B2MG as candidate biomarkers for representing the tumor burden of myeloma. We also selected WBC and lymphocyte counts as indices of the host immune status. The present study demonstrated that the simple model using the κ/λ ratio (or B2MG), and lymphocyte counts easily predicted the durable efficacy of elotuzumab treatment. Patients with a total score of 0, who had a low tumor burden (non-deviated κ/λ ratio level or lower B2MG) and preserved host immune cells (higher lymphocyte counts), were the best candidates for elotuzumab treatment. They could obtain the benefit of elotuzumab treatment for long duration with better prognosis. Because a previous report showed that the neutrophil-to-lymphocyte ratio is correlated with the prognosis of MM[27], we also analyzed neutrophil counts, monocyte counts, the neutrophil/lymphocyte ratio and the monocyte/lymphocyte ratio as indices of host immunity. However, none of these parameters was correlated with the TTNT of elotuzumab (data not shown). Our scoring system could identify the scenarios where elotuzumab might find itself more useful, the usefulness of our scoring system needs to be substantiated by other treatment for MM in other cohort studies.

Since soluble SLAMF7 (sSLAMF7) impaired anti-SLAMF7 antibody mediated ADCC activity, sSLAMF7 levels could be a predictive biomarker for elotuzumab therapy[28,29]. However, it is difficult to predict the best treatment response of elotuzumab beforehand at the present, since the measurement of sSLAMF7 is not available in clinical practice. Our study design focused on TTNT in order to establish a model for predicting patients with a durable response to elotuzumab treatment. When we compared the c-index values of each model, we found that the c-indices of model 1 and model 2 for the ERd regimen were 0.722 and 0.592, respectively. On the other hand, the c-indices of model 1 and model 2 for the EPd regimen were 0.693 and 0.76, respectively. We plan to use model 1 for future study because the c-index in model 1 was higher than that of model 2 as a whole, and also the κ/λ ratio is more frequently analyzed than B2MG in clinical practice in Japan.

We acknowledge that universal prognostic markers, such as B2MG or International Staging System (ISS), which mainly reflect tumor burden, correlated with the TTNT of elotuzumab treatment[2,6]. However, the c-index of our predictive models (model 1: 0.728, model 2: 0.641) are higher than that of B2MG (0.518) or of ISS (0.625). Also, by adding the parameters which correlate to host immune status to the universal prognostic markers, we could more efficiently select the proper patients for elotuzumab treatment as shown in score 1 in model 1 and model 2. Our results indicate that elotuzumab treatments were particularly effective to those with higher lymphocyte counts. These results are supported by the previous reports which demonstrated that elotuzumab could


A
Time to next treatment
TTNT (median) 95% CI
6.29 months (5.18-9.20)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
201 74 35 19 11 6
B
Time to next treatment
p<0.001
κ/λ ratio TTNT(m) 95% CI
0.1-10 14.39 (8.97-22.74)
<0.1, ≥10 4.11 (3.15-5.16)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
0.1-10 78 43 22 11 5 3
≤0.1, ≥10 89 17 7 2 1 1
C
Time to next treatment
p=0.001
B2MG TTNT 95% CI
<5.5 mg/L 8.15 (5.06-14.39)
≥5.5mg/L 3.22 (1.48-6.05)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<5.5 101 42 22 11 7 4
≥5.5 19 1 1 0 0 0
D
Time to next treatment
p=0.004
WBC counts TTNT(m) 95% CI
<3500/μL 5.19 (4.40-7.00)
≥3500/μL 8.97 (5.55-13.83)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<3500 93 27 11 5 2 0
≥3500 107 47 24 14 9 6
E
Time to next treatment
p=0.011
Lymphocyte counts TTNT(m) 95% CI
<1400/μL 5.55 (4.40-8.48)
≥1400/μL 11.04 (5.49-22.74)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<700 142 45 22 11 5 2
≥1400 58 29 13 8 6 4

◂**Figure 1.** (**A**) The time to next treatment (TTNT) of the multiple myeloma (MM) patients treated with elotuzumab. The median TTNT (months) and 95% CI are shown. (**B**) The TTNT of the MM patients treated with elotuzumab classified according to the κ/λ ratio: 0.1 to 10 (*black*) and less than 0.1 or 10 or more (*red*). The median TTNT (months) and 95% CI are shown. (**C**) The TTNT of the MM patients treated with elotuzumab according to the β_2 microglobulin (B2MG); less than 5.5 mg/L (*black*) and 5.5 mg/L or more (*red*). The median TTNT (months) and 95% CI are shown. (**D**) The TTNT of the MM patients treated with elotuzumab classified according to the white blood cell (WBC) counts: less than 3500/μL (*black*) and 3500/μL or more (*red*). The median TTNT (months) and 95% CI are shown. (**E**) The TTNT of the MM patients treated with elotuzumab classified according to the lymphocyte counts: less than 1400/μL (*black*) and 1400/μL or more (*red*). The median TTNT (months) and 95% CI are shown. The number of patients at risk in each group is shown in the lower panel of each figure. CI: confidence interval.

change the immune-suppressive tumor microenvironment to enhance anti-tumor effect by blocking SLAMF7 signaling and eliminating immunosuppressive T cells[30–32]. Although the TTNT of the patients with a total score of 1 was shorter than the TTNT of the patients with a total score of 0 in model 1, the OS after the first elotuzumab treatment was nearly equivalent to that of the patients with a total score of 0. The same trend was also observed in model 2. Although the durability of elotuzumab treatment for patients with a total score of 1 was limited, we consider that the following treatment after elotuzumab improved the prognosis of these patients. It is also worth mentioning that the elotuzumab treatment did not interfere with the subsequent treatment regimens in these patients. Therefore, elotuzumab is a suitable treatment option for both types of patients—i.e., those with a total score of 0 or 1. Because the patients with a score of 2 showed shorter TTNT of elotuzumab treatment and worse prognosis after the first elotuzumab treatment compared to those with a score of 0 or 1, we might consider a treatment other than elotuzumab for these patients.

The present study also showed that the effectiveness of elotuzumab was attenuated by the prior use of daratumumab. The mechanism of action of elotuzumab in MM patients involves the activation of natural killer (NK) cells through both CD16-mediated antibody dependent cellular cytotoxicity and direct co-stimulation via engagement with SLAMF7 as well as promoting antibody-dependent cellular phagocytosis by macrophages[7,8,33]. As it has been reported that daratumumab decreases the number of NK cells, the depletion of NK cells via daratumumab could attenuate the effectiveness of elotuzumab[7,8,33,34]. Since we do not routinely check the NK cell counts in practice, we could not confirm the existence of this mechanism. However, higher lymphocyte counts may be a prerequisite for the higher NK cell counts, which needs to be confirmed by another study. We interpreted that the sequence of treatment is important. As daratumumab is more frequently used as a front- or early-line therapy today, candidates for elotuzumab treatment are limited to patients with a low tumor burden after treatment with protease inhibitors and/or immunomodulatory drugs without daratumumab treatment. As the effectiveness of elotuzumab could be attenuated by the prior use of daratumumab, it might be useful to use daratumumab after elotuzumab treatment.

There are limitations in this study. First, this was a retrospective observation study in which the individual physicians decided the treatment. Because this was not a randomized prospective study, a potential selection bias for elotuzumab treatment cannot be ruled out and could not be controlled for in the multivariate analysis. We adapted boot strap method to perform internal validation. However, it was difficult to confirm external validation in our cohort because of the limited number of analyzed patients. Therefore, prospective cohort studies of elotuzumab treatment will be needed to substantiate our results. Second, we could not include the data regarding high-risk cytogenetic abnormalities in our multivariate analysis due to limited data. As high-risk cytogenic abnormalities are one of important prognostic factors, this should also be validated by other studies. Third, we could not analyze the detailed fraction of lymphocytes (such as CD4 + T cells, CD8 + T cells, regulatory T cell, etc.) for further understating the mechanism of elotuzumab. In spite of these limitations, to our knowledge this is the first study to demonstrate that the efficacy of elotuzumab, and potentially other immunotherapies could be predicted by the balance between the tumor burden and host immune status. The strength of our study lies in the point that we tried to identify the predictive markers for elotuzumab treatment using the factors which are easily available in actual clinical practice.

In conclusion, we proposed a new scoring system using lymphocyte counts and the κ/λ ratio or B2MG to predict the TTNT of elotuzumab treatment. This scoring system would be useful for differentiating patients who could benefit from elotuzumab treatment.

Data availability

The KMF database is only available to the KMF members. However, the data of this study are available from the corresponding author, JK, upon reasonable request.

Factors		Univariate analysis		
		TTNT (months)	95% CI	*p*-value
Age at elotuzumab treatment	< 65 years	7	3.58–9.66	0.191
	≥ 65 years	6.08	5.09–10.28	
Gender	Male	6.21	5.19–9.99	0.954
	Female	6.08	4.40–10.05	
Type of treatment regimen	ERd	7.1	5.49–9.99	0.076
	EPd	4.86	2.99–9.92	
High risk cytogenic abnormalities	None	11.96	7.10–17.08	0.002
	One or more	5.09	2.10–6.51	
White blood cell counts	< 3500/μl	5.19	4.40–7.00	0.004
	≥ 3500/μl	8.97	5.55–13.83	
Neutrophil counts	< 3000/μl	6.05	4.90–8.74	0.102
	≥ 3000/μl	8.64	4.40–22.74	
Lymphocyte counts	< 1400/μl	5.55	4.40–8.48	0.011
	≥ 1400/μl	11.04	5.49–22.74	
Monocyte counts	< 300/μl	6.21	4.90–12.68	0.311
	≥ 300/μL	10.32	6.05–17.08	
κ/λ ratio	0.1–10	14.39	8.97–22.74	< 0.001
	< 0.1, ≥ 10	4.11	3.15–5.16	
B2MG	< 3.5 mg/L	8.15	5.06–14.39	0.001
	≥ 3.5 mg/L	3.22	1.48–6.05	
Number of treatments	First	7	5.36–9.89	0.149
	Second	4.86	1.38–9.92	
Prior regimen numbers	< 4	18.96	7.10-NA	< 0.001
	≥ 4	5.36	4.50–7.13	
Prior use of daratumumab	No	8.97	5.85–13.17	< 0.001
	Yes	3.65	2.30–5.49	

Table 2. Univariate analysis for TTNT. TTNT was calculated from the time of elotuzumab treatment to the time of next treatment. Univariate analyses against TTNT in MM patients treated with elotuzumab were performed for each factor. The log-rank test was used for comparisons among groups. TTNT (months) is shown with the 95% confidence interval (CI) and *p*-value. TTNT, CI, ERd, EPd, B2MG and NA. TTNT: time to next treatment; CI: confidence interval; ERd: elotuzumab, lenalidomide and dexamethasone regimen; EPd: elotuzumab, pomalidomide and dexamethasone regimen; B2MG: β_2 microglobulin; NA: not available.

Factors		Multivariate analysis		
		Hazard ratio	95% CI	*p*-value
Type of treatment regimen	ERd	1		0.202
	EPd	0.694	0.395–1.217	
White blood cell counts	< 3500/μl	1		0.776
	≥ 3500/μl	0.935	0.591–1.481	
Lymphocyte counts	< 1400/μl	1		0.009
	≥ 1400/μl	0.491	0.289–0.835	
κ/λ ratio	0.1–10	1		0.05
	< 0.1, ≥ 10	1.628	0.999–2.653	
B2MG	< 5.5 mg/L	1		0.008
	≥ 5.5 mg/L	2.09	1.212–3.605	
Prior regimen numbers	< 4	1		0.088
	≥ 4	1.718	0.923–3.198	
Prior use of daratumumab	No	1		< 0.001
	Yes	3.009	1.815–4.989	

Table 3. Multivariate analysis for TTNT. Multivariate analyses against TTNT in MM patients treated with elotuzumab were performed using the factors that showed $p < 0.1$ in univariate analysis. The Cox proportional hazard model was used to calculate the hazard ratio for each variable; the 95% CI and *p*-value are shown. TTNT, CI, ERd, EPd and B2MG. TTNT: time to next treatment; CI: confidence interval; ERd: elotuzumab, lenalidomide and dexamethasone regimen; EPd: elotuzumab, pomalidomide and dexamethasone regimen; B2MG: β_2 microglobulin.

Factors		Model 1				Model 2			
		Hazard ratio	95% CI	*p*-value	*p*-value*	Hazard ratio	95% CI	*p*-value	*p*-value*
Type of treatment regimen	ERd	1		0.143	0.151	1		0.431	0.432
	EPd	0.713	0.453–1.121			0.801	0.460–1.393		
Lymphocyte Free light chain score	0	1		< 0.001	< 0.001				
	1	2.395	1.236–4.639						
	2	4.069	2.063–8.026						
Lymphocyte B2MG score	0					1		< 0.001	< 0.001
	1					2.123	1.178–3.829		
	2					4.608	2.144–9.904		
Prior regimen numbers	< 4	1		0.009	0.007	1		0.292	0.228
	≥ 4	1.967	1.178–3.285			1.358	0.768–2.399		
Prior use of daratumumab	No	1		0.021	0.005	1		< 0.001	< 0.001
	Yes	1.627	1.075–2.463			3.247	1.974–5.343		

Table 4. Multivariate analysis for TTNT. Multivariate analyses against TTNT in MM patients treated with elotuzumab were performed using the scoring system (model 1 and model 2) as factors. In model 1, we picked up the following factors: type of treatment regimen, WBC counts, lymphocyte free light chain score, number of prior regimens and prior use of daratumumab. In model 2, we picked up the following factors: type of treatment regimen, WBC counts, lymphocyte B2MG score, number of prior regimens and prior use of daratumumab. The Cox proportional hazard model was used to calculate the hazard ratio for each variable; the 95% CI and *p*-value are shown. **P*-value after the bootstrapping process (1000 samples). TTNT, CI, ERd, EPd and B2MG. TTNT: time to next treatment; CI: confidence interval; ERd: elotuzumab, lenalidomide and dexamethasone regimen; EPd: elotuzumab, pomalidomide and dexamethasone regimen; B2MG: β_2 microglobulin.

