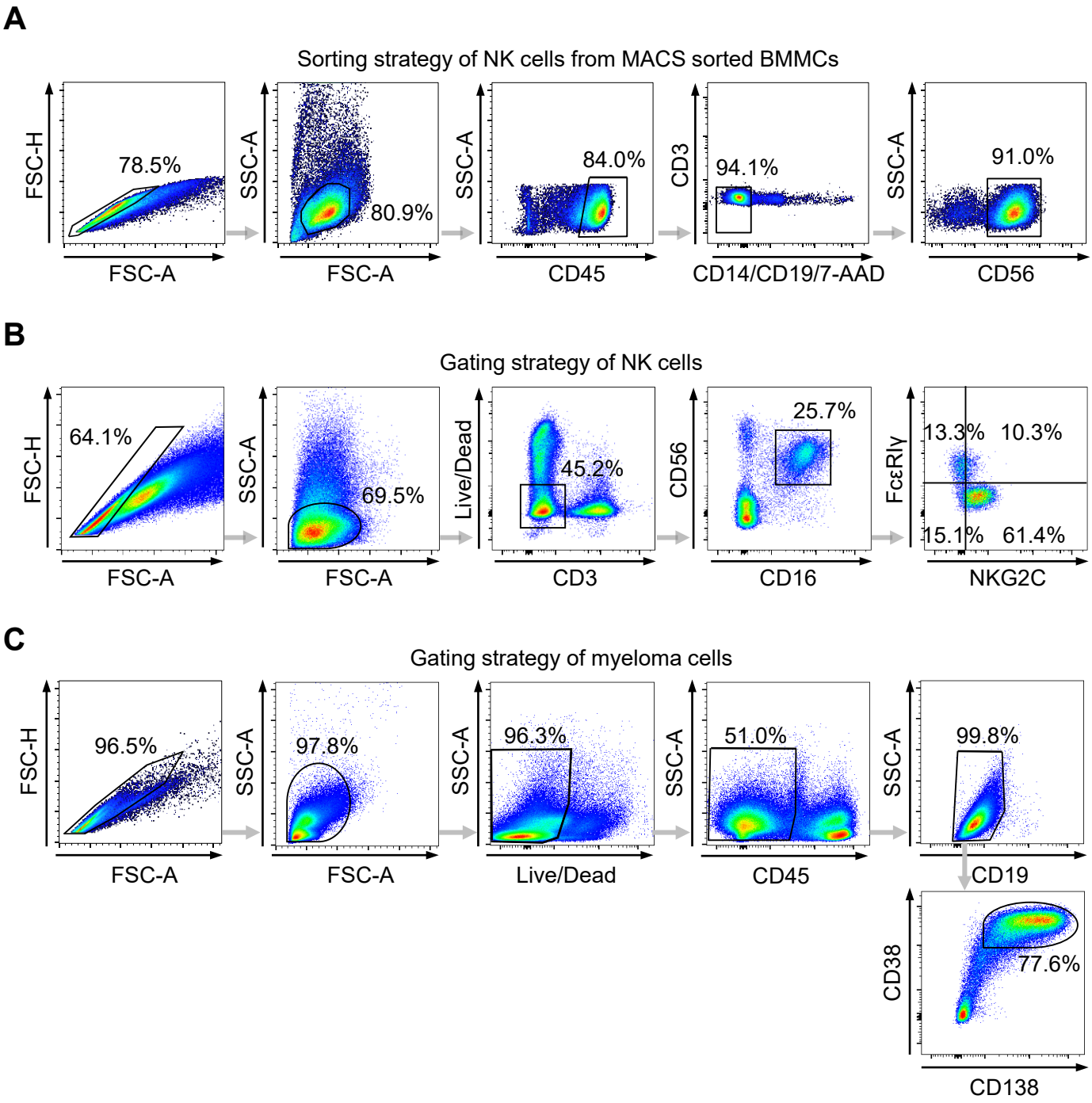
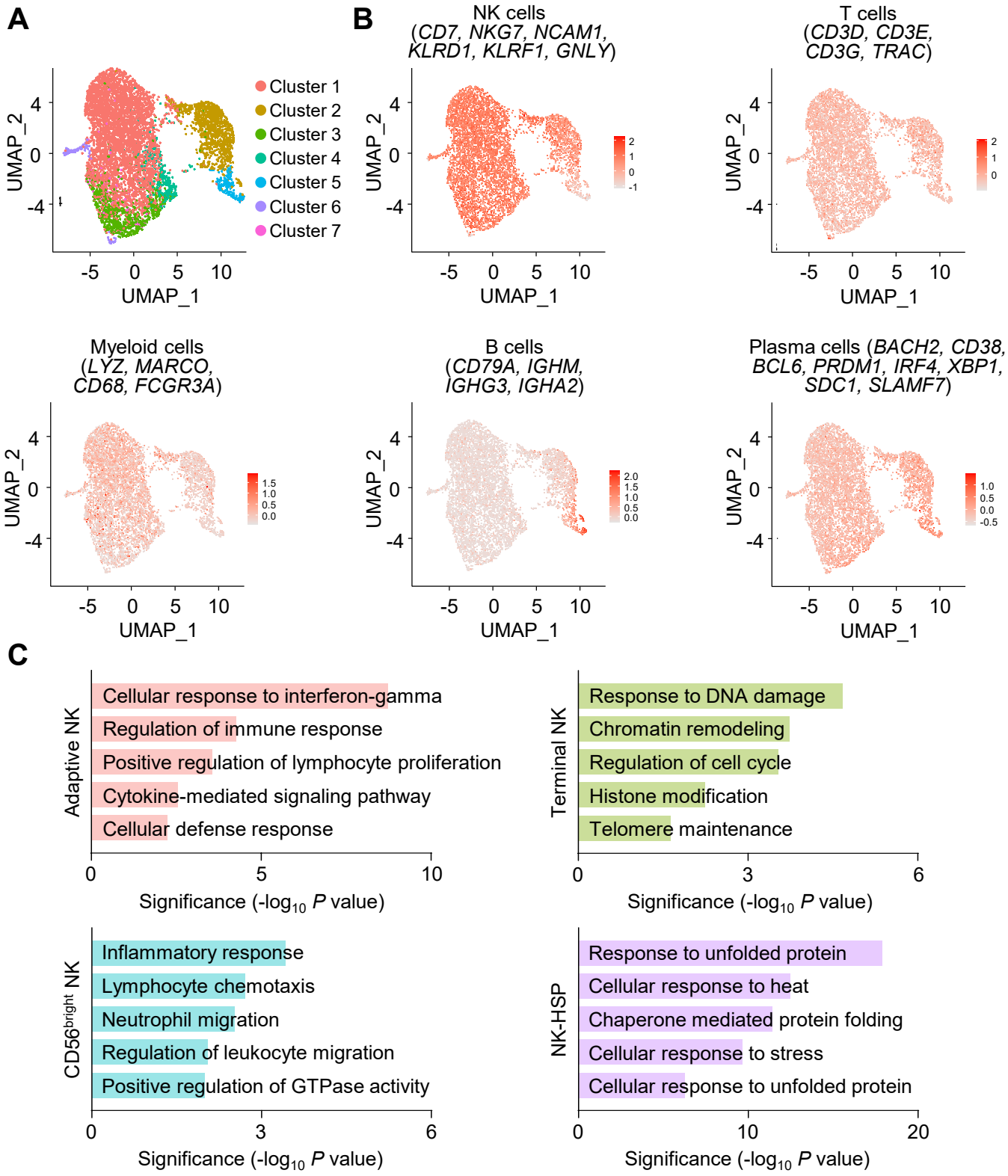
