

**Supplementary Table 1. Characteristics of newly diagnosed multiple myeloma patients**

Characteristics	NDMM patients (N = 25) (%)
Age, years; median (range)	64 (46-80)
Sex (M/F)	15 (60)/10 (40)
Serum M-protein	
IgG	12 (48)
IgA	6 (24)
Light chain, kappa	4 (16)
Light chain, lambda	2 (8)
Others	1 (4)
Durie-Salmon stage	
IIIa/ IIIb	17 (68)/8 (32)
ISS stage	
I/II/III	5 (20)/12 (48)/8 (32)
Cytogenetics*	
Standard risk/ High risk/NA	17 (68)/7 (28)/1 (4)
Myeloma bone disease on plain radiographs yes/no	19 (76)/6 (24)
Serum M-protein at diagnosis <sup>†</sup> , g/dL, median (range)	4.12 (1.62-5.54)
Cr at diagnosis, mg/dL, median (range)	1.2 (1.0-5.0)
β2-microglobulin at diagnosis, mg/mL, median (range)	3.9 (1.9-12.6)
Hb at diagnosis, g/dL, median (range)	10.0 (5.7-14.3)
Ca at diagnosis, mg/dL, median (range)	9.0 (7.7-14.7)
LDH at diagnosis, U/L, median (range)	429 (148-790)

Ca, calcium; Cr, creatinine; F, female; Hb, hemoglobin; LDH, lactate dehydrogenase; M, male; NA, non-available; NDMM, newly diagnosed multiple myeloma

\* High-risk cytogenetics is defined as hypodiploidy or deletion of chr13 on conventional cytogenetics or presence of t(4;14), t(14;16), -17p on fluorescent *in situ* hybridization and/or conventional cytogenetics. All other cytogenetic abnormalities were considered standard risk.

<sup>†</sup> Patients with measurable serum M protein of at least 1 g per 100mL were included.

**Supplementary Table 2. Immune cell populations in NDMM and RRMM**

Parameters	Healthy volunteers (n = 38)	Multiple myeloma patients	
		NDMM (n = 25)	RRMM (Prior to Len-dex) (n = 90)
Frequency of cell population (%), mean $\pm$ SE			
CD3 <sup>+</sup>	63.75 $\pm$ 1.79	55.76 $\pm$ 4.00	51.65 $\pm$ 1.79
CD4 <sup>+</sup>	40.08 $\pm$ 1.61	36.39 $\pm$ 3.28	22.49 $\pm$ 1.29
CD8 <sup>+</sup>	21.68 $\pm$ 1.35	17.35 $\pm$ 1.91	28.16 $\pm$ 1.35
NK cell (CD16 <sup>+</sup> CD56 <sup>+</sup> )	10.90 $\pm$ 1.00	12.15 $\pm$ 1.88	11.07 $\pm$ 0.76
NKT-like cell (CD3 <sup>+</sup> CD56 <sup>+</sup> )	4.72 $\pm$ 0.80	3.32 $\pm$ 0.85	2.30 $\pm$ 0.22
G-MDSC	0.09 $\pm$ 0.02	0.09 $\pm$ 0.02	0.11 $\pm$ 0.01
M-MDSC	0.27 $\pm$ 0.04	2.19 $\pm$ 0.54	0.35 $\pm$ 0.04
Absolute count of cell population, cells/ $\mu$ L, mean $\pm$ SE			
CD3 <sup>+</sup>	-	1206.65 $\pm$ 115.81	1042.66 $\pm$ 61.14
CD4 <sup>+</sup>	-	785.57 $\pm$ 92.06	447.52 $\pm$ 33.57
CD8 <sup>+</sup>	-	378.20 $\pm$ 48.45	575.80 $\pm$ 40.50
NK cell (CD16 <sup>+</sup> CD56 <sup>+</sup> )	-	240.50 $\pm$ 35.21	214.3 $\pm$ 17.03
NKT-like cell (CD3 <sup>+</sup> CD56 <sup>+</sup> )	-	69.37 $\pm$ 19.11	46.51 $\pm$ 5.38
G-MDSC	-	1.80 $\pm$ 0.48	2.05 $\pm$ 0.20
M-MDSC	-	46.78 $\pm$ 13.51	6.46 $\pm$ 0.78

G, granulocytic; Len-dex, lenalidomide and low-dose dexamethasone; M, monocytic; MDSC, myeloid-derived suppressor cell; NDMM, newly diagnosed multiple myeloma; NK, natural killer; RRMM, refractory/relapsed multiple myeloma; SE, standard error