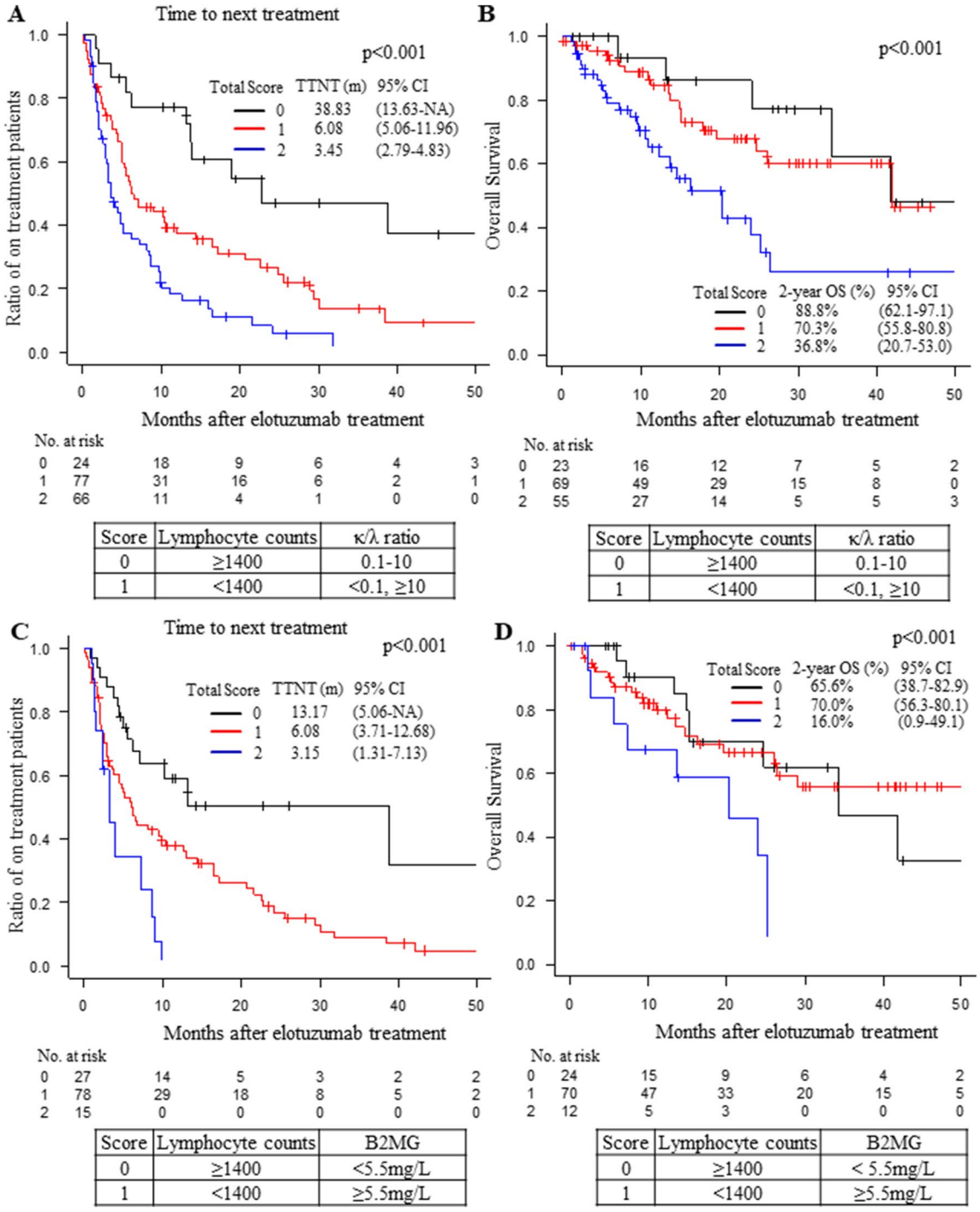


Figure 2. (**A**) The TTNT of the MM patients treated with elotuzumab according to a three-point scoring system: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). Total scores were calculated according to the lymphocyte counts (0 points when ≥ 1400/μL and 1 point when < 1400/μL) and κ/λ ratio (0 points when 0.1–10 and 1 point when < 0.1 or ≥ 10) before elotuzumab treatment (model 1). The median TTNT (months) and 95% CI are shown in the figure. The TTNT values were corrected by the prior regimen numbers and the prior use of daratumumab. NA indicates not applicable. (**B**) The overall survival (OS) of the MM patients treated with elotuzumab according to the scoring system of model 1: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). Only the patients with the first use of elotuzumab were analyzed. The 2-year OS of each group and 95% CI are shown in the figure. The OS values were corrected by the prior regimen numbers and the prior use of daratumumab. (**C**) The TTNT of the MM patients treated with elotuzumab according to the scoring system of model 2: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). Total scores were calculated according to the lymphocyte counts (0 points when ≥ 1400/μL and 1 point when < 1400/μL) and β_2 microglobulin (B2MG; 0 points when 5.5 mg/L and 1 point when ≥ 5.5 mg/L) before elotuzumab treatment (model 2). The median TTNT (months) and 95% CI are shown in the figure. The TTNT values were corrected by the prior use of daratumumab. NA indicates not applicable. (**D**) The overall survival (OS) of the MM patients treated with elotuzumab according to the scoring system of model 2: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). Only the patients with the 1st use of elotuzumab were analyzed. The 2-year OS of each group and 95% CI are shown in the figure. The OS values were corrected by the prior use of daratumumab. The number of patients at risk in each group is shown in the lower panel of each figure. CI: confidence interval.

Received: 13 December 2022; Accepted: 27 March 2023
Published online: 29 March 2023

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Acknowledgements

This study was conducted by the support of the KMF. The authors would like to thank all the myeloma patients registered in KMF and all the KMF investigators, particularly Ms. Okuyama, for their scientific supports.

Author contributions

Y.S. and J.K. performed the research, collected data, analyzed data and wrote the paper; S.K., T.I., H.K., Y.S., S.F., K.F., H.T., S.Y., K.O., R.Y., Y.T., H.U., Y.O., Y.A., H.H., R.T., M.M., T.T. performed the research and collected data. K.I., N.U., H.Y., H.S., T.M., M.H., N.H., S.N., I.M., C.S., A.T.-K. and J.K. supervised the study and performed writing reviewing.

Funding
The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests
J. Kanda received honorarium from Bristol-Myers Squibb Co., Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Sanofi K.K. and Ono Pharmaceutical Co., Ltd., and is an advisory role in Janssen Pharmaceutical K.K, and Novartis Pharma K.K. T.I. honorarium from Bristol-Myers Squibb Co., Takeda Pharmaceutical Co., Ltd. and Sanofi K.K.; and research funding from Bristol-Myers Squibb Co. K.I. received honorarium from Bristol-Myers Squibb Co., Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Novartis Pharma K.K., Kyowa Kirin Co., Ltd., Celgene K.K., Nippon Shinyaku Co., Ltd., Chugai Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co. Ltd., Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd. and Meiji Seika Pharma Co. Ltd. S.F. received honorarium from Takeda Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Sanofi K.K., Ono Pharmaceutical Co., Ltd., and Bristol-Myers Squibb Co. H.T. received personal fees from Bristol-Myers Squibb Co. (Celgene K.K.), personal fees from Novartis Pharma K.K., grants from Kyowa Kirin Co., Ltd. H.S. reports honoraria from Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Novartis Pharma K.K., Celgene K.K., Janssen Pharmaceutical K.K., Chugai Pharmaceutical Co., Ltd., Sanofi K.K., AstraZeneca K.K., AbbVie G.K., SymBio Pharmaceuticals Ltd., Eisai Co., Ltd., and Kyowa Kirin Co., Ltd.; and research funding from Pharma Essentia Japan K.K., Janssen Pharmaceutical K.K., Ono Pharmaceutical Co., Ltd., Celgene K.K., Novartis Pharma K.K., Sanofi K.K., AstraZeneca K.K., AbbVie G.K., Eisai Co., Ltd., HUYA Bioscience International, LLC., and Chugai Pharmaceutical Co., Ltd.; and scholarship endowment from Astellas Pharma Inc., Teijin Pharma Ltd., Shionogi & Co., Ltd., Eisai Co., Ltd., Sanofi K.K., Taiho Pharmaceutical Co., Ltd., and Nippon Shinyaku Co., Ltd. I.M. received personal fees from Bristol-Myers Squibb Co. (Celgene K.K.), personal fees from Novartis Pharma K.K., grants and personal fees from Otsuka Pharmaceutical Co., Ltd., personal fees from Pfizer Japan Inc., during the conduct of the study; grants from Ono Pharmaceutical Co., Ltd., personal fees from Janssen Pharmaceutical K.K, grants from Nippon Shinyaku Co., Ltd., grants from Kyowa Kirin Co., Ltd., grants from Sumitomo Dainippon Pharma Co., Ltd., grants from Shionogi & Co., Ltd., grants from Teijin Pharma limited., grants from Boehringer Ingelheim Co., Ltd., grants from Sanofi K.K., grants from Chugai Pharmaceutical Co., Ltd., grants from Eisai Co., Ltd., grants from MSD K.K, grants from Asahi Kasei Pharma Corporation, grants and personal fees from Astellas Pharma Inc., grants and personal fees from Takeda Pharmaceutical Co., Ltd., grants from Japan Blood Products Organization, grants from Nihon Pharmaceutical Co., Ltd., grants and personal fees from Daiichi Sankyo Co., Ltd., grants and personal fees from AbbVie GK, grants from Taiho Pharmaceutical Co., Ltd., grants from Mitsubishi Tanabe Pharma Corporation, grants from Nippon Kayaku Co., Ltd., grants from CSL Behring LLC, grants from Mundipharma K.K, grants from Ayumi Pharmaceutical Corporation, grants from Eli Lilly Japan K.K., grants from Actelion Pharmaceuticals Japan Ltd., personal fees from Amgen BioPharma K.K., outside the submitted work. C.S. received honoraria from Janssen Pharmaceutical K.K., Sanofi K.K., and Bristol-Myers Squibb. Co. A. Takaori-Kondo serves as an advisor for Megakaryon and receives research fundings from Ono Pharmaceutical Co., Ltd., DSK, and Cognano. J. Kuroda. received research funding from Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi K.K., Eisai, Bristol-Myers Squibb Co., Sysmex, Dainippon Sumitomo Pharma Co., Ltd., Nippon Shinyaku Co., Ltd., AbbVie GK, Teijin Pharma Ltd. and Otsuka Pharmaceutical Co., Ltd., has received honoraria from Janssen Pharmaceutical K.K, Kyowa Kirin Co., Ltd., Chugai Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi K.K., Eisai Co., Ltd., SymBio Pharmaceuticals Ltd., Bristol-Myers Squibb Co, Astellas Pharma Inc., Pfizer Japan Inc., Nippon Shinyaku Co., Ltd., Daiichi Sankyo Co., Ltd., Dainippon Sumitomo Pharma Co., Ltd., AbbVie GK and Otsuka Pharmaceutical Co., Ltd., and is a consultant for Janssen Pharmaceutical K.K, and Bristol-Myers Squibb Co. The other authors have no conflict of interest.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-023-32426-6.

Correspondence and requests for materials should be addressed to J.K.

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Supplemental Materials

Efficacy of elotuzumab for multiple myeloma in reference to lymphocyte counts and kappa/lambda ratio or B2 microglobulin

Yutaka Shimazu[1], Junya Kanda[1*], Satoru Kosugi[2], Tomoki Ito[3], Hitomi Kaneko[4], Kazunori Imada[4], Yuji Shimura[5], Shin-ichi Fuchida[6], Kentaro Fukushima[7], Hirokazu Tanaka[8], Satoshi Yoshihara[9], Kensuke Ohta[10], Nobuhiko Uoshima[11], Hideo Yagi[12], Hirohiko Shibayama[13], Ryosuke Yamamura[14], Yasuhiro Tanaka[15], Hitoji Uchiyama[16], Yoshiyuki Onda[17], Yoko Adachi[18], Hitoshi Hanamoto[19], Ryoichi Takahashi[20], Mitsuhiro Matsuda[21], Takashi Miyoshi[22], Teruhito Takakuwa[23], Masayuki Hino[23], Naoki Hosen[7], Shosaku Nomura[3], Chihiro Shimazaki[6], Itaru Matsumura[8], Akifumi Takaori-Kondo[1] and Junya Kuroda[5], Kansai Myeloma Forum[24]

Inventory of Supplemental Information

Figure S10.

Supplemental Figure Legends

Figure S1. (A-F) The histogram of white blood cell counts **(A)**, neutrophil counts **(B)**, monocyte counts **(C)**, lymphocyte counts **(D)**, β_2 microglobulin (B2MG) **(D)** and κ/λ ratio **(E)**. The horizontal axis was plot in log scale. The median, 25th percentile and 75th percentile values are described in the left upper panel of each figure.

Figure S2. (A) The time to next treatment (TTNT) of the multiple myeloma (MM) patients according to the β_2 microglobulin (B2MG) level: B2MG less than 3.5 mg/L (*black*), 3.5 mg/L or more to less than 5.5 mg/L (*red*) and 5.5 mg/L or more (*red*). The median TTNT (months) and 95% CI are shown. The hazard ratio (HR) of B2MG <3.5mg/L as a reference and 95% CI are also described. **(B)** TTNT of the MM patients according to the white blood cell (WBC) counts: less than 2500/μL (*black*), 2500/μL or more to less than 3500/μL (*red*), 3500/μL or more to less than 4500/μL (*blue*) and 4500/μL or more (*green*). The median TTNT (months) and 95% CI are shown. The HR of WBC counts <2500/μL and 95% CI are also described as a reference. **(C)** TTNT of the MM patients according to the lymphocyte counts: less than 700/μL (*black*), 700/μL or more to less than 1000/μL (*red*), 1000/μL or more to less than 1400/μL (*blue*) and 1400/μL or more (*green*). The median TTNT (months) and 95% CI are shown. The HR of lymphocyte counts <700/μL and 95% CI are also described as a reference. **(D)** TTNT of the MM patients according to the neutrophile counts: less than 1000/μL (*black*), 1000/μL or more to less than 2000/μL (*red*), 2000/μL or more to less than 3000/μL (*blue*) and 3000/μL or more (*green*). The median TTNT (months) and 95% CI are shown. The HR of neutrophile counts <1000/μL and 95% CI are also described as a reference. **(E)** TTNT of the MM patients according to the monocyte counts: less than 200/μL (*black*), 200/μL or

more to less than 300/μL (*red*), 300/μL or more to less than 400/μL (*blue*) and 400/μL or more (*green*). The median TTNT (months) and 95% CI are shown. The HR of monocyte counts <200/μL and 95% CI are also described as a reference. The number of patients at risk in each group is shown in the lower panel of each figure.
Abbreviations: CI. CI: confidence interval.

Figure S3. The proportion of the best treatment response against elotuzumab treatment. The overall response rate includes CR, VGPR and PR.
Abbreviations: CR, VGPR, PR, SD and PD. CR: complete remission; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease.

Figure S4. (A) The time to next treatment (TTNT) of the multiple myeloma (MM) patients according to the treatment regimen: elotuzumab, lenalidomide and dexamethasone (ERd, *black*) and elotuzumab, pomalidomide and dexamethasone (EPd, *red*). The median TTNT (months) and 95% CI are shown. **(B)** The TTNT of the MM patients according to the number of elotuzumab treatments: first time (*black*) and second time (*red*). The median TTNT (months) and 95% CI are shown. The number of patients at risk in each group is shown in the lower panel of each figure.
Abbreviations: CI. CI: confidence interval.

Figure S5. (A) The TTNT of the MM patients treated with elotuzumab according to the neutrophil counts: less than 3000/μL (*black*) and 3000/μL or more (*red*). **(B)** The TTNT of the MM patients treated with elotuzumab according to the monocyte counts: less than 300/μL (*black*) and 300/μL or more (*red*). The number of patients at risk in each group is

shown in the lower panel of each figure.

Abbreviations: CI. CI: confidence interval.

Figure S6. (A) The TTNT of the MM patients treated with elotuzumab according to the prior regimen number: fewer than 4 prior regimens (*black*) and 4 or more prior regimens (*red*). The median TTNT (months) and 95% CI are shown. NA indicates not applicable. **(B)** The TTNT of the MM patients treated with elotuzumab according to prior daratumumab use: nonuse of daratumumab (*black*) and prior use of daratumumab (*red*). The median TTNT (months) and 95% CI are shown. **(C)** The TTNT of the MM patients treated with elotuzumab according to the period from prior daratumumab use: less than 6 months (*black*) and 6 months or more (*red*). The median TTNT (months) and 95% CI are shown. The number of patients at risk in each group is shown in the lower panel of each figure.

Abbreviations: CI. CI: confidence interval.

Figure S7. Comparing the lymphocyte counts between prior use of daratumumab (not used or previously used). Average lymphocyte counts with standard deviation (SD) of each group were shown in the figure.

Figure S8. (A) The TTNT of the MM patients treated with elotuzumab, lenalidomide and dexamethasone (ERd) regimen according to the scoring system used in model 1: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). Total scores were calculated according to the lymphocyte counts (0 points when ≥1400/μL and 1 point when <1400/μL) and κ/λ ratio (0 points when 0.1-10 and 1 point when <0.1 or ≥10) before elotuzumab treatment

(model 1). The median TTNT (months) and 95% CI values are shown in the figure. The hazard ratio (HR) of total score 0 as a reference with 95% CI is also described. The TTNT values were corrected by the following factors: prior treatment regimen and the use of daratumumab before. **(B)** The TTNT of the MM patients treated with a regimen of elotuzumab, pomalidomide and dexamethasone (EPd) according to the scoring system used in model 1 and described above in panel **(A)**. The median TTNT (months) and 95% CI are shown in the figure. The hazard ratio (HR) of total score 0 as a reference with 95% CI is also described. The TTNT values were corrected by the following factors: prior treatment regimen and prior use of daratumumab. The number of patients at risk in each group is shown in the lower panel of each figure.
Abbreviations: CI and NA. CI: confidence interval; NA: not applicable.

Figure S9. (A) The TTNT of the MM patients treated with a regimen of elotuzumab, pomalidomide and dexamethasone (EPd) according to the scoring system used in model 1: 0 points (*black*), 1 point (*red*) and 2 points (*blue*). Total scores were calculated according to the lymphocyte counts (0 points when ≥1400/μL and 1 point when <1400/μL) and B2MG (0 points when less than 5.5mg/L and 1 point when 5.5mg/L or more) before elotuzumab treatment (model 2). The median TTNT (months) and 95% CI are shown in the figure. The hazard ratio (HR) of the total score 0 and 95% CI are also described as a reference. The TTNT values were corrected by the prior use of daratumumab. **(B)** The TTNT of the MM patients treated with a regimen of elotuzumab, pomalidomide and dexamethasone (EPd) according to the scoring system (model 1) as in panel **(A)**. The median TTNT (months) and 95% CI are shown in the figure. The hazard ratio (HR) of the total score 0 and 95% CI are also described as a reference. The TTNT

were corrected by the prior use of daratumumab. The number of patients at risk in each group is shown in the lower panel of each figure.

Abbreviations: CI and NA. CI: confidence interval; NA: not applicable.

Figure S10. The treatment algorithm according to the scoring system.