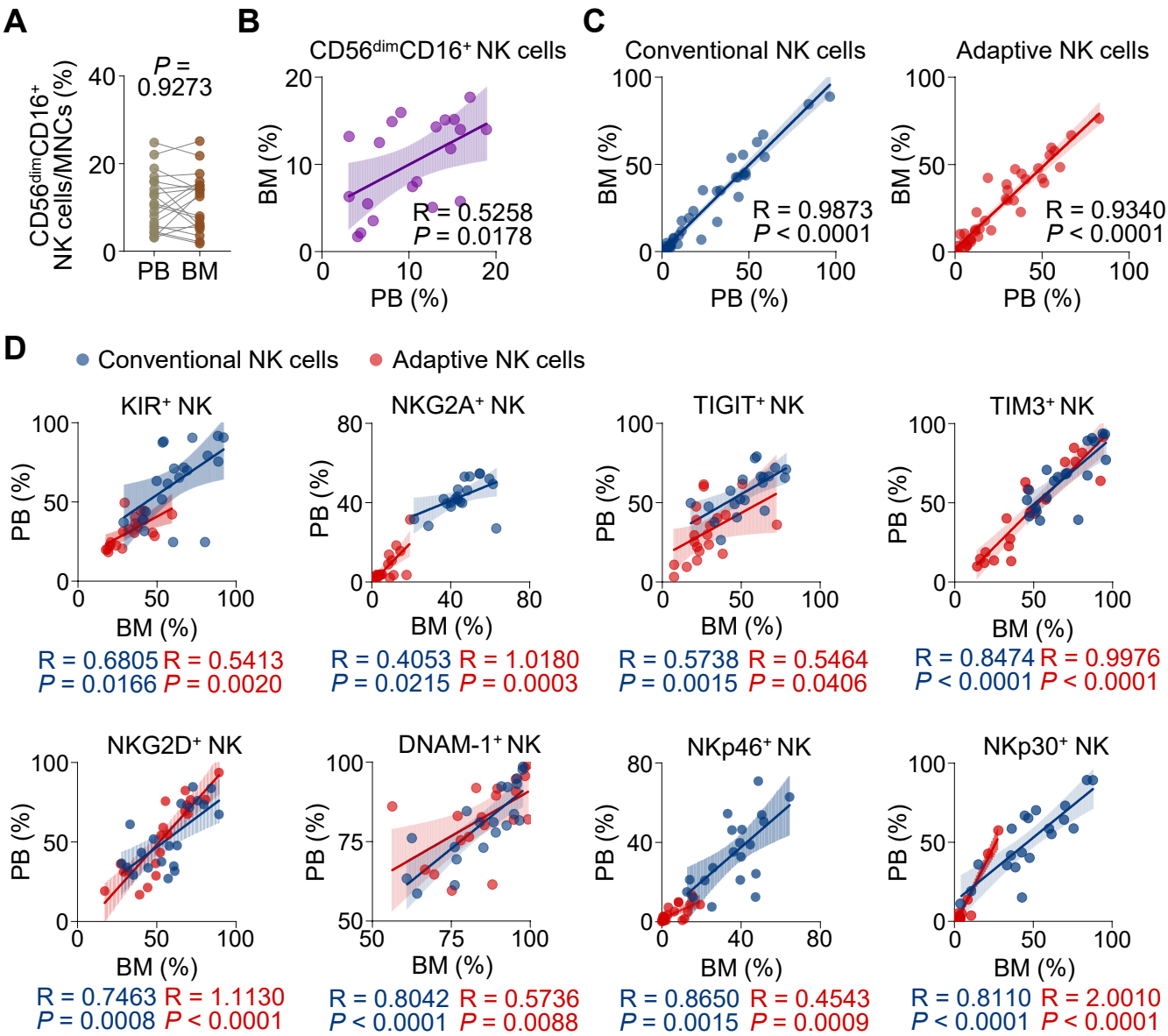