**Supplementary Table 3. Univariate analyses of predictive factors for response, TTNT, and TTP**

Univariate variables	Response ( $\geq$ VGPR)		TTNT		TTP	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
<b>Frequency of cell population (%), baseline</b>						
CD3 <sup>+</sup>	0.99 (0.96-1.01)	0.352	1.01 (0.99-1.04)	0.298	1.00 (0.98-1.02)	0.830
CD4 <sup>+</sup>	1.01 (0.97-1.05)	0.610	1.00 (0.97-1.03)	0.970	1.00 (0.98-1.03)	0.771
CD8 <sup>+</sup>	0.97 (0.94-1.01)	0.117	1.02 (0.99-1.05)	0.176	1.00 (0.98-1.03)	0.875
NK cell (CD16 <sup>+</sup> CD56 <sup>+</sup> )	1.00 (0.94-1.07)	0.941	1.01 (0.96-1.06)	0.773	1.00 (0.96-1.04)	0.963
NKT-like cell (CD3 <sup>+</sup> CD56 <sup>+</sup> )	0.90 (0.72-1.13)	0.365	0.96 (0.79-1.16)	0.640	0.84 (0.70-1.02)	0.072
G-MDSC	0.33 (0.01-26.44)	0.622	11.19 (0.70-177.8)	0.087	5.95 (0.31-114.0)	0.236
M-MDSC	1.94 (0.53-7.08)	0.317	1.21 (1.53-2.77)	0.645	1.17 (0.57-2.40)	0.663
<b>Frequency of cell population (%), after 3 cycles</b>						
CD3 <sup>+</sup>	1.01 (0.98-1.05)	0.520	0.98 (0.96-1.01)	0.235	0.99 (0.96-1.01)	0.163
CD4 <sup>+</sup>	1.00 (0.96-1.05)	0.861	0.99 (0.95-1.03)	0.497	0.98 (0.95-1.02)	0.334
CD8 <sup>+</sup>	1.02 (0.96-1.08)	0.578	0.98 (0.93-1.02)	0.317	0.98 (0.94-1.02)	0.237
NK cell (CD16 <sup>+</sup> CD56 <sup>+</sup> )	0.97 (0.92-1.04)	0.399	1.03 (0.99-1.07)	0.212	1.01 (0.97-1.05)	0.713
NKT-like cell (CD3 <sup>+</sup> CD56 <sup>+</sup> )	1.03 (0.74-1.42)	0.873	0.95 (0.74-1.23)	0.695	0.90 (0.71-1.15)	0.401
G-MDSC	0.13 (0.01-31.45)	0.468	45.89 (0.54-3931.7)	0.092	0.04 (0.00-22.59)	0.315
M-MDSC	0.43 (0.14-1.31)	0.138	1.03 (0.83-1.28)	0.793	1.01 (0.83-1.22)	0.936
<b>Ratio of cell frequency after 3 cycles relative to baseline</b>						
CD3 <sup>+</sup>	8.89 (1.10-72.11)	0.041	0.19 (0.04-0.89)	0.035	0.50 (0.16-1.51)	0.217
CD4 <sup>+</sup>	4.37 (0.74-25.86)	0.104	0.31 (0.08-1.30)	0.110	0.58 (0.22-1.57)	0.286
CD8 <sup>+</sup>	4.35 (0.82-23.22)	0.085	0.24 (0.06-1.07)	0.061	0.46 (0.16-1.30)	0.144
NK cell	0.73 (0.35-1.52)	0.398	1.24 (0.86-1.78)	0.249	1.20 (0.87-1.65)	0.272
NKT-like cell	2.18 (0.86-5.48)	0.099	0.86 (0.45-1.64)	0.654	1.41 (0.84-2.37)	0.194
G-MDSC	1.08 (0.79-1.46)	0.634	1.13 (0.91-1.40)	0.260	1.03 (0.82-1.30)	0.782
M-MDSC	0.84 (0.68-1.03)	0.085	1.02 (0.90-1.14)	0.796	1.02 (0.93-1.12)	0.709