Figure S1

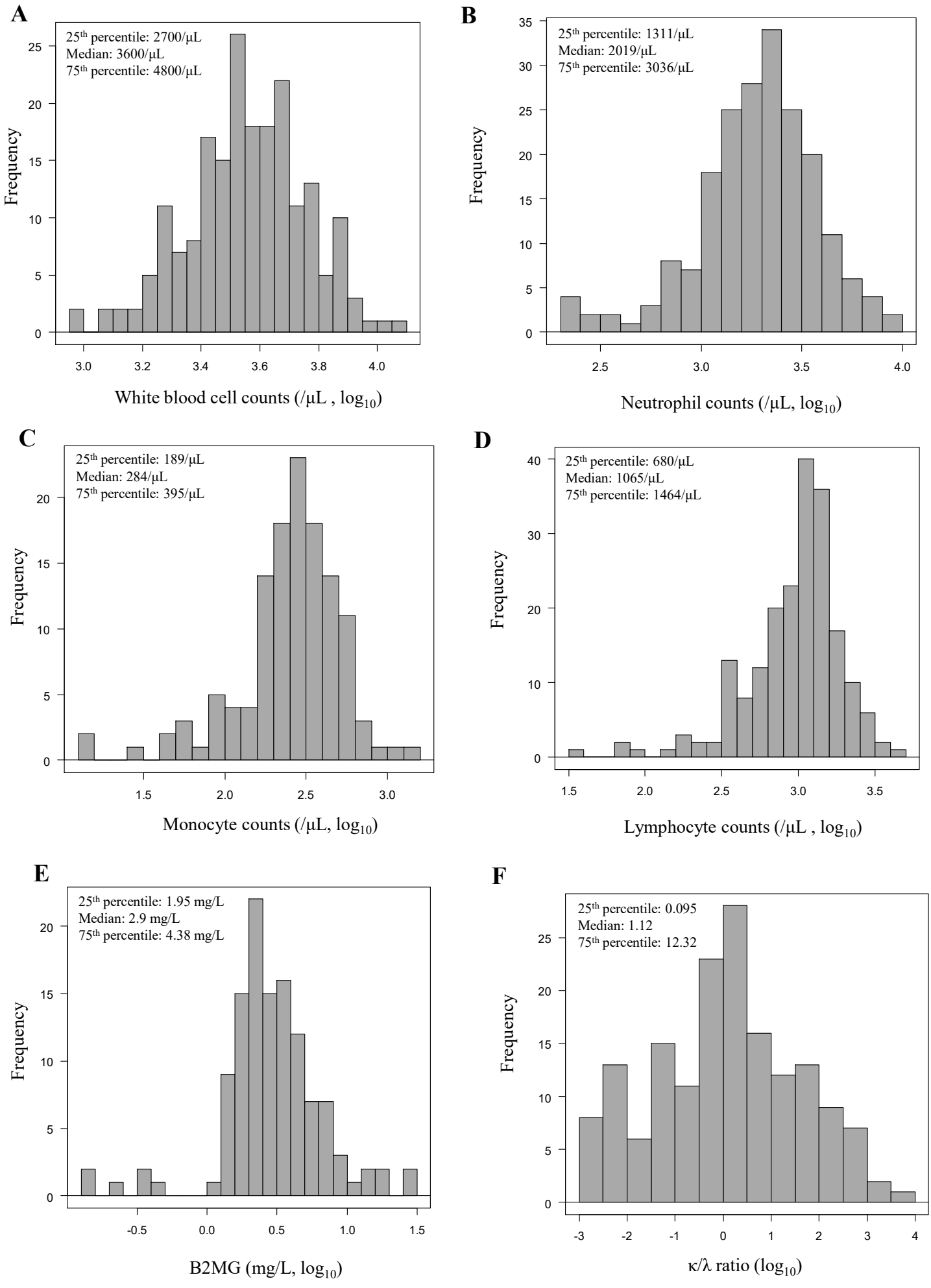

A
25th percentile: 2700/μL
Median: 3600/μL
75th percentile: 4800/μL
Frequency
White blood cell counts (/μL , log10)
B
25th percentile: 1311/μL
Median: 2019/μL
75th percentile: 3036/μL
Frequency
Neutrophil counts (/μL, log10)
C
25th percentile: 189/μL
Median: 284/μL
75th percentile: 395/μL
Frequency
Monocyte counts (/μL, log10)
D
25th percentile: 680/μL
Median: 1065/μL
75th percentile: 1464/μL
Frequency
Lymphocyte counts (/μL , log10)
E
25th percentile: 1.95 mg/L
Median: 2.9 mg/L
75th percentile: 4.38 mg/L
Frequency
B2MG (mg/L, log10)
F
25th percentile: 0.095
Median: 1.12
75th percentile: 12.32
Frequency
κ/λ ratio (log10)

Figure S2

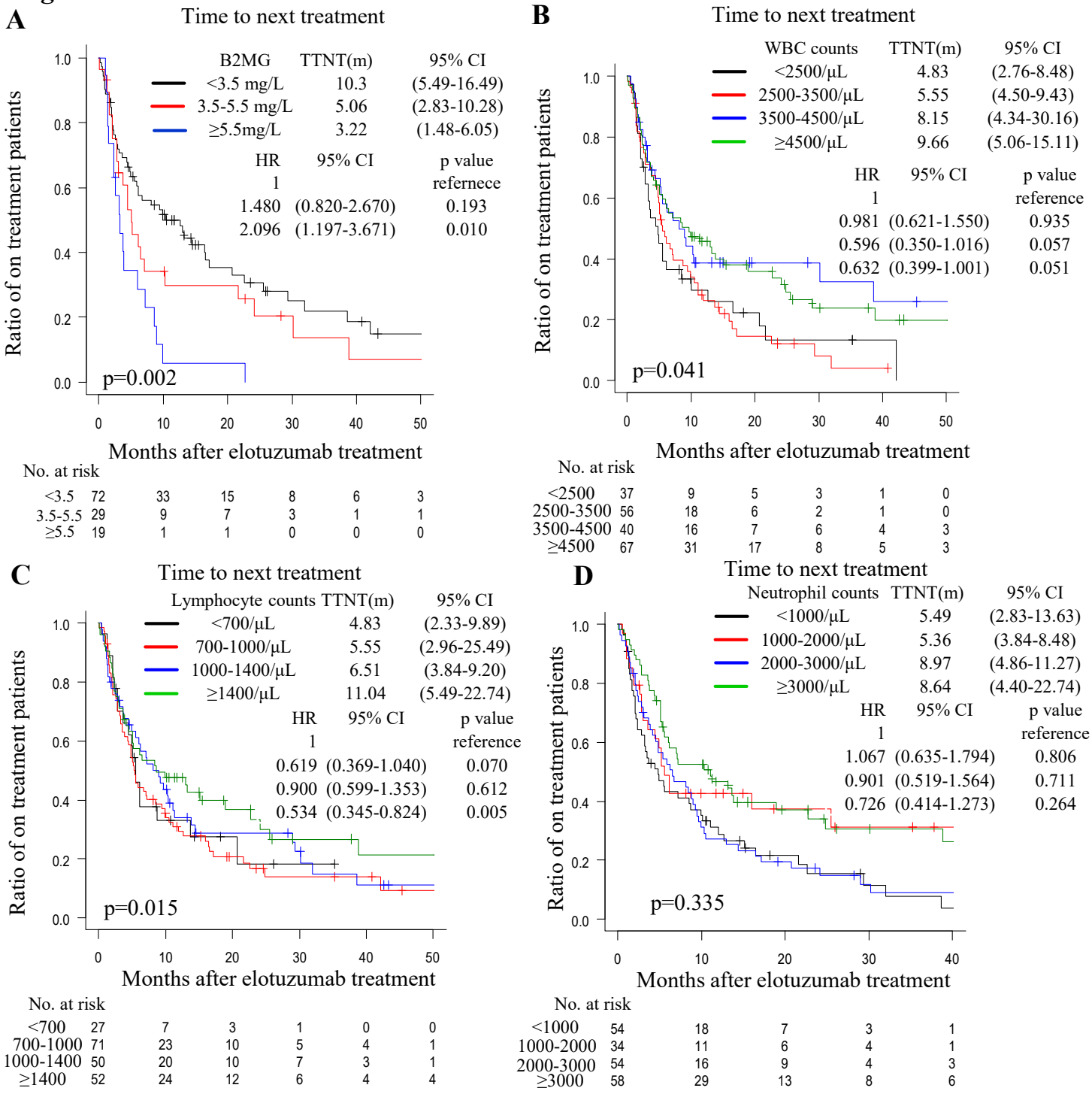

A
Time to next treatment
B2MG TTNT(m) 95% CI
<3.5 mg/L 10.3 (5.49-16.49)
3.5-5.5 mg/L 5.06 (2.83-10.28)
≥5.5mg/L 3.22 (1.48-6.05)
HR 95% CI p value
1 refernece
1.480 (0.820-2.670) 0.193
2.096 (1.197-3.671) 0.010
p=0.002
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<3.5 72 33 15 8 6 3
3.5-5.5 29 9 7 3 1 1
≥5.5 19 1 1 0 0 0
B
Time to next treatment
WBC counts TTNT(m) 95% CI
<2500/μL 4.83 (2.76-8.48)
2500-3500/μL 5.55 (4.50-9.43)
3500-4500/μL 8.15 (4.34-30.16)
≥4500/μL 9.66 (5.06-15.11)
HR 95% CI p value
1 reference
0.981 (0.621-1.550) 0.935
0.596 (0.350-1.016) 0.057
0.632 (0.399-1.001) 0.051
p=0.041
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<2500 37 9 5 3 1 0
2500-3500 56 18 6 2 1 0
3500-4500 40 16 7 6 4 3
≥4500 67 31 17 8 5 3
C
Time to next treatment
Lymphocyte counts TTNT(m) 95% CI
<700/μL 4.83 (2.33-9.89)
700-1000/μL 5.55 (2.96-25.49)
1000-1400/μL 6.51 (3.84-9.20)
≥1400/μL 11.04 (5.49-22.74)
HR 95% CI p value
1 reference
0.619 (0.369-1.040) 0.070
0.900 (0.599-1.353) 0.612
0.534 (0.345-0.824) 0.005
p=0.015
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<700 27 7 3 1 0 0
700-1000 71 23 10 5 4 1
1000-1400 50 20 10 7 3 1
≥1400 52 24 12 6 4 4
D
Time to next treatment
Neutrophil counts TTNT(m) 95% CI
<1000/μL 5.49 (2.83-13.63)
1000-2000/μL 5.36 (3.84-8.48)
2000-3000/μL 8.97 (4.86-11.27)
≥3000/μL 8.64 (4.40-22.74)
HR 95% CI p value
1 reference
1.067 (0.635-1.794) 0.806
0.901 (0.519-1.564) 0.711
0.726 (0.414-1.273) 0.264
p=0.335
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<1000 54 18 7 3 1
1000-2000 34 11 6 4 1
2000-3000 54 16 9 4 3
≥3000 58 29 13 8 6
E
Time to next treatment
Monocyte counts TTNT(m) 95% CI
<200/μL 6.08 (4.40-14.39)
200-300/μL 10.28 (5.09-16.00)
300-400/μL 9.66 (5.52-42.09)
≥400/μL 11.04 (2.33-22.74)
HR 95% CI p value
1 reference
0.815 (0.473-1.406) 0.462
0.619 (0.332-1.155) 0.132
0.821 (0.471-1.430) 0.486
p=0.51
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<200 36 12 7 2 1 0
200-300 34 16 8 4 1 0
300-400 25 11 5 5 4 3
≥400 31 17 8 4 3 2

Figure S3

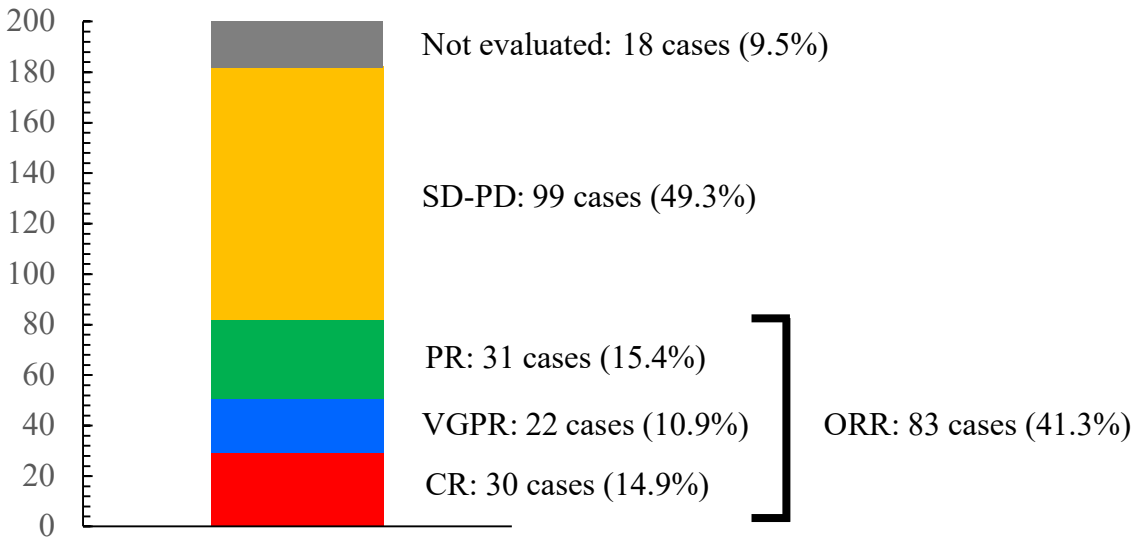
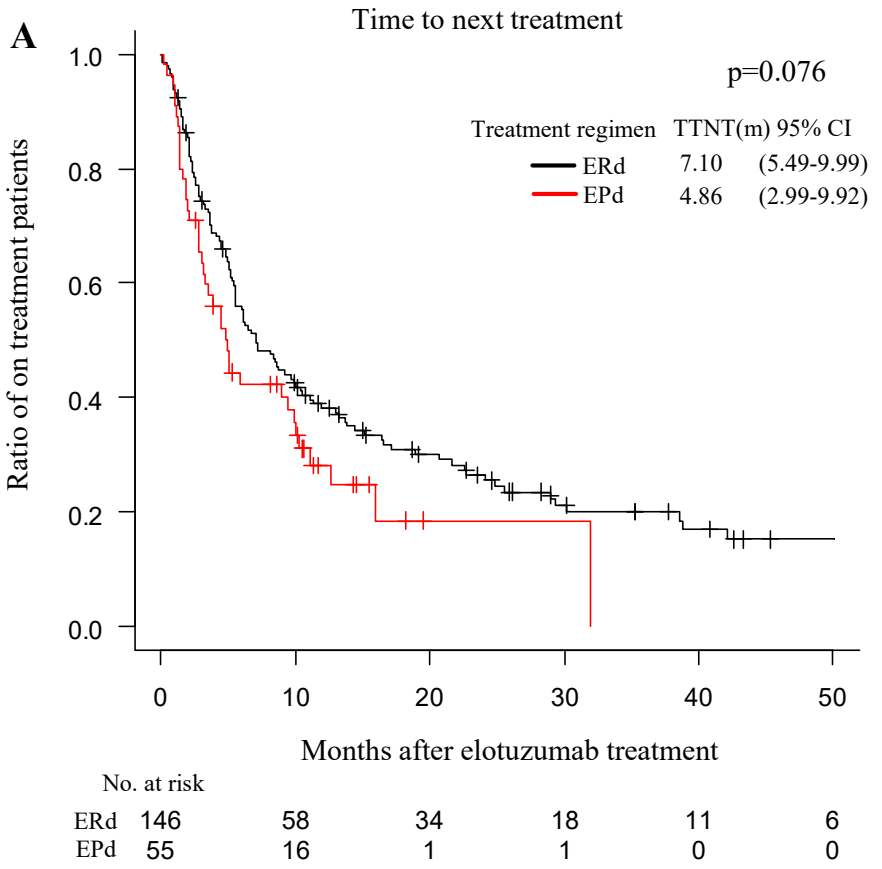

200
180
160
140
120
100
80
60
40
20
0
Not evaluated: 18 cases (9.5%)
SD-PD: 99 cases (49.3%)
PR: 31 cases (15.4%)
VGPR: 22 cases (10.9%)
CR: 30 cases (14.9%)
ORR: 83 cases (41.3%)

Figure S4


A
Time to next treatment
p=0.076
Treatment regimen TTNT(m) 95% CI
ERd 7.10 (5.49-9.99)
EPd 4.86 (2.99-9.92)
Ratio of on treatment patients
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Months after elotuzumab treatment
No. at risk
ERd 146 58 34 18 11 6
EPd 55 16 1 1 0 0