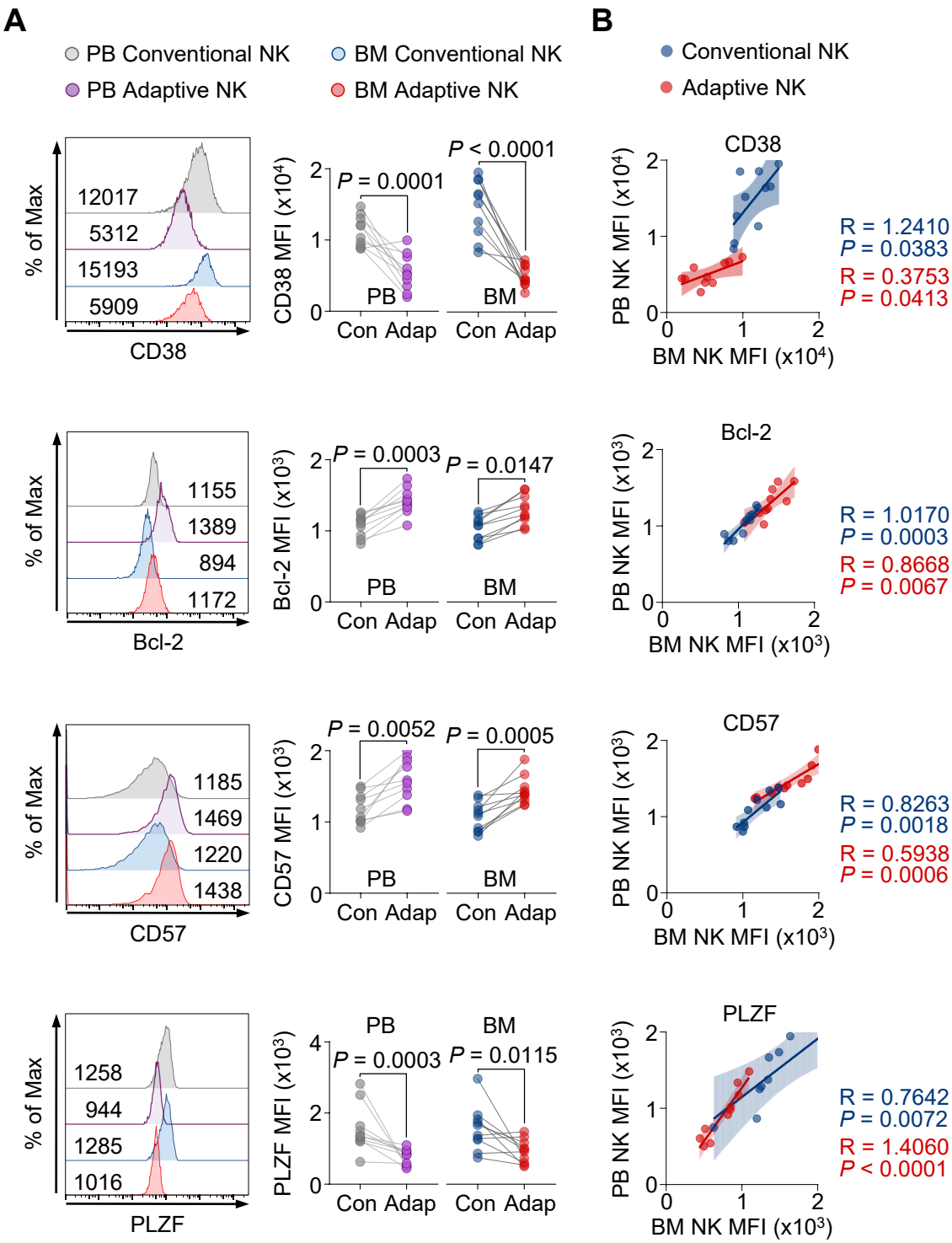

**Supplementary Figure 1. Sorting and gating strategy of NK cells and gating strategy of malignant plasma cells in BMMCs from patients with MM at diagnosis.**
**(A)** Representative flow cytometric analysis with sorting and **(B)** gating strategy for NK cells in BMMCs from a patient with MM at diagnosis. **(C)** Representative flow cytometric analysis with gating strategy for myeloma cells in BMMCs from MM patients at diagnosis.



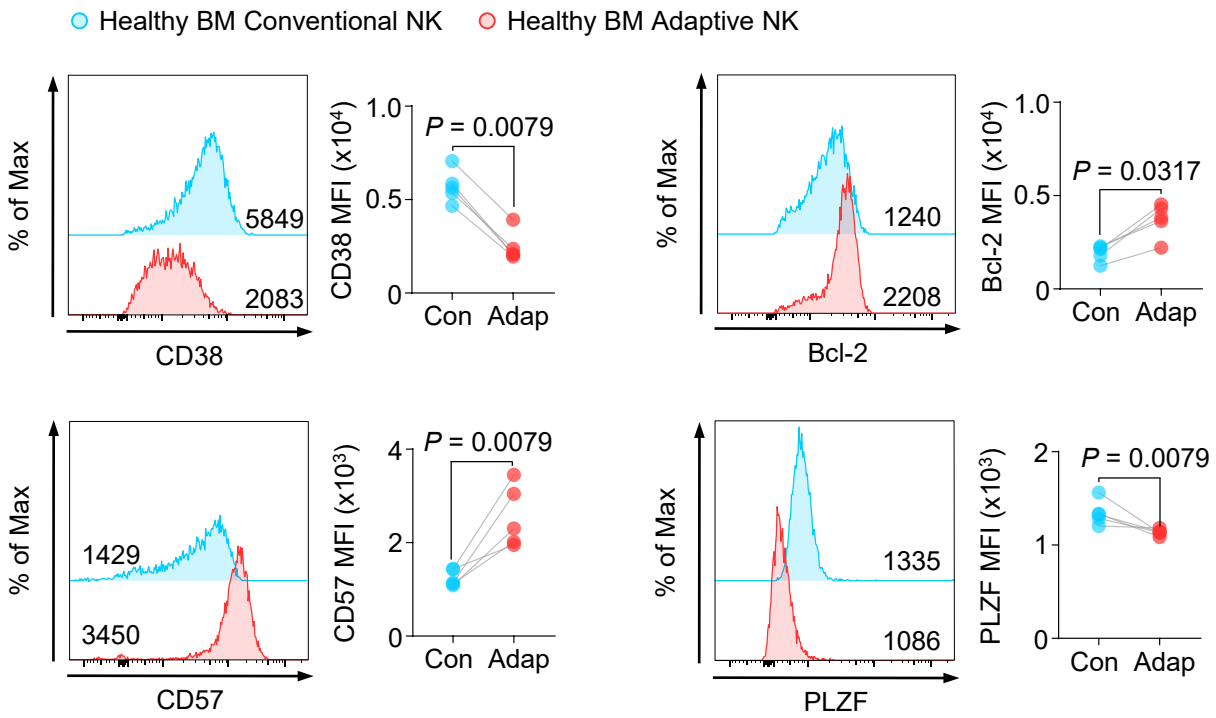

**Supplementary Figure 2. Gene ontology suggests discrete functions of NK cell subsets in MM patients.**
**(A)** Uniform manifold approximation and projection (UMAP) visualization of sorted NK cells derived from three newly diagnosed MM patients. Each cluster is represented by a specific color and number by unsupervised clustering. **(B)** Validation of NK cells and decontamination of B cells, plasma cells, T cells, and myeloid cells based on their marker gene expression projected on a UMAP plot based on the dataset depicted in **(A)**. **(C)** Significantly enriched GO terms for each NK cluster. Selected GO terms with a false discovery rate < 0.05 by the Mann-Whitney *U* test are presented.