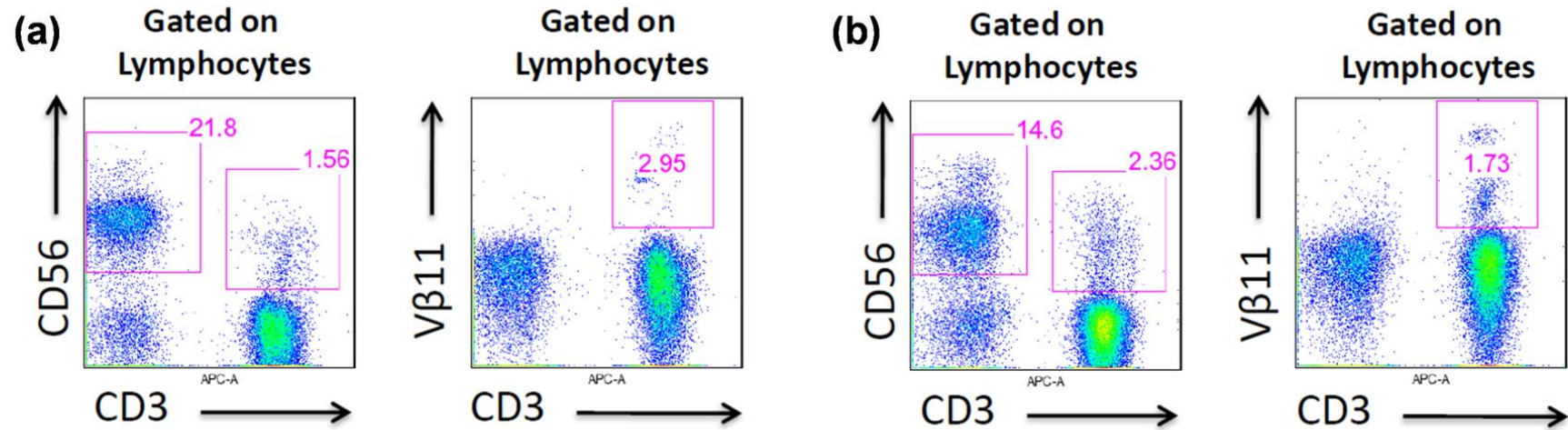
CI, confidence interval; G, granulocytic; M, monocytic; MDSC, myeloid-derived suppressor cell; NK, natural killer; TTNT, time to next treatment; TTP, time to progression; VGPR, very good partial response.

**Supplementary Table 4. Univariate analyses of clinical predictive factors for response, TTNT, and TTP**

Univariate variables	Response ( $\geq$ VGPR)		TTNT		TTP	
	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P	Hazard ratio (95% CI)	P
Age (years), continuous	1.06 (1.00-1.11)	0.045	1.00 (0.96-1.03)	0.867	1.01 (0.98-1.05)	0.458
Sex (F vs. M)	1.22 (0.51-2.96)	0.653	1.99 (0.98-4.03)	0.057	2.39 (1.30-4.41)	0.005
Immunoglobulin type (others vs. LCD)	0.65 (0.21-1.99)	0.445	0.70 (0.31-1.55)	0.374	1.13 (0.53-2.44)	0.749
ISS stage (II-III vs. I)	1.58 (0.54-4.63)	0.403	0.64 (0.30-1.40)	0.264	0.61 (0.31-1.19)	0.147
Cytogenetics (high risk vs. standard)	1.08 (0.37-3.16)	0.891	1.62 (0.76-3.45)	0.213	1.42 (0.72-2.79)	0.313
Lytic bone lesions (no vs. yes)	0.65 (0.20-2.13)	0.472	1.32 (0.57-3.04)	0.522	0.85 (0.38-1.91)	0.695
Hb (g/dL), continuous	1.23 (0.96-1.57)	0.098	0.85 (0.71-1.03)	0.090	0.86 (0.72-1.02)	0.084
Platelet ( $\times 10^9/L$ ), continuous	1.01 (1.00-1.01)	0.043	1.00 (1.00-1.00)	0.159	1.00 (0.99-1.00)	0.184
Ca (mg/dL), continuous	1.87 (0.98-3.57)	0.060	0.66 (0.37-1.17)	0.155	0.85 (0.55-1.32)	0.467
Cr (mg/dL), continuous	0.91 (0.66-1.26)	0.565	0.86 (0.63-1.17)	0.343	0.83 (0.61-1.12)	0.226
Albumin (mg/dL), continuous	1.61 (0.70-3.68)	0.263	0.57 (0.31-1.05)	0.071	0.62 (0.36-1.05)	0.075
LDH (U/L), continuous	1.00 (1.00-1.00)	0.756	1.00 (1.00-1.00)	0.495	1.00 (1.00-1.00)	0.421

Ca, calcium; Cr, creatinine; CI, confidence interval; F, female; Hb, hemoglobin; LCD, light chain disease; LDH, lactate dehydrogenase; M, male; TTNT, time to next treatment; TTP, time to progression; VGPR, very good partial response.

Supplementary Figure 1. NKT cells marking CD3+CD56+ (left panel of a and b) vs. Vβ11+CD3+ (right panel of a and b) were shown in two representative patients.



**Supplementary Figure 2. Changes in the level of various cytokines according to the response to Len-dex.** Changes in the level of each cytokine between baseline and after 3 cycles of Len-dex are indicated. There was no significant change in any cytokine after 3 cycles of Len-dex therapy in both the  $\geq$ VGPR group and  $\leq$ PR group. Data are presented as mean  $\pm$  SEM and 2-tailed Student t-tests were used to compare the continuous variables (baseline vs. after 3 cycles of Len-dex). Boxes indicate the first and third quartiles and the median is indicated with an interior line. Whiskers indicate minimum and maximum.