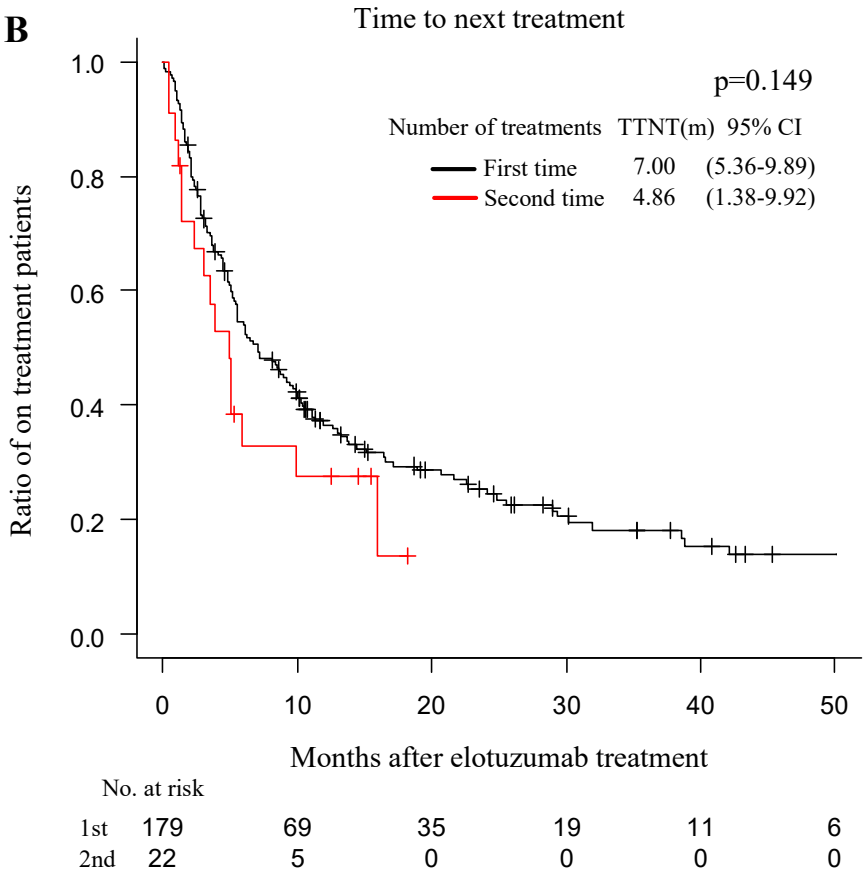
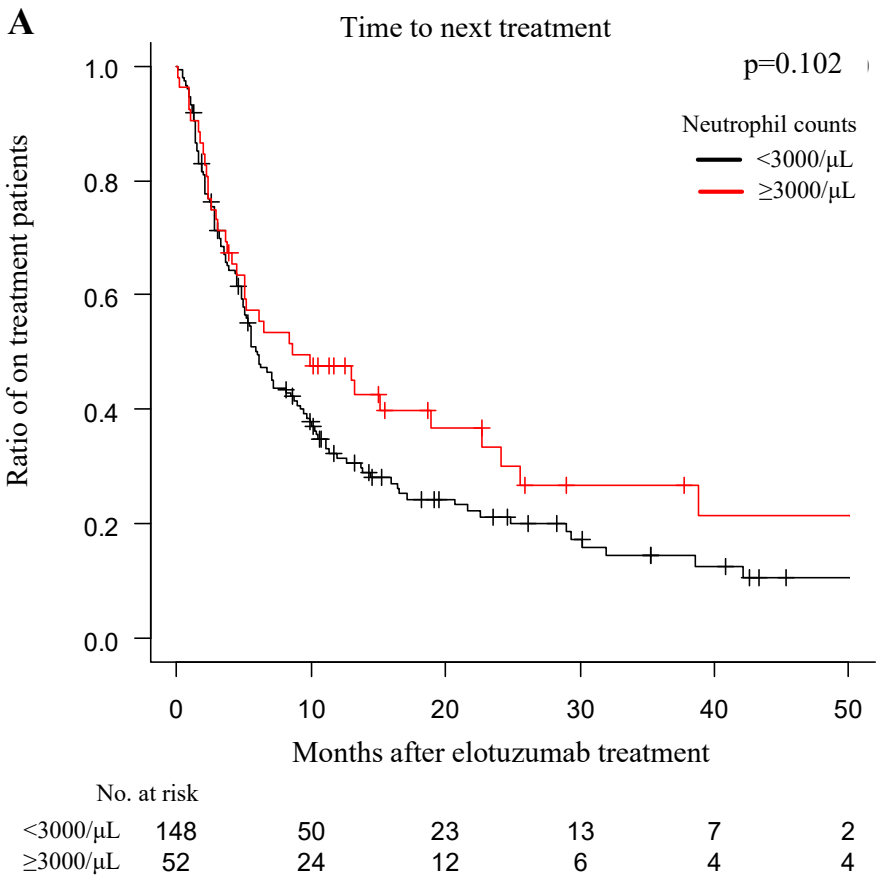

B
Time to next treatment
p=0.149
Number of treatments TTNT(m) 95% CI
First time 7.00 (5.36-9.89)
Second time 4.86 (1.38-9.92)
Ratio of on treatment patients
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Months after elotuzumab treatment
No. at risk
1st 179 69 35 19 11 6
2nd 22 5 0 0 0 0

Figure S5


A
Time to next treatment
p=0.102
Neutrophil counts
<3000/μL
≥3000/μL
Ratio of on treatment patients
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
50
Months after elotuzumab treatment
No. at risk
<3000/μL 148 50 23 13 7 2
≥3000/μL 52 24 12 6 4 4

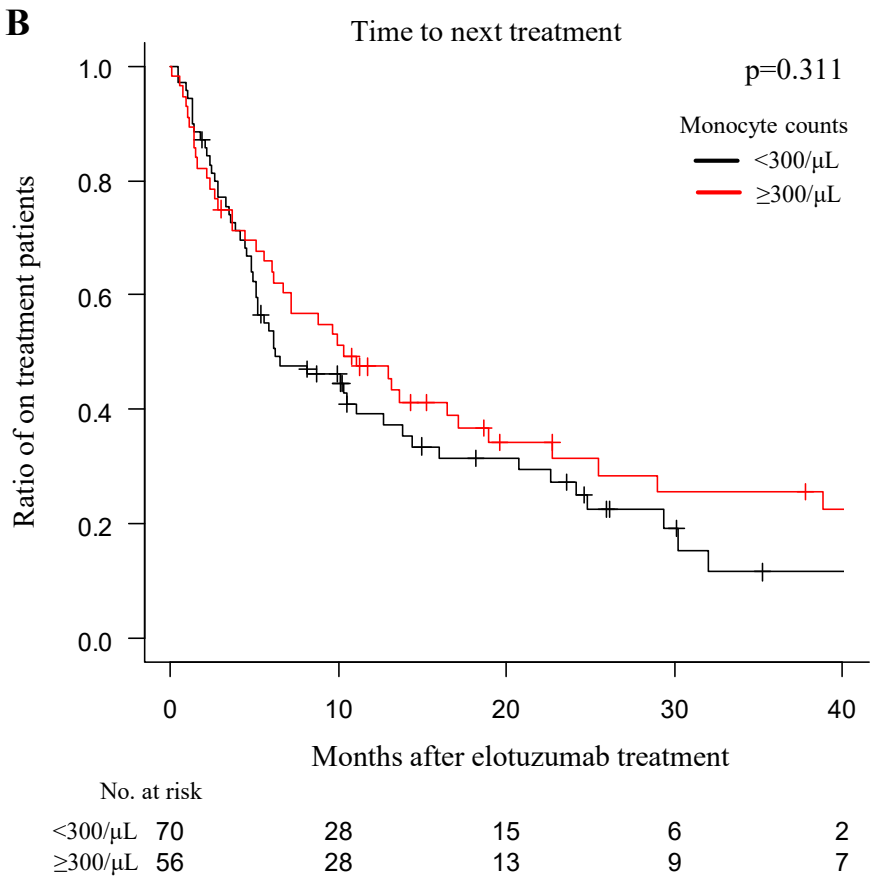
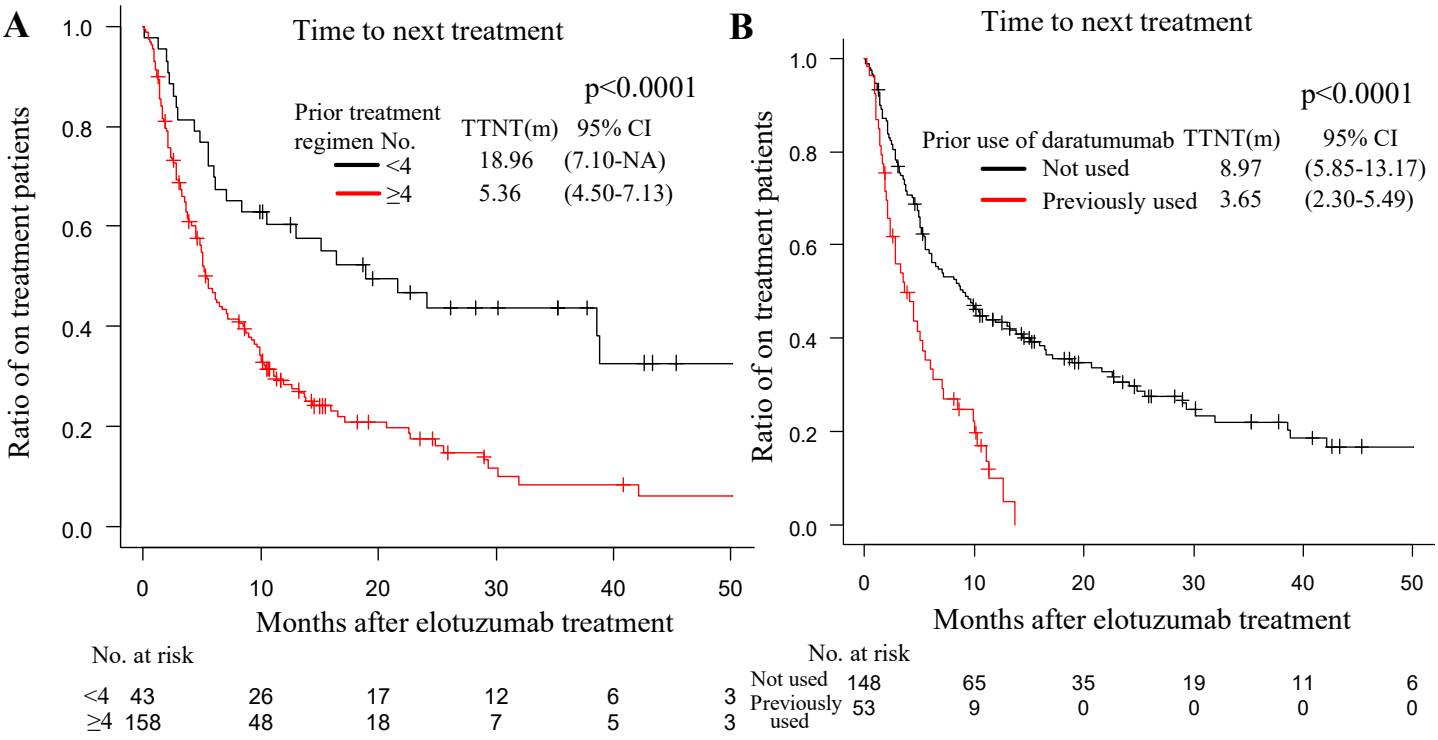

B
Time to next treatment
p=0.311
Monocyte counts
<300/μL
≥300/μL
Ratio of on treatment patients
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40
Months after elotuzumab treatment
No. at risk
<300/μL 70 28 15 6 2
≥300/μL 56 28 13 9 7

Figure S6


A
Time to next treatment
p<0.0001
Prior treatment regimen No.
TTNT(m) 95% CI
<4 18.96 (7.10-NA)
≥4 5.36 (4.50-7.13)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<4 43 26 17 12 6 3
≥4 158 48 18 7 5 3
B
Time to next treatment
p<0.0001
Prior use of daratumumab TTNT(m) 95% CI
Not used 8.97 (5.85-13.17)
Previously used 3.65 (2.30-5.49)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
Not used 148 65 35 19 11 6
Previously used 53 9 0 0 0 0

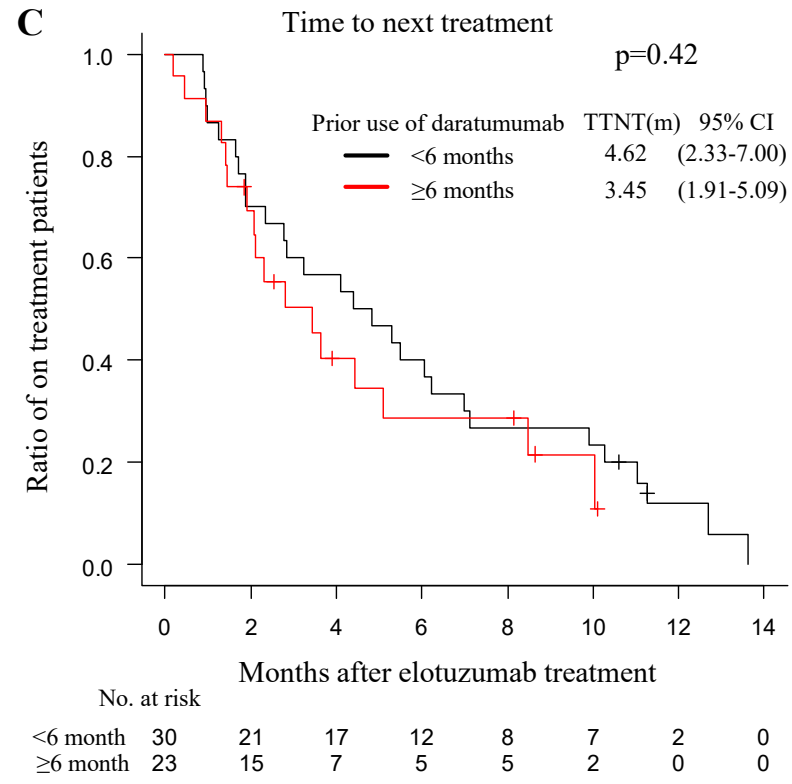

C
Time to next treatment
p=0.42
Prior use of daratumumab TTNT(m) 95% CI
<6 months 4.62 (2.33-7.00)
≥6 months 3.45 (1.91-5.09)
Ratio of on treatment patients
Months after elotuzumab treatment
No. at risk
<6 month 30 21 17 12 8 7 2 0
≥6 month 23 15 7 5 5 2 0 0

Figure S7

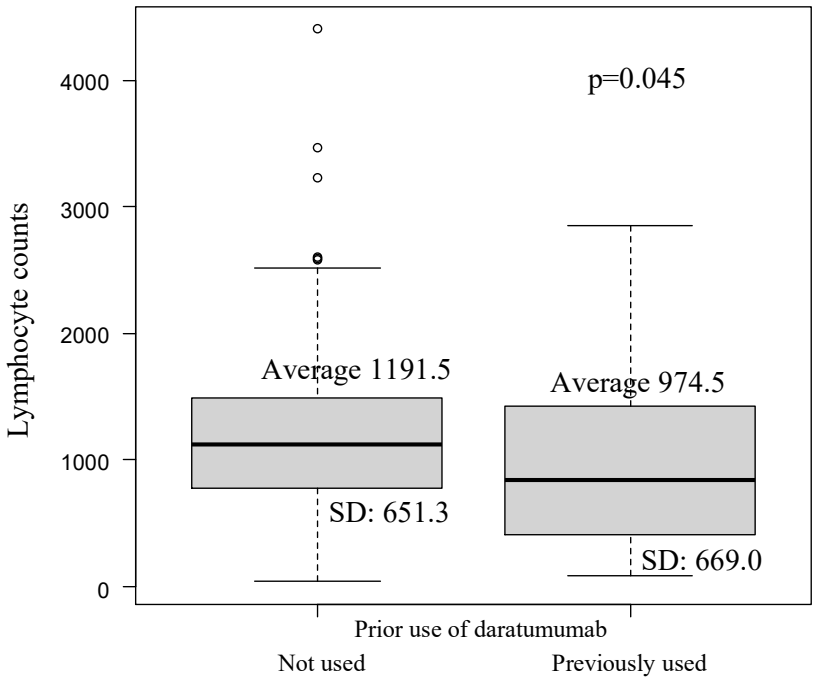
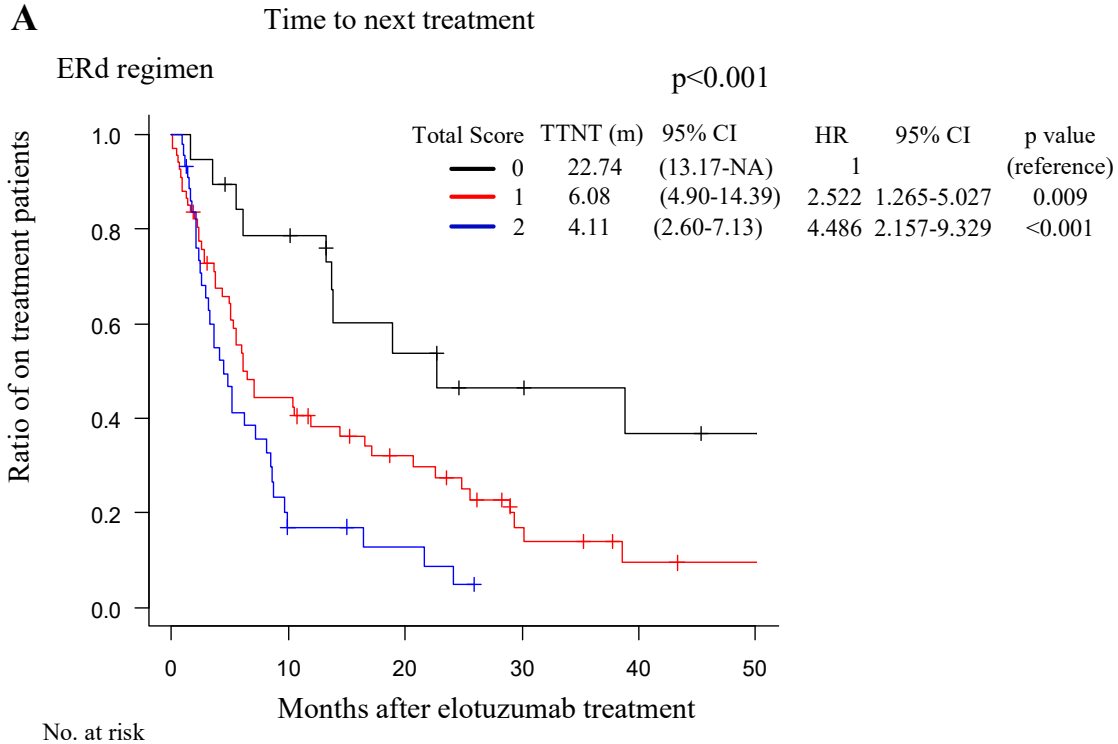