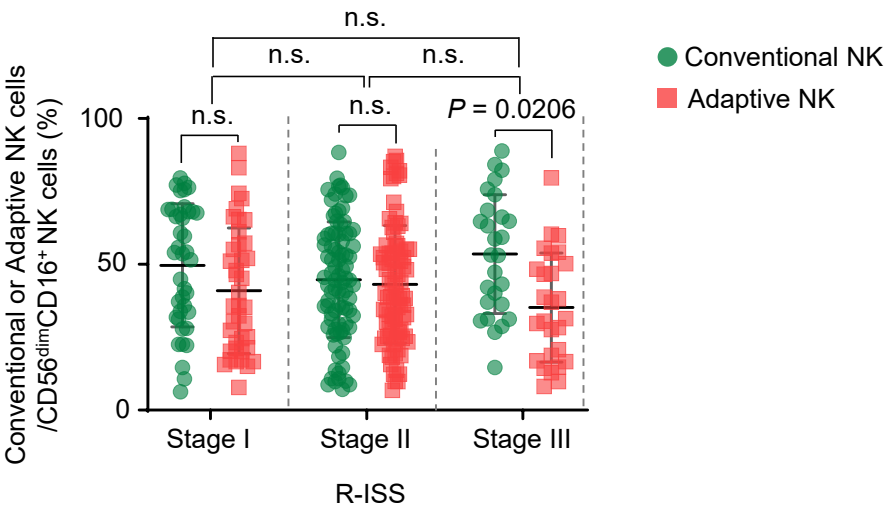

**Supplementary Figure 3. Immunophenotype of peripheral conventional and adaptive NK cells mirror those from the BM.**
**(A)** Percentages and **(B)** correlation of CD56$^{dim}$CD16$^{+}$ NK cells among mononuclear cells (MNCs) in paired PB and BM from patients with NDMM. *P*-values were determined versus PB using the Mann-Whitney *U* test in **(A)** and correlation coefficient (R) and *P*-value determined by Spearman's rank-order correlation test in **(B)**. **(C)** Correlation of conventional or adaptive NK cells among CD56$^{dim}$CD16$^{+}$ NK cells in paired PB and BM from NDMM patients ($n$ = 20). Correlation coefficients (R) and *P*-values were determined by Spearman's rank-order correlation test. **(D)** Correlation of the frequency of the indicated proteins on conventional or adaptive NK cells in paired PB and BM from patients with NDMM. Correlation coefficients (R) and *P*-values were determined by Spearman's rank-order correlation test. Each dot indicates a value obtained from one patient and $n$ = 20 patients per group from two independent experiments **(A-D)**.