Lymphocyte counts
4000
3000
2000
1000
0
p=0.045
Average 1191.5
SD: 651.3
Average 974.5
SD: 669.0
Prior use of daratumumab
Not used
Previously used

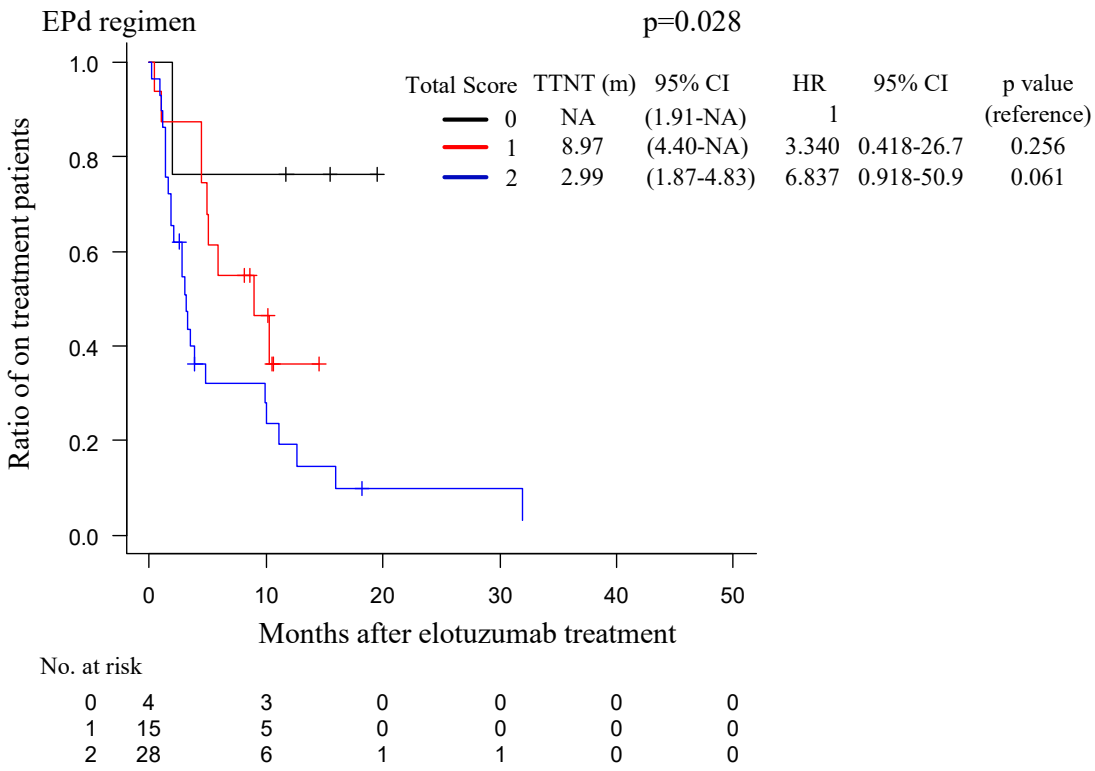
Figure S8

A



Score	Lymphocyte counts	κ/λ ratio
0	≥1400	0.1-10
1	<1400	<0.1, ≥10

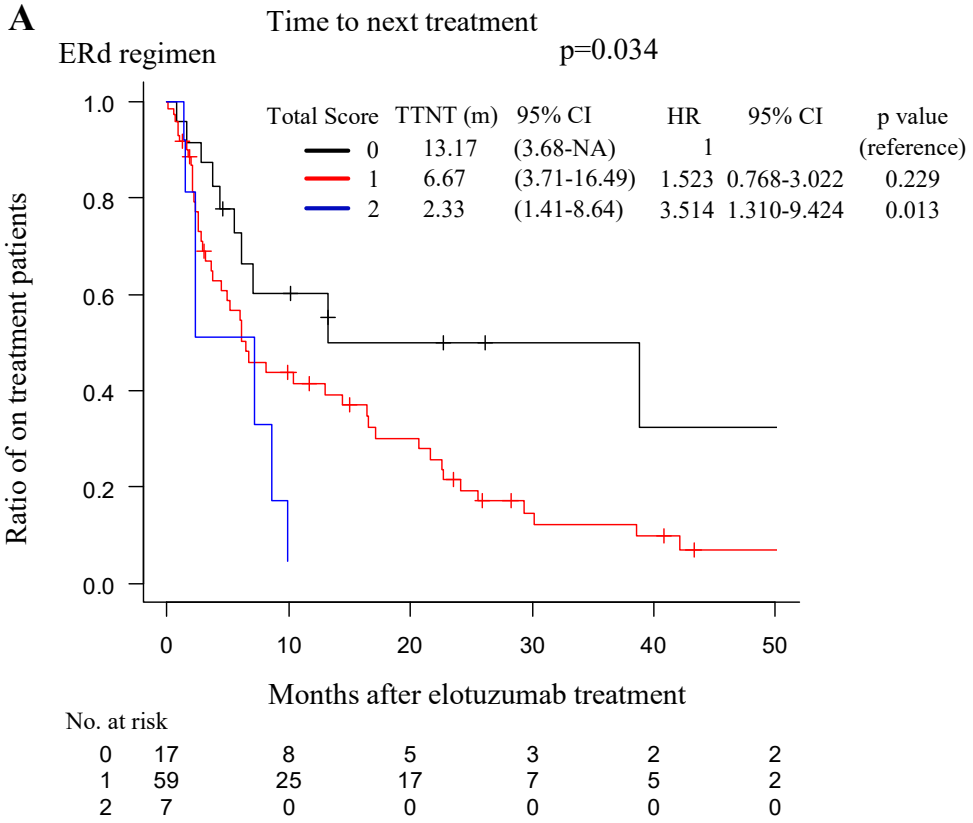
B



Score	Lymphocyte counts	κ/λ ratio
0	≥1400	0.1-10
1	<1400	<0.1, ≥10

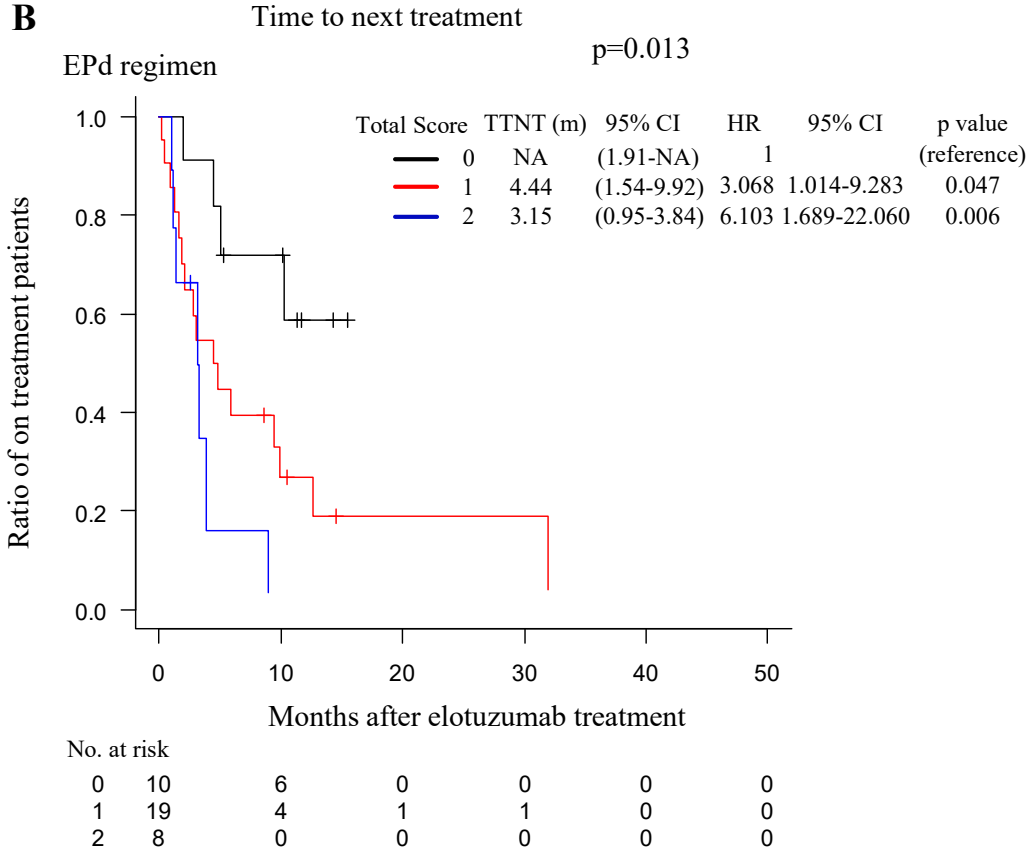
Figure S9

A



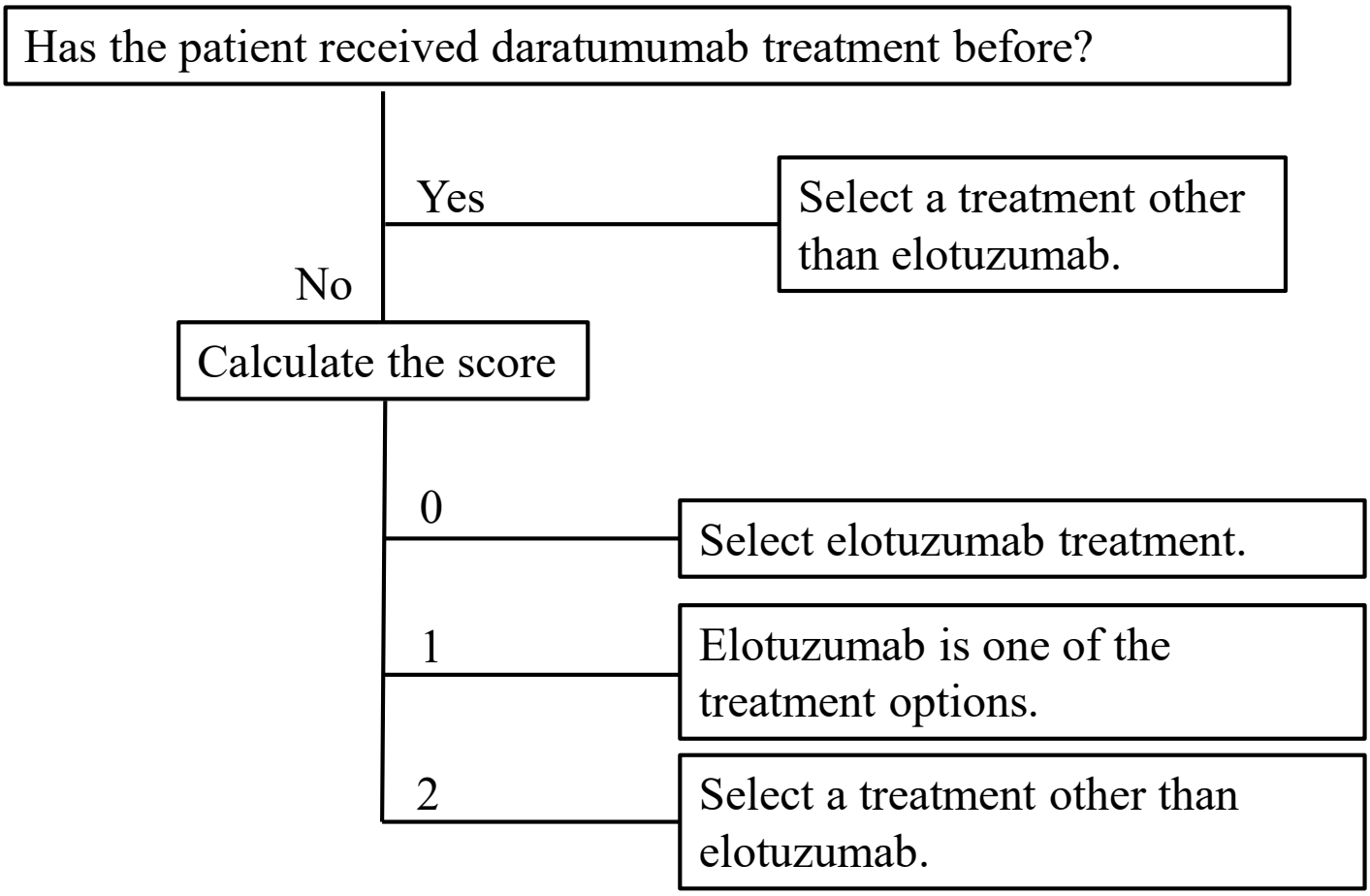
Score	Lymphocyte counts	B2MG
0	≥1400	<5.5mg/L
1	<1400	≥5.5mg/L

B



Score	Lymphocyte counts	B2MG
0	≥1400	< 5.5mg/L
1	<1400	≥5.5mg/L

Figure S10


Has the patient received daratumumab treatment before?
Yes
Select a treatment other than elotuzumab.
No
Calculate the score
0
Select elotuzumab treatment.
1
Elotuzumab is one of the treatment options.
2
Select a treatment other than elotuzumab.

Received: 27 July 2021 | Revised: 24 September 2021 | Accepted: 26 September 2021

DOI: 10.1111/cas.15163

ORIGINAL ARTICLE

Cancer Science WILEY

Improved survival of multiple myeloma patients treated with autologous transplantation in the modern era of new medicine

Yutaka Shimazu[1] | Shohei Mizuno[2] | Shin-ichi Fuchida[3] | Kazuhito Suzuki[4] | Nobuhiro Tsukada[5] | Akira Hanagaishi[6] | Mitsuhiro Itagaki[7] | Keisuke Kataoka[8] | Shinichi Kako[9] | Emiko Sakaida[10] | Satoshi Yoshioka[11] | Shinsuke Iida[12] | Noriko Doki[13] | Tatsuo Oyake[14] | Tatsuo Ichinohe[15] | Yoshinobu Kanda[16] | Yoshiko Astuta[17,18] | Hiroyuki Takamatsu[19] | the working group of the Japan Society for Transplantation, Cellular Therapy

[1]Department of Hematology, Kyoto University Hospital, Kyoto, Japan

[2]Division of Hematology, Department of Internal Medicine, Aichi Medical University School of Medicine, Nagakute, Japan

[3]Department of Hematology, JCHO Kyoto Kuramaguchi Medical Center, Kyoto, Japan

[4]Department of Clinical Oncology/Hematology, Jikei University Kashiwa Hospital, Chiba, Japan

[5]Department of Hematology, Japanese Red Cross Medical Center, Tokyo, Japan

[6]Department of Hematology, National Center for Global Health and Medicine, Tokyo, Japan

[7]Department of Hematology, Hiroshima Red Cross Hospital and Atomic-bomb Survivors Hospital, Hiroshima, Japan

[8]Division of Hematology, Department of Medicine, Keio University School of Medicine, Tokyo, Japan

[9]Division of Hematology, Jichi Medical University Saitama Medical Center, Saitama, Japan

[10]Department of Hematology, Chiba University Hospital, Chiba, Japan

[11]Department of Hematology, Kobe City Medical Center General Hospital, Hyogo, Japan

[12]Division of Hematology and Oncology, Nagoya City University Hospital, Aichi, Japan

[13]Hematology Division, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, Tokyo, Japan

[14]Division of Hematology and Oncology, Iwate Medical University, Iwate, Japan

[15]Department of Hematology and Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan

[16]Division of Hematology, Department of Medicine, Jichi Medical University, Saitama, Japan

[17]Japanese Data Center for Hematopoietic Cell Transplantation, Aichi, Japan

[18]Department of Registry Science for Transplant and Cellular Therapy, Aichi Medical University School of Medicine, Aichi, Japan

[19]Department of Hematology, Kanazawa University, Ishikawa, Japan

Correspondence
Yutaka Shimazu, Department of Hematology, Kyoto University Hospital, 54 Kawaramachi, Shogoin, Sakyoku 60-8507, Kyoto, Japan.
Email: yshimazu@kuhp.kyoto-u.ac.jp

Abstract

New drugs for multiple myeloma (MM) have dramatically improved patients' overall survival (OS). Autologous stem cell transplantation (ASCT) remains the mainstay for transplant-eligible MM patients. To investigate whether the post-ASCT prognosis of MM patients has been improved by new drugs, we undertook a retrospective

Abbreviations: Allo-SCT, allogenic stem cell transplantation; ASCT, autologous stem cell transplantation; EMM, extramedullary multiple myeloma; CI, confidence interval; CR, complete response; IMiD, immunomodulatory drug; ISS, International Staging System; JSTCT, Japanese Society for Transplantation and Cellular Therapy; MM, multiple myeloma; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; PS, performance status; SD, stable disease; TRUMP, Transplant Registry Unified Management Program; VGPR, very good partial response.

Funding information
Japan Agency for Medical Research and Development, Grant/Award Number: 18ek0510023h0002

observational analysis using the Transplant Registry Unified Management Program database in Japan. We analyzed 7323 patients (4135 men and 3188 women; median age, 59 years; range 16-77 years) who underwent upfront ASCT between January 2007 and December 2018. We categorized them by when they underwent ASCT according to the drugs' introduction in Japan: group 1 (2007-2010), group 2 (2011-2016), and group 3 (2017-2018). We compared the groups' post-ASCT OS. The 2-year OS rates (95% confidence interval [CI]) of groups 1, 2, and 3 were 85.8% (84.1%-87.4%), 89.1% (88.0%-90.1%), and 92.3% (90.0%-94.2%) ($P < .0001$) and the 5-year OS (95% CI) rates were 64.9% (62.4%-67.3%), 71.6% (69.7%-73.3%), and not applicable, respectively ($P < .0001$). A multivariate analysis showed that the post-ASCT OS was superior with these factors: age less than 65 years, performance status 0/1, low International Staging System (ISS) stage, receiving SCT for 180 days or less post-diagnosis, better treatment response pre-ASCT, later year of ASCT, and receiving SCT twice. A subgroup analysis showed poor prognoses for the patients with unfavorable karyotype and poor treatment response post-ASCT. The post-ASCT OS has thus improved over time (group 1 < 2 < 3) with the introduction of new drugs for MM. As the prognosis of high-risk-karyotype patients with ISS stage III remains poor, their treatment requires improvement.

KEYWORDS
autologous stem cell transplantation, multiple myeloma, overall survival, prognosis, new medicine

1 | INTRODUCTION

The development of new drugs for MM, especially PI and IMiDs, has dramatically improved the OS of patients with MM.[1] In addition to PI and IMiDs, mAbs such as elotuzumab, daratumumab, and isatuximab could further improve the prognosis of MM.[2] Even in the modern era, however, ASCT remains the mainstay for transplant-eligible MM patients.[3] The impact of novel drugs used to treat MM patients after they have undergone ASCT has not been fully clarified.

Our group reported that the prognosis of MM patients after ASCT improved with the introduction of PI.[4] However, only patients who underwent ASCT before 2011 were recruited in that study. Nishimura et al recently reported that long-term survival of MM patients after ASCT improved with the introduction of novel therapeutics after 2014.[5] They analyzed 4329 MM patients including those treated during the pre-novel medicine era, and they documented the improvement of prognosis with the introduction of thalidomide and bortezomib.[5]

To further clarify the impact of the drugs introduced after bortezomib on the prognosis of MM after ASCT and to investigate the prognostic factors in the modern era, we undertook a retrospective observational analysis using the TRUMP database of the JSTCT.

2 | MATERIALS AND METHODS

2.1 | Data source and patients

We analyzed the TRUMP database, which includes physician-reviewed data (with patient-informed consent) and yearly follow-ups.[6,7] This study was approved by the Data Management Committee of the JSTCT and the Kyoto University Hospital institutional review board (approval no. R1437). Bortezomib, thalidomide, lenalidomide, pomalidomide, elotuzumab, carfilzomib, ixazomib, daratumumab, and isatuximab were approved in Japan for the treatment of relapsed/refractory MM between December 2006 and August 2020. The approval dates of these drugs are provided in Table S1.

The database cases included 7323 patients (4135 men and 3188 women) with the median age of 59 (range, 16-77) years who underwent ASCT after treatment with high-dose melphalan (200 mg/m^2) for newly diagnosed symptomatic MM; we included the patients who underwent ASCT in Japan between January 2007 and December 2018. Given that we did not have the data regarding the details of the patients' treatment regimens before and after ASCT, we arbitrarily categorized the patients into three treatment cohorts

according to the year that ASCT was carried out: group 1, 2007-2010; group 2, 2011-2016; and group 3, 2017-2018.

In addition to conventional drugs, bortezomib, thalidomide, and lenalidomide were available for treatment in group 1. In group 2, pomalidomide, elotuzumab, and carfilzomib were available in addition to the drugs in group 1. In group 3, ixazomib and daratumumab were also available in addition to those in group 2. The patients who received an Allo-SCT after ASCT were censored at the day of Allo-SCT. All of the patients were diagnosed as having MM based on institutional assessment.

The patients' responses to treatment were assessed based on the criteria of the European Group for Blood and Marrow Transplantation[8] and the international uniform response criteria for MM.[9] The patients' responses before and after SCT were classified by institutional physicians into five categories: CR, VGPR, PR, SD, and PD.

We classified the patients into three categories by referring to the consensus of the International Myeloma Working Group with slight modification[10]: unfavorable cytogenetic abnormality, not-unfavorable cytogenetic abnormality, and unknown/insufficient data, based on the physicians' input data. "Unfavorable cytogenetic abnormality" included deletion 13q, deletion 17p, t(4;14), t(14;16), t(14;20), and 1q gain. Deletion 13q was identified by a karyotype analysis, and other unfavorable cytogenetic abnormalities were categorized by both a karyotype analysis and a FISH analysis. We categorized the patients with a cytogenetic abnormality other than an unfavorable cytogenetic abnormality into the "not-unfavorable cytogenetic abnormality" group. When mitosis figures could not be obtained or the karyotype data were not available, we categorized the case as "unknown," and if the karyotype data were insufficient for analysis, we categorized the case as "insufficient data."

2.2 | Statistical analyses

The distribution of categorical and continuous variables of groups 1, 2, and 3 were compared using Pearson's χ^2 test and the Kruskal-Wallis test, respectively. The OS was calculated from the time of the first ASCT until the date of death by any cause, the date of last contact, or censored at the day of Allo-SCT. Survival curves were plotted using the Kaplan-Meier method, and the log-rank test was used for comparisons among groups. The Cox proportional hazard model was used to calculate the hazard ratios for each variable along with the 95% CI. A multivariate analysis was carried out for all variables that were significant ($P < .05$) in a univariate analysis. The cytogenetic abnormality analyses were excluded from the multivariate analysis and analyzed as subgroups due to insufficient data. All statistical analyses were carried out using the EZR (version 1.54) software package (Saitama Medical Center/Jichi Medical University) along with a graphical user interface for the R software package (version 4.0.3; The R Foundation for Statistical Computing).[11] P values less than .05 were considered significant in all analyses.

3 | RESULTS

3.1 | Overall survival of MM patients after ASCT in the era of new medicine

The characteristics of patients are summarized in Table 1. We divided the patients into three groups according to the years during which they underwent ASCT. There were no significant differences among the groups with regards to gender or MM type of heavy chain (Table 1). However, the following characteristics differed significantly among the groups: patient age at ASCT, PS at ASCT, ISS categorization at diagnosis, MM type of light chain, karyotype, number of collected $CD34^+$ cells per body weight, number of days from diagnosis at first ASCT, treatment response before and after first ASCT, number of ASCTs, and the follow-up period of survivors (Table 1). The median number of days from the diagnosis to ASCT was not significantly different among groups 1, 2, and 3 at 212, 232, and 213 days, respectively (Figure S1). Information about the patients' induction regimens and median cycles of induction therapies is summarized in Table S2.

When we analyzed the OS of the MM patients who had undergone ASCT during the years 2007-2018, we observed that OS significantly improved over time (Figure 1A, Table 2; $P < .0001$). The 2-year OS rates of groups 1, 2, and 3 were 85.8% (95% CI, 84.1-87.4), 89.1% (95% CI, 88.0-90.1), and 92.3% (95% CI, 90.0-94.2%), respectively. The median follow-up time of the survivors in groups 1, 2, and 3 were 2397, 1365, and 417 days, respectively. The median OS of groups 1, 2, and 3 were 2701 days, not reached, and not reached, respectively.

The other factors associated with superior OS in the univariate analysis were age 65 years or younger at the time of ASCT ($P < .0001$), female gender ($P < .0001$), a good PS (PS 0 or 1) ($P < .0001$), low ISS stage ($P < .0001$), and the treatment response before ASCT ($P < .0001$; Figures 1B–D, 2, and S2-S4, Table 2). The number of $CD34^+$ cell counts, the timing of ASCT 180 days or less after the diagnosis, and the number of ASCTs were not significant in the univariate analysis (Table 2). Because of insufficient data, we undertook a subgroup analysis for unfavorable cytogenetic abnormalities at the time of diagnosis and the treatment response after ASCT. This analysis revealed that both not having an unfavorable cytogenetic abnormality ($P < .0001$) and achieving a good response after ASCT ($P < .0001$) resulted in superior OS (Figures 3 and S5, Table 2).

We undertook a multivariate analysis regarding the patients' OS by analyzing all of the baseline factors except cytogenetic abnormality (unfavorable or not) and post-ASCT response, because of insufficient data. The factors that were independently associated with superior OS were age 64 years or less ($P = .0010$), a good PS (PS 0/1; $P = .0016$), low ISS stage ($P < .0001$), having undergone ASCT at 180 days or less after diagnosis ($P = .0226$), good treatment response before ASCT ($P < .0001$), the year of ASCT ($P = .0001$), and having undergone two ASCTs ($P = .0051$; Table 2).

TABLE 1 Characteristics of Japanese patients with multiple myeloma who underwent autologous stem cell transplant (ASCT)

		ASCT period (years)			
		2007-2010	2011-2016	2017-2018	*P* value
No. of cases		1816	3916	1591	
Age at ASCT, y; median (range)		58 (18-75)	60 (16-77)	61 (24-76)	<.0001
Age ≤65 y at ASCT		1656 (91.2)	3344 (85.4)	1201 (75.5)	<0.0001
Gender	Male	1051 (57.9)	2207 (56.4)	877 (55.1)	.2660
PS at ASCT	0 and 1	1514 (86.5)	3453 (89.9)	1437 (93.5)	<.0001
	2 or more	232 (13.3)	381 (9.9)	97 (6.3)	
	Unknown	4 (0.2)	6 (0.2)	3 (0.2)	
ISS stage at diagnosis	I	510 (33.0)	1159 (34.1)	485 (35.9)	<.0001
	II	547 (35.4)	1252 (36.9)	509 (37.7)	
	III	329 (21.3)	826 (24.3)	334 (24.7)	
	Unknown	161 (10.4)	160 (4.7)	23 (1.7)	
Myeloma type	IgG	918 (52.1)	2070 (53.9)	805 (52.4)	.0520
	IgA	341 (19.4)	744 (19.4)	299 (19.5)	
	BJP	351 (19.9)	742 (19.3)	336 (21.9)	
	IgD	57 (3.2)	104 (2.7)	40 (2.6)	
	IgM	1 (0.1)	16 (0.4)	5 (0.3)	
	IgE	1 (0.1)	4 (0.1)	1 (0.1)	
	Nonsecreting	54 (3.1)	82 (2.1)	32 (2.1)	
	Unknown	39 (2.2)	82 (2.1)	17 (1.1)	
Light chain	λ	683 (37.6)	1528 (39.0)	635 (39.9)	<.0001
	κ	951 (52.4)	2119 (54.1)	846 (53.2)	
	Unknown	182 (10.0)	269 (6.9)	110 (6.9)	
Cytogenetic abnormality	Not unfavorable	1426 (78.5)	3082 (78.7)	1188 (74.7)	<.0001
	Unfavorable	174 (9.6)	435 (11.1)	239 (15.0)	
	Unknown/insufficient data	216 (11.9)	399 (10.2)	164 (10.3)	
Collected CD34 cells per body weight ($\times 10^5$/kg)	<1.0	192 (14.6)	408 (19.0)	157 (18.0)	.0043
	≥1.0	1121 (85.4)	1743 (81.0)	717 (82.0)	
Time from diagnosis to first ASCT, d	≤180	617 (34.9)	1081 (28.1)	491 (31.9)	<.0001
	>180	1152 (65.1)	2768 (71.9)	1047 (68.1)	
Treatment response before first ASCT	CR	165 (10.5)	659 (18.8)	324 (23.3)	<.0001
	VGPR	496 (31.5)	1118 (32.0)	505 (36.3)	
	PR	718 (45.6)	1497 (42.8)	497 (35.7)	
	SD-PD	197 (12.5)	225 (6.4)	67 (4.8)	
	Unknown	240 (13.2)	417 (10.6)	198 (12.4)	
Treatment response after first ASCT	CR	88 (4.8)	1065 (27.2)	686 (43.1)	<.0001
	VGPR	45 (2.4)	629 (16.1)	385 (24.2)	
	PR	53 (2.9)	594 (15.2)	259 (16.3)	
	SD-PD	23 (1.3)	109 (2.8)	47 (3.0)	
	Unknown	1607 (88.5)	1519 (38.8)	214 (13.5)	
No. of ASCTs	1	1315 (72.8)	344 (88.4)	1493 (97.0)	<.0001
	2	491 (27.2)	449 (11.6)	46 (3.0)	
Follow-up period of survivor, d; median (range)		2397 (13-4569)	1365 (0-3147)	417 (0-980)	<.0001

Note: Data are shown as n (%) unless otherwise specified. The distribution of categorical and continuous variables of groups 1, 2, and 3 were compared using Pearson's χ^2 test and the Kruskal-Wallis test, respectively.

Abbreviations: CR, complete response; ISS, International Staging System; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; VGPR, very good partial response.