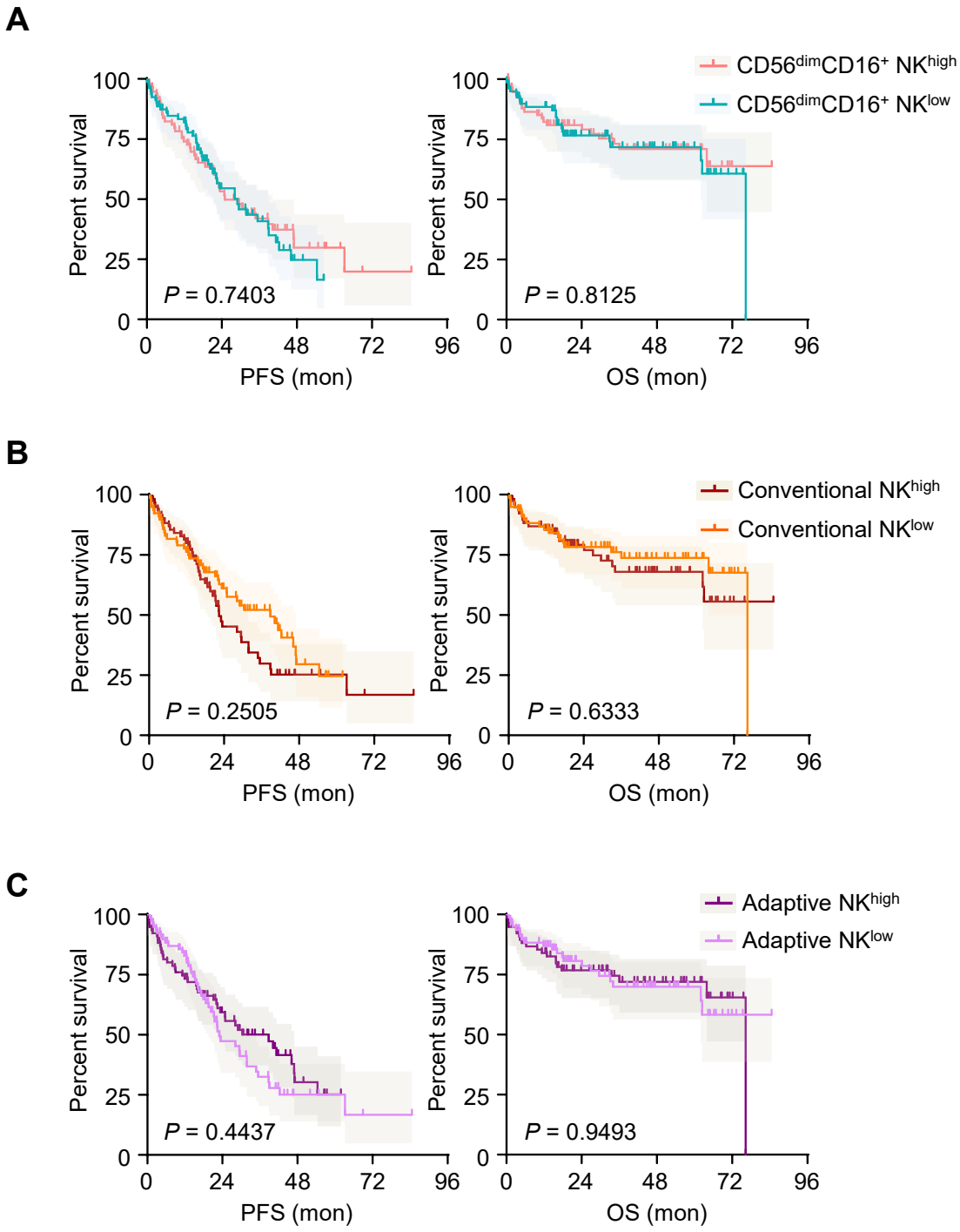

**Supplementary Figure 4. Adaptive NK cells in MM patients have lower CD38 expression with features of long-term memory and terminal differentiation.**
**(A)** Representative FACS histograms showing the expression of indicated proteins and their mean fluorescence intensity (MFI) among the gated conventional (Con) or adaptive (Adap) NK cells from patients with NDMM. *P*-values were determined versus conventional NK cells using the Mann-Whitney *U* test. **(B)** MFI correlation of conventional and adaptive NK cells presented in (**A**). Correlation coefficient (R) and *P*-value determined by Spearman's rank-order correlation test. Each dot indicates a value obtained from one patient and *n* = 10 patients per group from two independent experiments **(A,B)**.




**Supplementary Figure 5. Immunophenotypic features of healthy donor adaptive NK cells are similar to those of MM patients.**
Representative FACS histograms (left panels) showing the expression of the indicated proteins and comparison of mean fluorescence intensity (MFI) among the gated conventional (Con) or adaptive (Adap) NK cells (right panels) from healthy donors. Each dot indicates a value obtained from one patient and $n = 5$ healthy donors per group from two independent experiments. *P*-values were determined versus conventional NK cells using the Mann-Whitney *U* test.

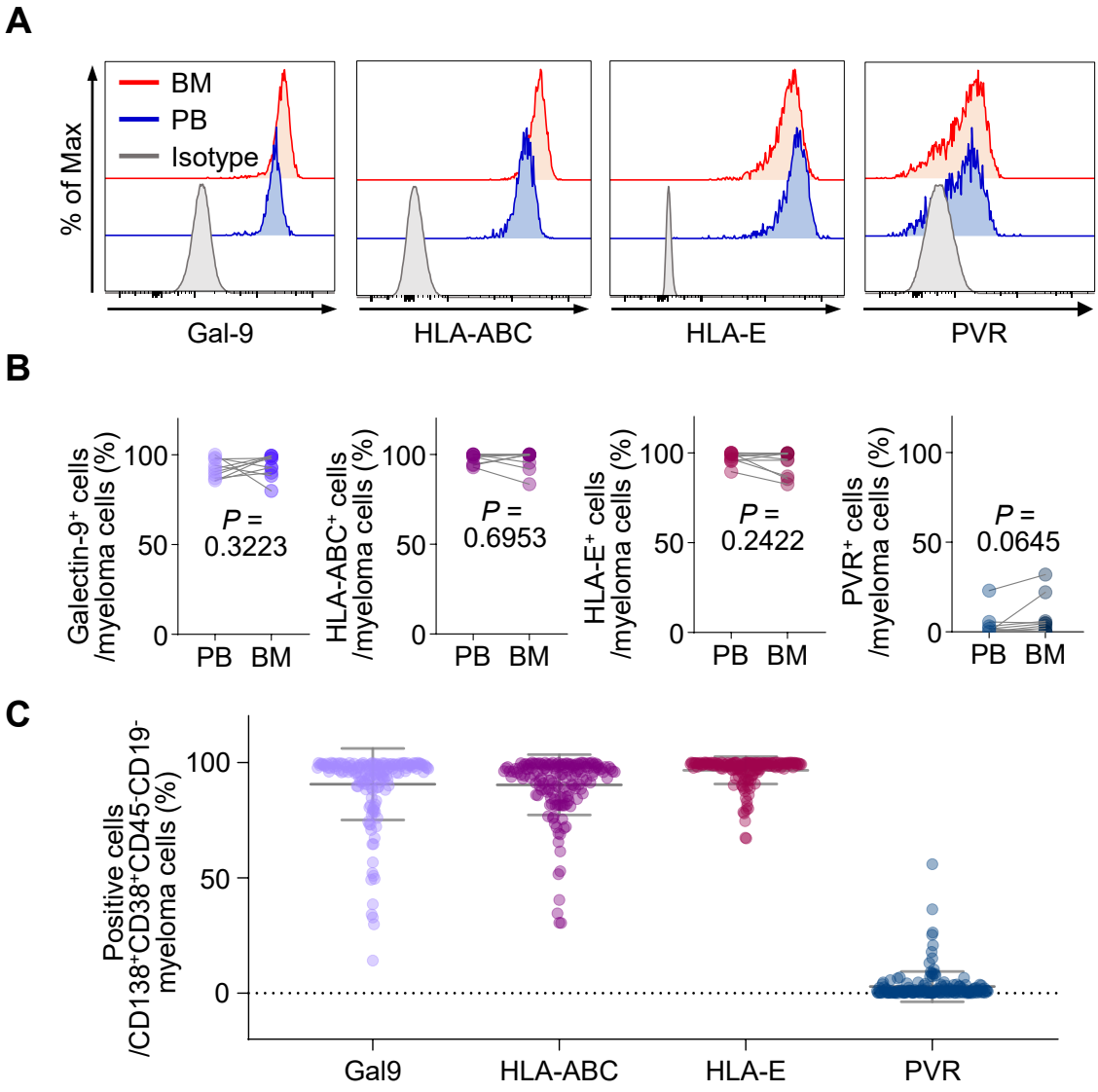



**Supplementary Figure 6. High-risk MM patients have lower proportion of adaptive NK cells.** Frequency of conventional or adaptive NK cells among $CD56^{dim}CD16^{+}$ NK cells according to the stage determined at diagnosis using revised international staging system (R-ISS). Each dot indicates a value of one patient and $n$ = 156 patients per group from the datasets presented in Supplementary Table 1. $P$-values were determined versus conventional NK cells, stage I, or stage II using the Mann-Whitney $U$ test. n.s., not significant.