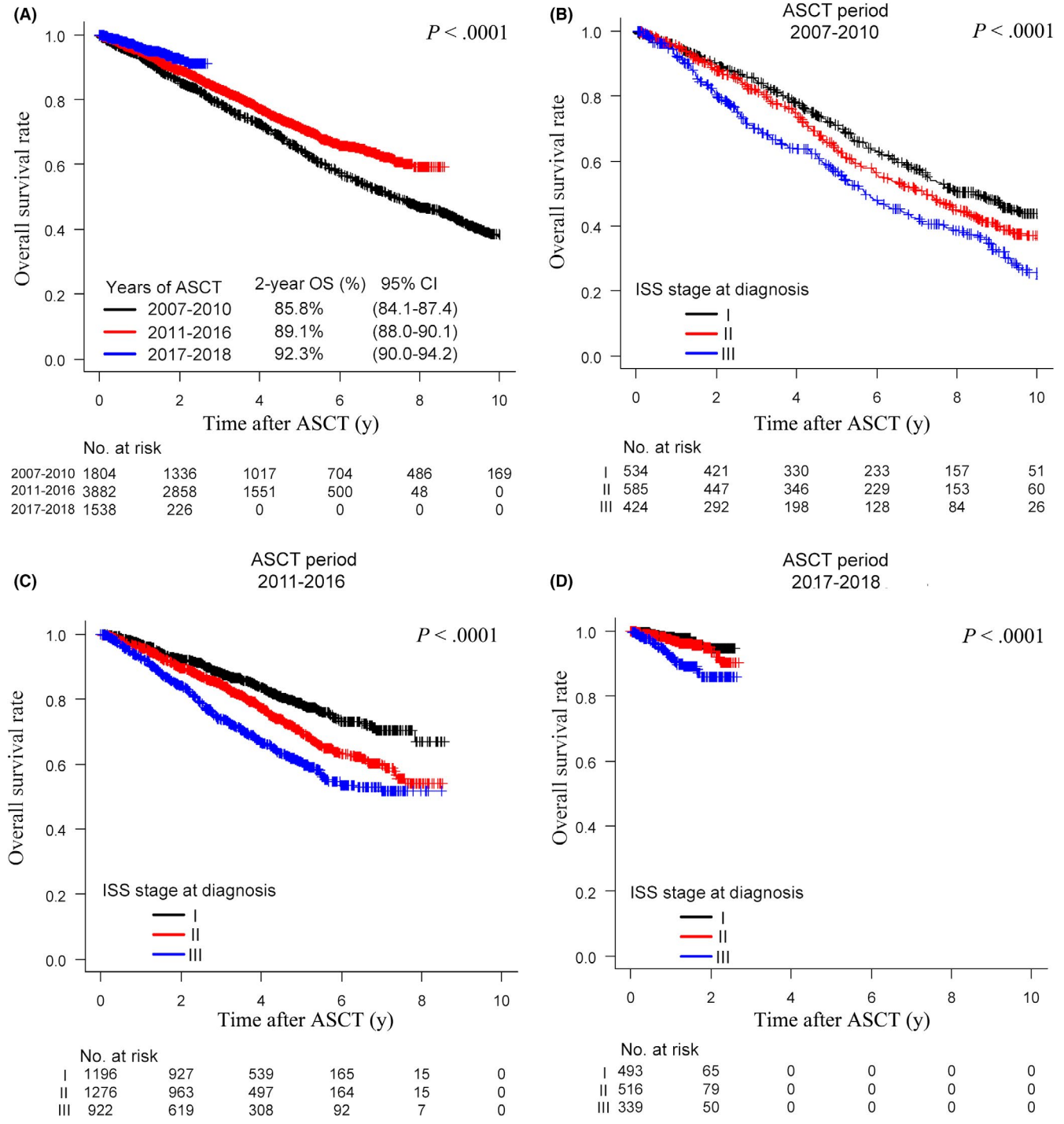


FIGURE 1 A, Overall survival (OS) from the time of autologous stem cell transplantation (ASCT) in Japanese patients with multiple myeloma (MM) who underwent ASCT in 2007-2010 (group 1; black), 2011-2016 (group 2; red), and 2017-2018 (group 3; blue). B–D, OS of MM patients after ASCT by the International Staging System (ISS) stage at diagnosis: stage I (black), stage II (red), and stage III (blue). The number of patients at risk in each group is shown in the lower panel of each figure

These results indicated that although traditional risk factors (such as older age, poor PS, high ISS stage, poor pre-ASCT response, and unfavorable cytogenetic abnormality) hold true in the modern era, the OS of patients in the era of new drugs for MM has significantly improved independently of the traditional risk factors.

3.2 | Impact of new drugs for treating MM across each risk factor

To further clarify the impact of new drugs for treating MM across various risk factors, we analyzed the differences in OS in relation to the years (period) of ASCT with respect to well-known

TABLE 2 Univariate and multivariate analysis for survival among patients with multiple myeloma who received autologous stem cell transplant (ASCT)

		Univariate analysis					Multivariate analysis		
Factor		2-year OS (%)	95% CI	5-year OS (%)	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age at ASCT, y	≤65	89.1	88.2-89.9	70.0	68.5-71.5	<.0001	1.0000		.0010
	>65	85.6	83.1-87.9	65.9	61.4-70.1		1.3430	1.126-1.602	
Gender	Male	87.4	86.2-88.5	67.1	65.1-69.0	<.0001			.1944
	Female	90.2	89.0-91.3	72.6	70.4-74.7				
PS at ASCT	0 or 1	89.9	89.0-90.7	70.5	69.0-72.0	<.0001	1.0000		.0016
	2 or more	77.6	74.1-80.7	60.1	55.6-64.4		1.3900	1.157-1.670	
	Unknown	73.8	38.5-90.8	49.2	16.4-75.8		0.4970	0.069-3.572	
ISS stage at diagnosis	I	92.0	90.7-93.2	76.3	73.8-78.7	<.0001	1.0000		<.0001
	II	89.8	88.3-91.1	67.8	65.1-70.4		1.2040	1.033-1.403	
	III	83.1	80.9-85.2	58.3	54.8-61.7		1.9400	1.662-2.264	
	Unknown	86.6	82.1-90.0	67.8	61.2-73.5		1.6370	1.145-2.340	
CD34 counts per body weights ($\times 10^5$/kg)	<1.0	86.6	83.7-89.0	65.7	60.8-70.1	.183			.2077
	≥1.0	89.5	88.3-90.6	69.1	67.1-71.1				
Time from diagnosis to ASCT, d	≤180	89.3	87.7-90.6	70.6	67.9-73.1	.442	1.0000		.0226
	>180	88.4	87.3-89.3	69.1	67.3-70.8		1.1740	1.023-1.348	
Pre-ASCT response	CR	94.1	92.3-95.4	78.1	74.4-81.4	<.0001	1.0000		<.0001
	VGPR	90.4	88.9-91.7	71.8	69.1-74.3		1.5030	1.202-1.881	
	PR	88.0	86.6-89.3	66.9	64.5-69.2		1.7970	1.448-2.230	
	SD-PD	70.6	66.0-74.8	43.9	38.3-49.3		3.3200	2.576-4.279	
Year of ASCT	2007-2010	85.8	84.1-87.4	64.9	62.4-67.3	<.0001	1.0000		.0001
	2011-2016	89.1	88.0-90.1	71.6	69.7-73.3		0.8070	0.705-0.923	
	2017-2018	92.3	90.0-94.2	NA	NA		0.5020	0.341-0.738	
No. of ASCT	1	87.8	86.9-88.7	68.9	67.2-70.5	.1760	1.0000		.0051
	2	93.2	91.4-94.7	73.0	69.6-76.0		0.8108	0.700-0.939	
Cytogenetic abnormality	Not unfavorable	90.2	89.3-91.0	71.5	69.9-73.0	<.0010			
	Unfavorable	79.6	76.3-82.5	56.2	51.2-60.8				
	Unknown/insufficient data	85.9	82.7-88.6	67.7	63.0-72.0				
Post-ASCT response	CR	94.7	93.4-95.8	79.5	76.3-82.4	<.0010			
	VGPR	90.8	88.5-92.6	73.3	68.7-77.3				
	PR	88.5	86.0-90.6	70.4	65.8-74.5				
	SD-PD	74.4	66.6-80.7	58.5	48.3-67.5				

Note: Overall survival (OS) was calculated from the time of ASCT. Univariate and multivariate analyses against OS were undertaken for the following factors. For the univariate analysis, age (>65 y at ASCT), gender, performance status (PS) at ASCT, International Staging System (ISS) stage at diagnosis, CD34 counts per body weight, days from diagnosis to ASCT, pre-ASCT response, year of ASCT, number of ASCTs, cytogenic abnormality and post-ASCT responses were chosen, and the percentage of 2-year and 5-year OS with the 95% confidence interval (CI) and *P* value are shown. For the multivariate analysis, the following factors were chosen: age (>65 y at ASCT), gender, PS at ASCT, ISS stage at diagnosis, CD34 counts per body weight, days from diagnosis to ASCT, pre-ASCT response, year of ASCT, and number of ASCTs were chosen. The Cox proportional hazard model was used to calculate the hazard ratio for each variable; the 95% CI and *P* value are shown.

Abbreviations: CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

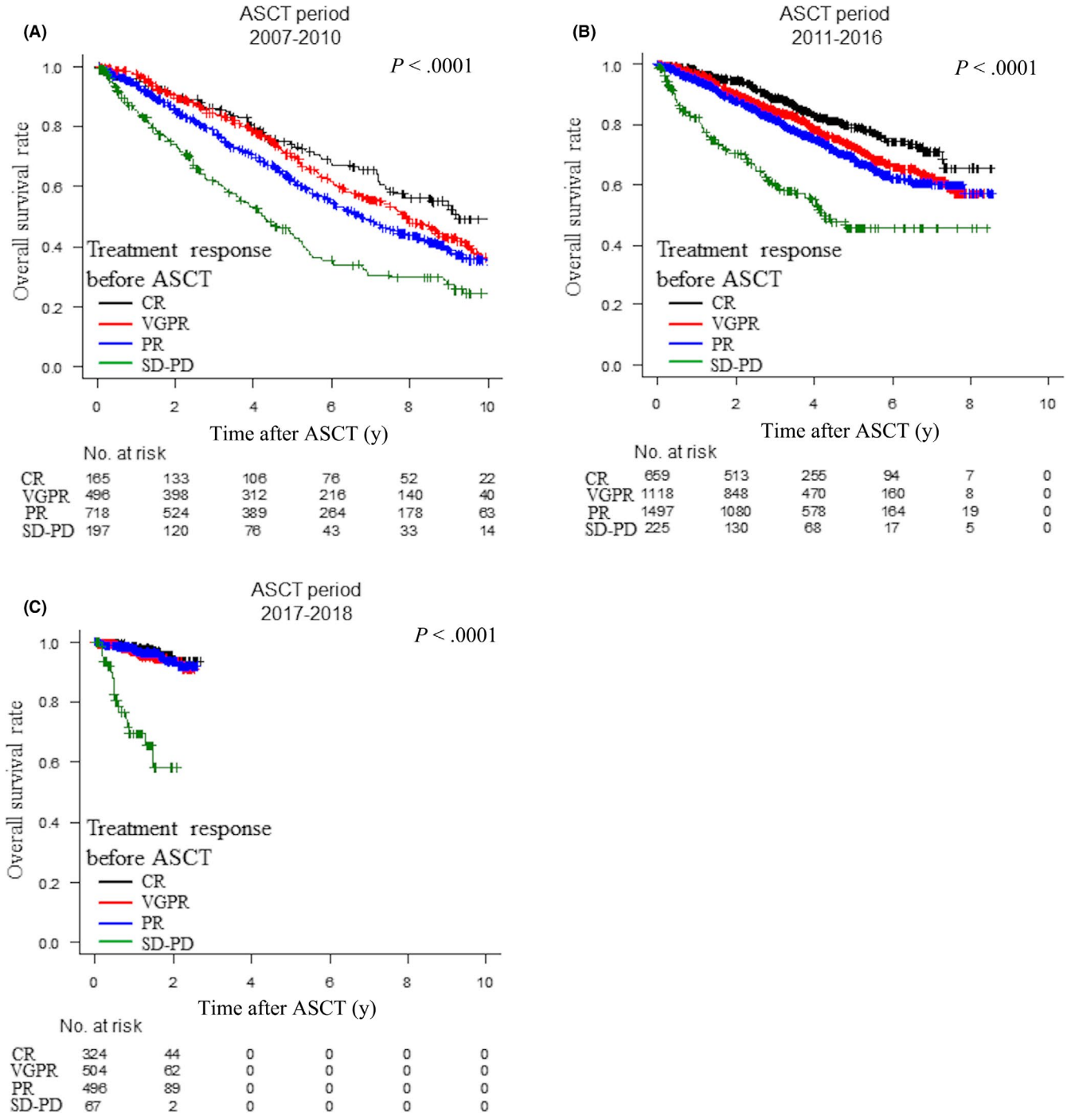


FIGURE 2 Overall survival of Japanese patients with multiple myeloma after autologous stem cell transplantation (ASCT) according to treatment response before ASCT: complete response (CR; black), very good partial response (VGPR; red), partial response (PR; blue), and stable disease-progressive disease (SD-PD; green). (A) Group 1, ASCT in 2007-2010. (B) Group 2, ASCT in 2011-2016. (C) Group 3, ASCT in 2017-2018

prognostic factors (Figure 4). When we compared OS between groups 1 and 2, we observed that patients in group 2 with the following factors showed better OS: any age ($P < .0001$ for age ≤65 years and $P = .0004$ for age >65 years), either gender ($P = .0001$ for males and $P < .0001$ for females), any PS ($P = .0009$ for PS = 0 or 1 and $P < .0001$ for PS > 1), ISS stages I ($P < .0001$) and II ($P = .0135$) at diagnosis, partial response before ASCT ($P = .0006$), and not having an unfavorable cytogenetic abnormality at diagnosis ($P < .0001$). When we compared OS between groups 2 and 3, the following factors showed superior OS in group 3: age 65 years or less ($P = .0044$), female gender ($P = .0259$), PS 0 or 1 ($P = .0494$), partial response before ASCT ($P = .0066$), and not having an unfavorable cytogenetic abnormality at diagnosis ($P = .0011$).

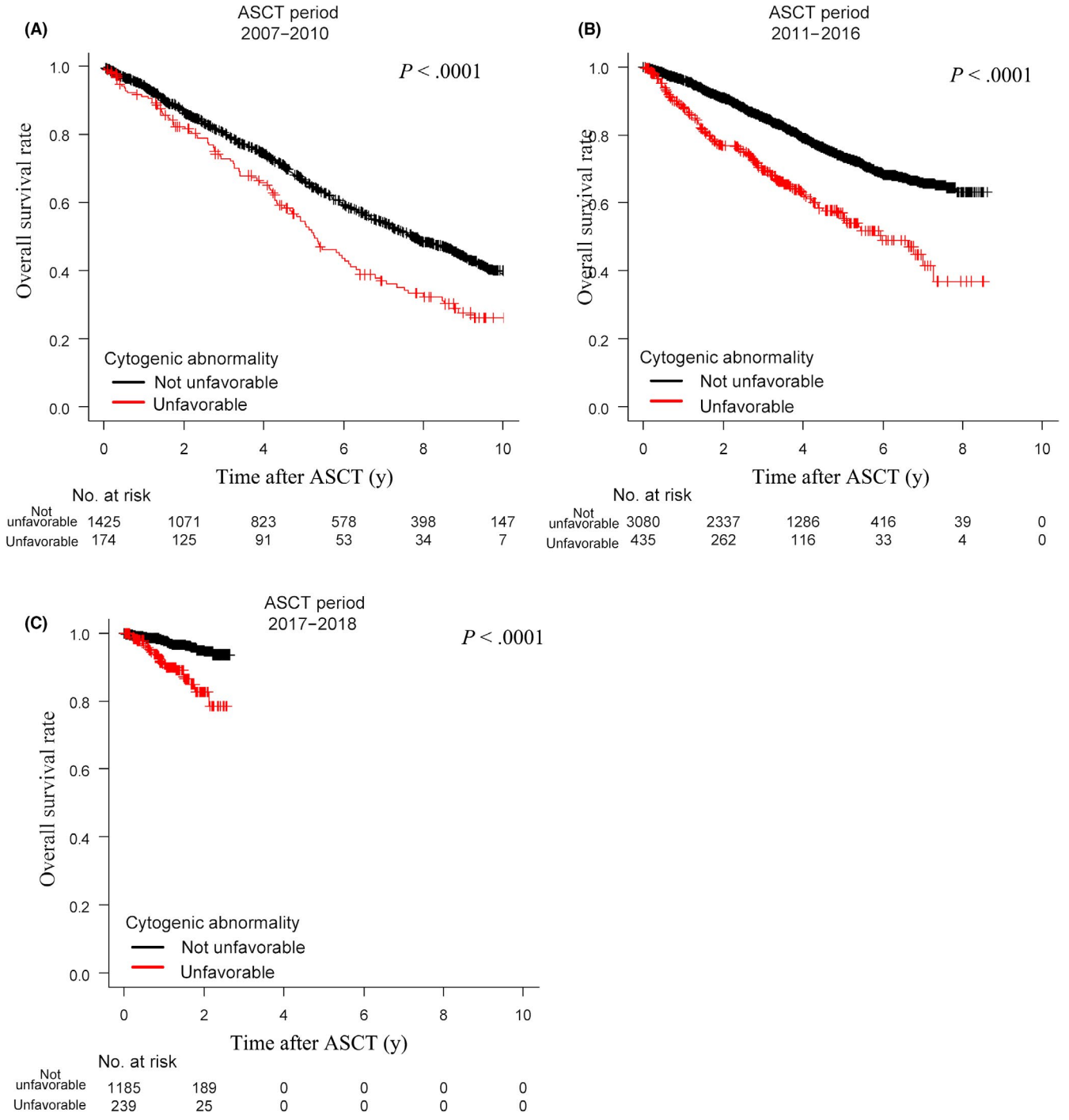


FIGURE 3 Overall survival of Japanese patients with multiple myeloma after autologous stem cell transplantation (ASCT) according to the type of cytogenic abnormality, ie, not-unfavorable cytogenic abnormality (black) and unfavorable cytogenic abnormality (red) in (A) group 1, ASCT in 2007-2010, (B) group 2, ASCT in 2011-2013, and (C) group 3, ASCT in 2017-2018

It may thus be concluded that: (a) the OS of MM patients improved significantly among both low-risk and high-risk patients in group 2 compared to group 1, and (b) the OS of MM patients improved significantly among the low-risk patients in group 3 (low-risk = with characteristics such as younger age, good PS, and not having an unfavorable cytogenetic abnormality).