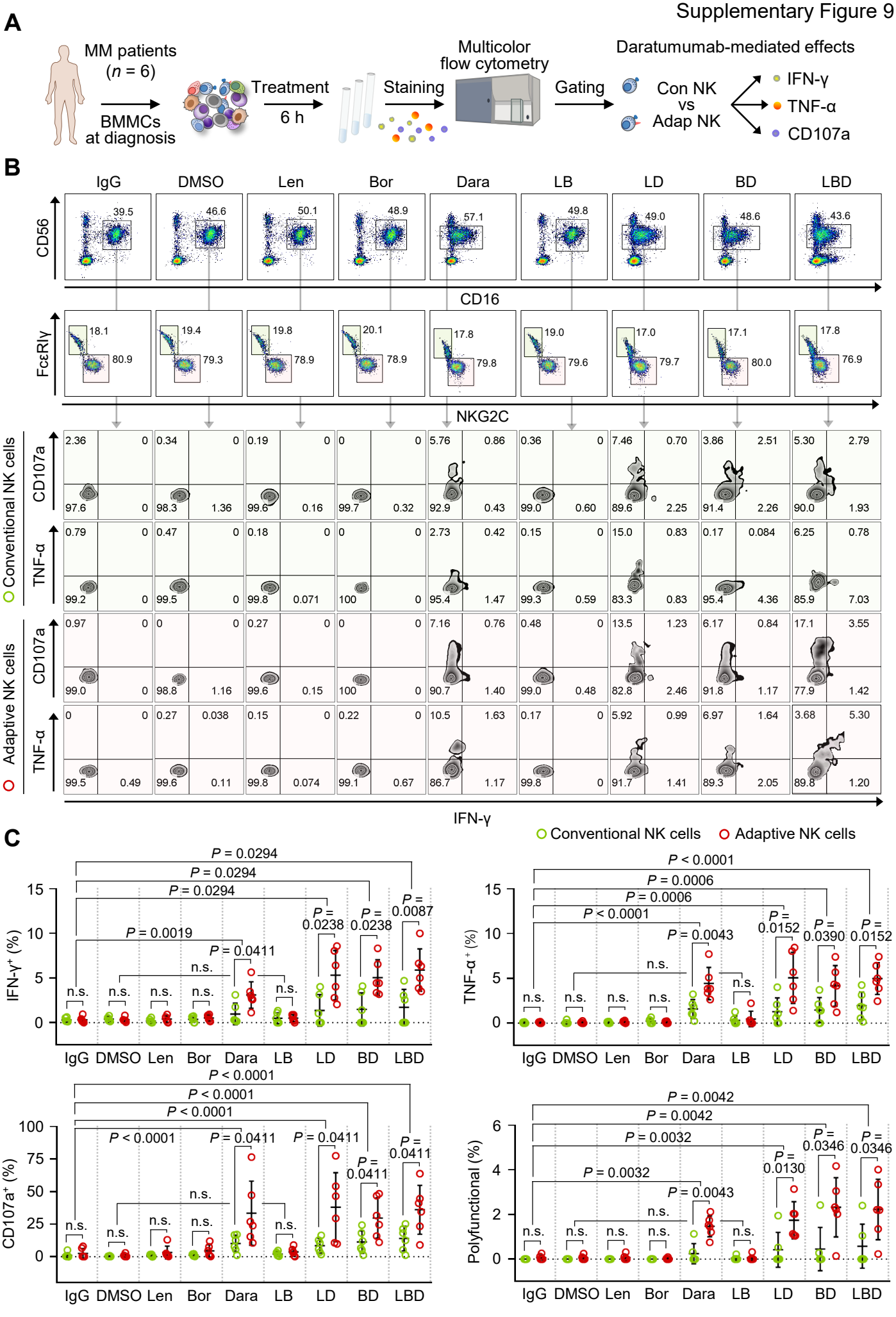

**Supplementary Figure 7. Minor association of the level of baseline BM NK cell subsets with the survival of MM patients treated without daratumumab.**

**(A-C)** Progression-free survival (PFS) and overall survival (OS) according to the proportion (low or high) of $CD56^{dim}CD16^{+}$ NK cells among BMMCs **(A)**, or according to the level of conventional **(B)** or adaptive **(C)** NK cells among $CD56^{dim}CD16^{+}$ NK cells in MM patients treated as described in Supplementary Table 1. NK subsets were dichotomized using the median cutoff values. Survivals were plotted using the Kaplan-Meier test and *P*-values were determined using the log-rank test.