3.3 | Correlation between pre- and post-ASCT responses and OS

We next analyzed the relationship between OS in the modern era and treatment response before ASCT. Our analyses revealed that in groups 1, 2, and 3, the rates of CR (10.5%, 18.8%, and 23.3%,

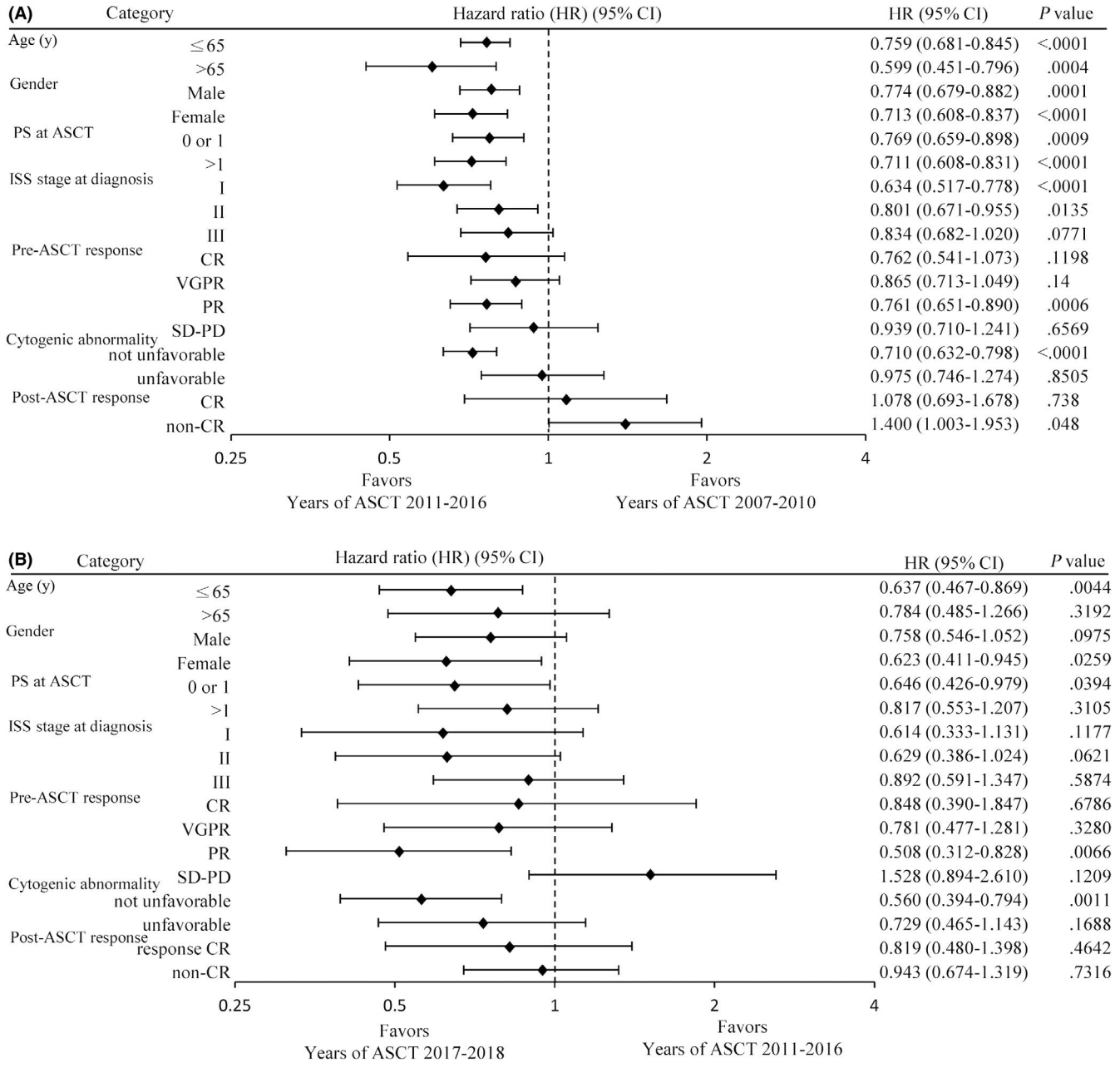


FIGURE 4 Impact of autologous stem cell transplantation (ASCT) on the overall survival of Japanese patients with multiple myeloma treated with new drugs. The effects of ASCT on each group are shown as forest plots. Diamonds on the lines indicate the hazard ratios (HR) for comparisons of (A) group 2 (ASCT in 2011-2013) with group 1 (ASCT in 2007-2010) and (B) group 3 (ASCT in 2017-2018) with group 2. Horizontal lines indicate corresponding 95% confidence interval (CI). CR, complete response; ISS, International Staging System; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; VGPR, very good partial response

respectively) and VGPR (31.6%, 31.9%, and 36.2%, respectively) increased over time (Figure 5A). In contrast, in groups 1, 2, and 3, the rates of PR (45.5%, 42.8%, and 35.7%, respectively) and SD to PD (12.5%, 6.4%, and 4.8%, respectively) decreased over time (Figure 5A). We also observed that the CR (42.1%, 44.4%, and 49.8%, respectively) and VGPR (21.5%, 26.2%, and 28.0%, respectively) rates after first ASCT increased over time (Figure 5B), and the rates of PR (25.4%, 24.8%, and 18.8%, respectively) and SD to PD (11.0%, 4.5%, and 3.4%, respectively) decreased over time (Figure 5B).

As depicted in Figure 2, the patients who had achieved a better response before ASCT were able to achieve better OS after ASCT. The patients who achieved a better response after their first ASCT showed superior OS over time ($P = .179$, $P < .0001$, and $P < .0001$ in groups 1-3, respectively; Figure S5). We thus concluded that the improvement

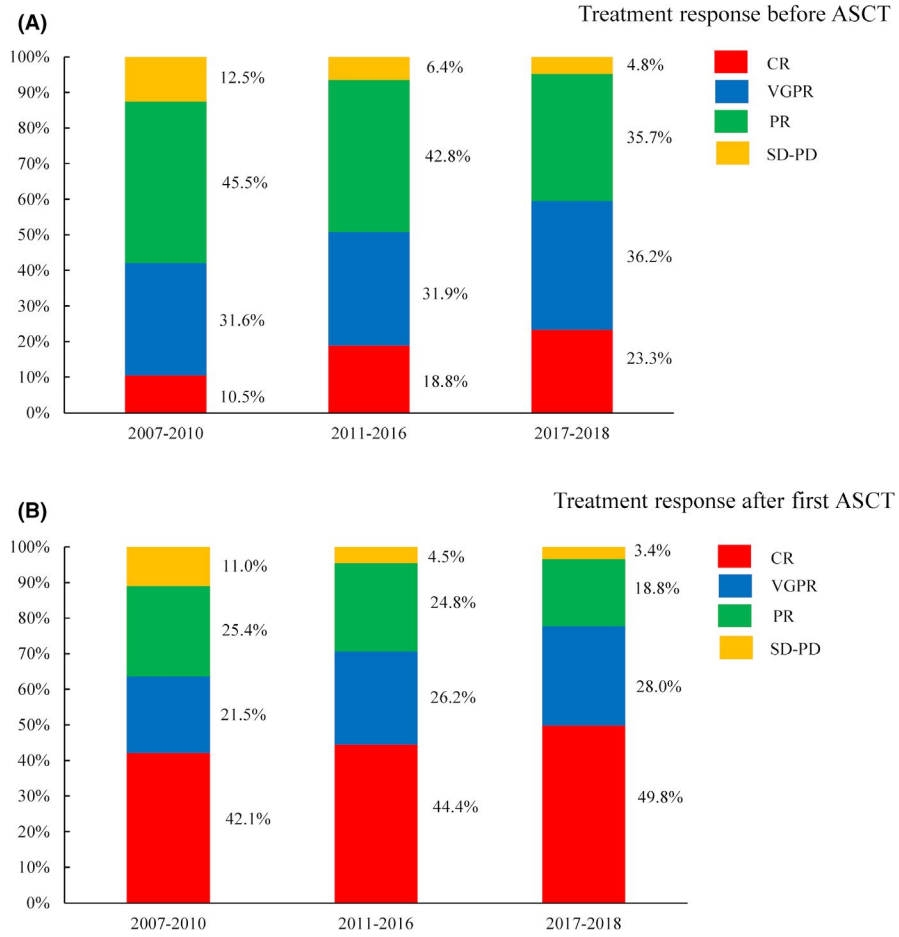


FIGURE 5 Percentages of treatment response (A) before and (B) after autologous stem cell transplantation (ASCT) in Japanese patients with multiple myeloma according to the year of ASCT: group 1, 2007-2010; group 2, 2011-2016; and group 3, 2017-2018. Treatment responses before and after ASCT were divided into four categories: complete response (CR; red), very good partial response (VGPR; blue), partial response (PR; green), and stable disease-progressive disease (SD-PD; yellow)

of both the pre- and post-ASCT responses enhanced the post-ASCT OS among MM patients in the modern era of new medicines.

4 | DISCUSSION

The results of our present analyses of 7323 Japanese patients with MM clearly showed the improvement of OS over time (group 1 [2007-2010] < group 2 [2011-2016] < group 3 [2017-2018]) with the introduction of new drugs for treating MM patients after ASCT. Our earlier study showed that the prognosis of MM patients after ASCT improved with the introduction of PI.[4] The present study further analyzed the impact of other new drugs brought into clinical settings after 2011.

The prognosis of MM was dramatically improved in the present group 2 compared to that of group 1. The prognosis of group 3 was improved compared to that of group 2, but the most marked improvement was limited to the traditionally low-risk patients (eg, those with younger age, a good PS, and not having an unfavorable karyotype). The standard error shown in Figure 4B is longer compared to that in Figure 4A; the difference between these two graphs might be due in part to the smaller number of patients analyzed in group 3. As we noted above, the observation period might be short for detecting the differences in OS, particularly in group 3.

When we focused on the treatment response before ASCT, we observed that the rates of CR and VGPR before ASCT increased over time. We speculate that the improvement in the patients' pre- and post-ASCT responses in the modern era of new MM drugs contributed to the improvement in the patients' OS.

The results of our analyses also confirmed the favorable prognostic factors in the modern era, ie, age less than 65 years, a good PS, a low ISS stage, early ASCT, a good treatment response before ASCT, receiving ASCT during the modern era, and double ASCT. We observed that these traditional prognostic factors (such as PS and ISS) are holding true even in the era of new MM drugs, but these traditional markers against the prognosis are becoming less important. However, the type of cytogenetic abnormality was revealed as an important prognostic factor (Figure 3).

Based on the improvement of both PFS and OS in the EMN02 study, ASCT became the mainstay for transplant-eligible MM patients.[12] The improvement of PFS was also demonstrated in the IFM 2009 study, but an improvement in OS was not detected in that study.[13] This result might indicate that the significance of early ASCT could change in the era of new drugs for treating MM.

Our findings could not verify some of the prognostic markers that were identified in previous studies.[14-16] First, in ASCT-eligible MM patients, it has been recommended that ASCT be undertaken at an early time point, particularly within 6 months after diagnosis.[14,15] The present study revealed the beneficial effects of early

ASCT on the patients' OS in the multivariate analysis, but not in the univariate analysis. We speculate that there is a subgroup of patients who could obtain benefit from double ASCT. However, it would be more important to achieve a better treatment response before ASCT regardless of other risk factors. The correlation between a deeper response during ASCT and favorable prognosis has been shown in other studies.[13,17,18]

Second, it was reported that the stem cell dose correlated with better OS before PI, IMiDs, and mAbs were available.[16] However, in our present investigation, the number of $CD34^+$ cells did not correlate with OS. The importance of early ASCT and the stem cell dose might be changing in the modern era of new medicine.

Another study reported the improvement of prognosis in high-risk MM patients by the introduction of bortezomib.[19] Our present findings are partly compatible with this result when we compare the prognoses of the ISS stage I and II patients in group 3. However, the prognosis of MM in patients with an unfavorable cytogenetic abnormality or ISS stage III remained worse in our study. The improvement of the prognosis of advanced-stage MM patients with high-risk cytogenetic abnormalities remains an important task.

Double ASCT did not improve the OS of MM patients as a whole in previous studies, and the question of whether high-risk patients might benefit from double ASCT has not been answered.[20,21] We observed a benefit of double ASCT on the patients' OS in the multivariate analysis but not in the univariate analysis (Table 2, Figures S6 and S7). Double ASCT might be beneficial for a subgroup of patients (particularly those in group 1), but we could not precisely determine the subgroup. Monoclonal Abs and carfilzomib could overcome the disadvantage of high-risk patients. It has been widely accepted that once an MM patient has relapsed, a second relapse would be unavoidable, and the interval before the second relapse would be shorter than that of the first relapse. The results of our analyses indicated that the treatment response before ASCT was correlated with OS in both the high-risk and non-high-risk patients. To overcome the poor prognosis of high-risk cases, we think that it is especially important to obtain as deep a response as possible by using the new drugs at an earlier time point of treatment. We plan to confirm this new treatment strategy in a future prospective study.

There are some limitations in this study. First, given that we did not have enough data regarding the details of the patients' treatment regimens, we arbitrarily categorized the patients into three treatment cohorts. The observation period in group 3 could be short, and the data from group 3 are considered to be exploratory. Second, we could not directly analyze the impact of each new drug on the patients' OS, because we did not have detailed information about the treatment regimens of groups 1, 2, and 3 in the TRUMP database. Third, we could not calculate the patients' PFS due to limited data regarding the relapse of MM in this study. Finally, we were able to analyze the cases of only some of the patients based on the risk of cytogenetic abnormality or post-ASCT response, because the information about cytogenetic abnormality and post-ASCT responses was limited. Additionally, we could not analyze the influence of new drugs against EMM, which is associated with poor prognosis due to relapse and refractoriness to treatment,[22] because the category of EMM has not been included in the TRUMP database. These limitations need to be analyzed in future studies.

In conclusion, the results of this study showed that the OS of patients with MM after ASCT has improved over time along with the introduction of new drugs for the treatment of MM. The prognosis of high-risk MM patients with a cytogenetic abnormality and ISS stage III requires further improvement.

ACKNOWLEDGMENTS

This study was undertaken with the support of the MM working group in JSTCT. This work was supported in part by the Practical Research Project for Allergic Diseases and Immunology (Research Technology of Medical Transplantation) from the Japan Agency for Medical Research and Development (Grant 18ek0510023h0002).

DISCLOSURE

S. Fuchida received personal fees from Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Janssen Pharmaceutical KK, Sanofi Pharmaceutical Co., Ltd., Bristol-Myers Squibb Co., Ltd., and Celgene Co., Ltd. outside the submitted work. N. Tsukada received personal fees from Takeda Pharmaceutical Co., Ltd. and Sanofi Pharmaceutical Co., Ltd. outside the submitted work. S. Kako received honoraria from Bristol-Myers Squibb Co., Ltd., Celgene Co., Ltd., Pfizer Pharmaceutical Co., Ltd., Sanofi Pharmaceutical Co., Ltd., and Takeda Pharmaceutical Co., Ltd. outside the submitted work. S. Iida received honoraria and research funds from Janssen Pharmaceutical KK, Takeda Pharmaceutical Co., Ltd., Ono Pharmaceutical Co., Ltd., Sanofi Pharmaceutical Co., Ltd., Celgene Co., Ltd., and Daiichi Sankyo Co., Ltd., and research funds from Bristol-Myers Squibb Co., Ltd., AbbVie Inc., Chugai Pharmaceutical Co., Ltd., and Kyowa Kirin Co., Ltd. outside the submitted work. Y. Kanda received honoraria from Celgene Co., Ltd. and research funds from Takeda Pharmaceutical Co., Ltd. and Ono Pharmaceutical Co., Ltd., outside the submitted work. The other authors have no conflict of interest.

ORCID

Yutaka Shimazu https://orcid.org/0000-0002-1604-7220
Shin-ichi Fuchida https://orcid.org/0000-0002-4147-9113
Satoshi Yoshioka https://orcid.org/0000-0003-3664-6324
Shinsuke Iida https://orcid.org/0000-0002-4951-960X

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SUPPORTING INFORMATION

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How to cite this article: Shimazu Y, Mizuno S, Fuchida S-I, et al; the working group of the Japan Society for Transplantation, Cellular Therapy. Improved survival of multiple myeloma patients treated with autologous transplantation in the modern era of new medicine. *Cancer Sci*. 2021;00:1–12. https://doi.org/10.1111/cas.15163