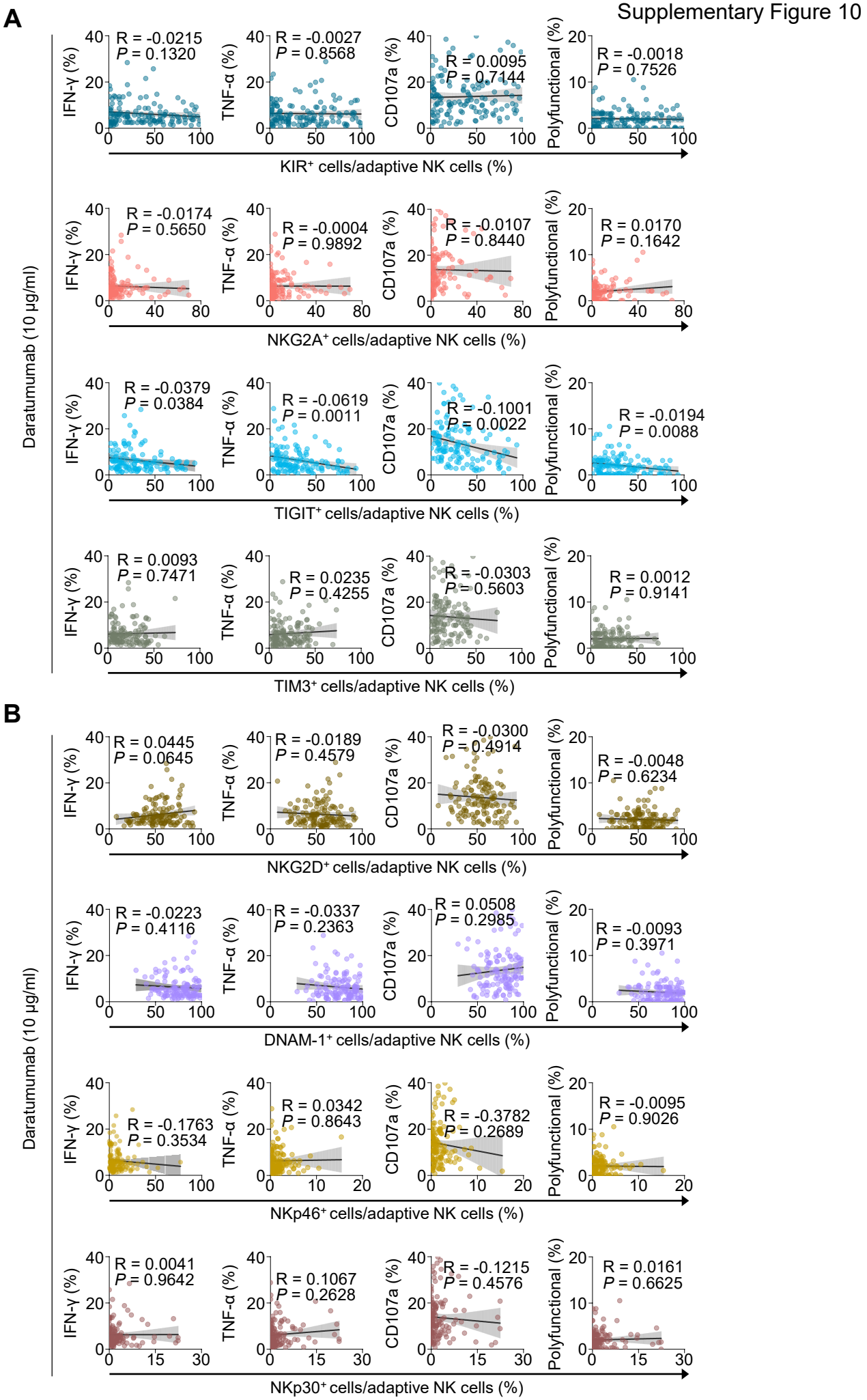



**Supplementary Figure 8. Immunophenotypes of malignant plasma cells in patients with MM at diagnosis.**

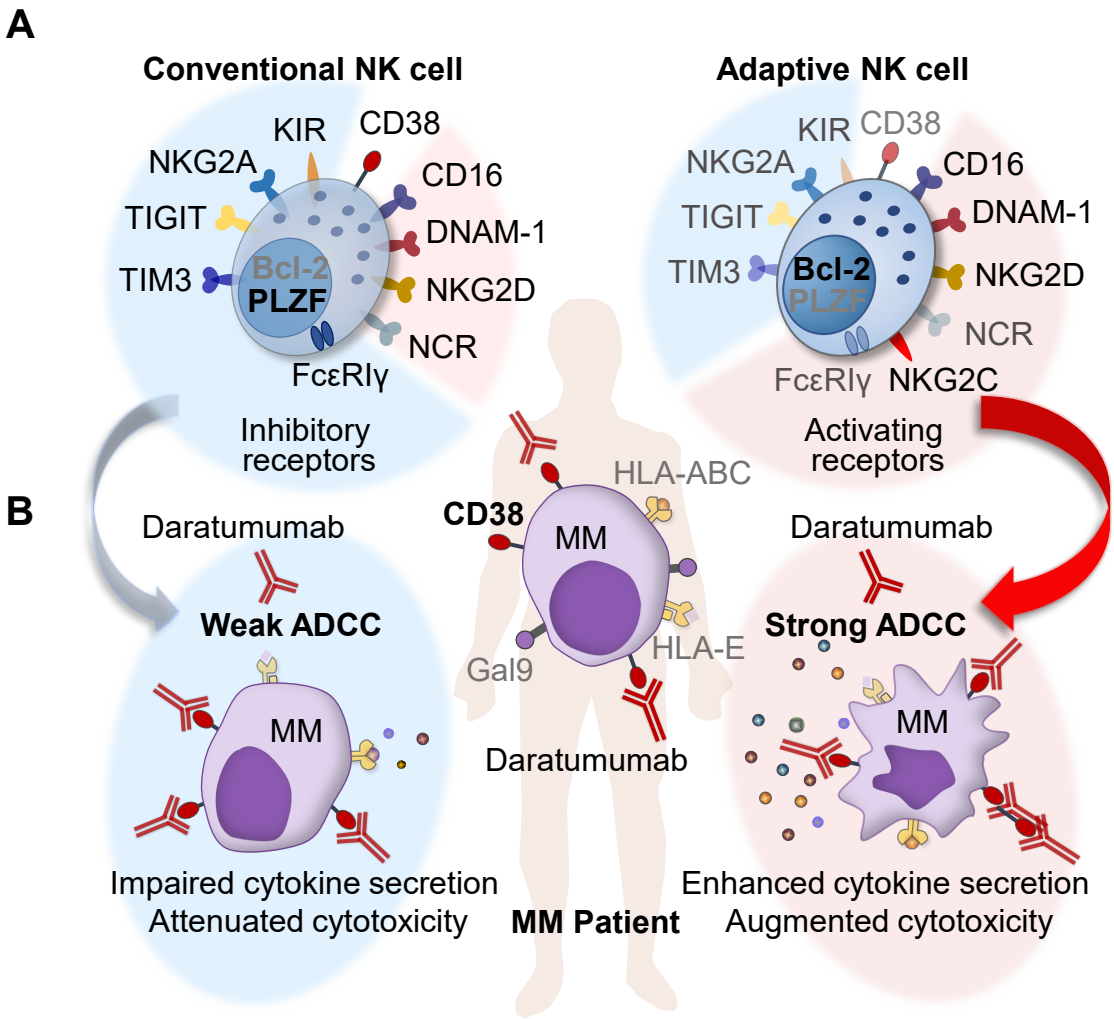
**(A)** Representative FACS histograms and **(B)** summary data showing the high level of expression of TIM-3 ligand Gal-9, KIR ligand HLA-ABC, and NKG2A ligand HLA-E, but low level of expression of TIGIT ligand PVR on malignant plasma cells in BMMCs (BM) and PBMCs (PB) from newly diagnosed MM patients. Each dot indicates a value obtained from one patient and $n$ = 10 patients per group from two independent experiments. $P$-values were determined versus PB using the Mann-Whitney $U$ test. **(C)** Validation of the plasma cell phenotype in all BM samples from newly diagnosed MM patients in this study. Each dot indicates a value obtained from one patient and $n$ = 157 patients per group from four independent experiments.


A
MM patients
(n = 6)
BMMCs
at diagnosis
Treatment
6 h
Staining
Multicolor
flow cytometry
Gating
Con NK
vs
Adap NK
Daratumumab-mediated effects
IFN-γ
TNF-α
CD107a
B
IgG
DMSO
Len
Bor
Dara
LB
LD
BD
LBD
CD56
CD16
FcεRIγ
NKG2C
Conventional NK cells
Adaptive NK cells
CD107a
TNF-α
IFN-γ
C
Conventional NK cells
Adaptive NK cells
IFN-γ+ (%)
TNF-α+ (%)
CD107a+ (%)
Polyfunctional (%)
n.s.

**Supplementary Figure 9. Minor roles of lenalidomide and bortezomib in differential functions of conventional and adaptive NK cells upon daratumumab treatment *ex vivo*.**
**(A)** Diagram depicting the analysis of effector functions of conventional (Con) or adaptive (Adap) NK cells by flow cytometry after *ex vivo* treatment of BMMCs from NDMM patients with IgG (10 μg/ml), DMSO (0.1%), lenalidomide (Len, 10 μM), bortezomib (Bor, 5 nM), daratumumab (Dara, 10 μg/ml), Len+Bor (LB), Len+Dara (LD), Bor+Dara (BD), or Len+Bor+Dara (LBD) for 6 h. **(B)** Representative flow cytometry plots of IFN-γ and TNF-α production, and CD107a expression after the indicated treatment among the conventional and adaptive NK cells gated from $CD56^{dim}CD16^{+}$ NK cells (*n* = 6 patients). **(C)** Summary of data in **(B)** showing the percentage of IFN-$\gamma^{+}$, TNF-$\alpha^{+}$, $CD107a^{+}$, and polyfunctional cells among the conventional and adaptive NK cells after the indicated treatment for 6 h. Each dot indicates a value obtained from one patient and *n* = 6 patients per group from three independent experiments. *P*-values were determined versus conventional NK cells within the treatment group or the indicated treatment group using the Mann-Whitney *U* test.


A
Daratumumab (10 μg/ml)
IFN-γ (%)
TNF-α (%)
CD107a (%)
Polyfunctional (%)
R = -0.0215
P = 0.1320
R = -0.0027
P = 0.8568
R = 0.0095
P = 0.7144
R = -0.0018
P = 0.7526
KIR+ cells/adaptive NK cells (%)
R = -0.0174
P = 0.5650
R = -0.0004
P = 0.9892
R = -0.0107
P = 0.8440
R = 0.0170
P = 0.1642
NKG2A+ cells/adaptive NK cells (%)
R = -0.0379
P = 0.0384
R = -0.0619
P = 0.0011
R = -0.1001
P = 0.0022
R = -0.0194
P = 0.0088
TIGIT+ cells/adaptive NK cells (%)
R = 0.0093
P = 0.7471
R = 0.0235
P = 0.4255
R = -0.0303
P = 0.5603
R = 0.0012
P = 0.9141
TIM3+ cells/adaptive NK cells (%)
B
Daratumumab (10 μg/ml)
R = 0.0445
P = 0.0645
R = -0.0189
P = 0.4579
R = -0.0300
P = 0.4914
R = -0.0048
P = 0.6234
NKG2D+ cells/adaptive NK cells (%)
R = -0.0223
P = 0.4116
R = -0.0337
P = 0.2363
R = 0.0508
P = 0.2985
R = -0.0093
P = 0.3971
DNAM-1+ cells/adaptive NK cells (%)
R = -0.1763
P = 0.3534
R = 0.0342
P = 0.8643
R = -0.3782
P = 0.2689
R = -0.0095
P = 0.9026
NKp46+ cells/adaptive NK cells (%)
R = 0.0041
P = 0.9642
R = 0.1067
P = 0.2628
R = -0.1215
P = 0.4576
R = 0.0161
P = 0.6625
NKp30+ cells/adaptive NK cells (%)

**Supplementary Figure 10. Correlation between NK inhibitory or activating receptor positivity and their functionality upon daratumumab treatment of adaptive NK cells *ex vivo*.**
**(A)** Correlation of the frequency of the indicated NK inhibitory receptor or **(B)** activating receptor positivity and the percentage of IFN-$\gamma^+$, TNF-$\alpha^+$, CD107a$^+$, and polyfunctional cells among the adaptive NK subpopulations after *ex vivo* daratumumab (10 μg/ml) treatment for 6 h in BMMCs from NDMM patients. Each dot indicates a value obtained from one patient and $n$ = 133 patients per group from four independent experiments.




**Supplementary Figure 11. Characteristic features of adaptive NK cells compared with conventional NK cells from patients with MM and their distinct responsiveness after daratumumab treatment.**
**(A)** Schematic images depicting the immunophenotypic differences between conventional NK cells and adaptive NK cells and their distinct responsiveness to anti-CD38 antibody daratumumab. Adaptive NK cells have attenuated expression of NK inhibitory receptors KIR, NKG2A, TIGIT, and TIM3, in addition to differential expression of activating receptors, including natural cytotoxicity receptors (NCRs) NKp46 and NKp30. **(B)** After daratumumab treatment, adaptive NK cells exhibit augmented effector functions with enhanced cytotoxicity against myeloma cells compared with conventional NK cells.