Genomic determinants impacting the clinical outcome of mogamulizumab treatment for adult T-cell leukemia/lymphoma

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MATERIAL AND METHODS

ATL patients and samples

Study subjects were mogamulizumab-naïve ATL patients without prior allogeneic HSCT, who had subsequently received mogamulizumab-containing treatment (n = 64). ATL diagnosis and clinical subtype assignment were according to the Japan Lymphoma Study Group recommendations.[2] The treatment strategy, which included mogamulizumab, was left to the clinical discretion of each investigator in the same manner as in the MIMOGA study (UMIN000008696).[12] Therapeutic efficacy of mogamulizumab treatment was assessed according to the international consensus response criteria and classified as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).[14] Fifty-three patients were from the cohort enrolled in the MIMOGA study, and another 11 received mogamulizumab-containing treatment at Nagoya City University Hospital (Nagoya, Japan), but were not participating in the MIMOGA study.[12] The current genomic study was approved by the Institutional Review Boards at all MIMOGA participating centers including Nagoya City University, as well as at the Japanese Foundation for Cancer Research, and Nagoya University Graduate School of Medicine. All patients provided written informed consent before blood or tissue sampling. Peripheral blood mononuclear cell (PBMC) or lymph node samples prior to mogamulizumab treatment were collected and prepared for exome and RNA-sequencing analysis. Exome sequencing was performed using paired tumor and normal DNA, derived from tumor cell- and normal cell-enriched samples, respectively, from the same patient. The latter were almost always PBMC from patients in hematological

remission after treatment.

DNA and RNA preparation for genomic analysis

Total DNA and RNA was extracted at JFCR using QIAamp DNA Micro Kits (QIAGEN, Hilden, Germany) and RNeasy Micro Kits (QIAGEN), respectively, according to the manufacturer's instructions. DNA quantity and quality were controlled using a NanoDrop 2000 (ThermoFisher, Waltham, MA) and Qubit 2.0 fluorometer (ThermoFisher), respectively. DNA with optical density 260/280 nm > 1.2 was used to select samples for exome sequencing. RNA quantity and quality were controlled with the NanoDrop 2000 (ThermoFisher) and Agilent 2100 Bioanalyzer (Agilent Technologies, Inc., Santa Clara, CA). RNA with optical density 260/280 nm > 0.8, RNA integrity number > 2 and DV200 > 38 was prepared for RNA-sequencing at JFCR. Samples from 64 and 63 patients finally passed these stringent quality assessments during exome and RNA-sequencing analyses, respectively.

Exome library preparation and sequencing

Two-hundred ng of DNA was subjected to shearing, end repair, phosphorylation and ligation to barcoded sequencing adaptors, and the ligated DNA was subjected to hybrid capture using the SureSelect Human All Exon V5 kit (Agilent Technologies, Inc.). The captured DNA was multiplexed and sequenced using an Illumina HiSeq2500.

RNA-sequencing

A total of 200 ng of RNA was converted into mRNA libraries using the TruSeq Stranded mRNA HT Sample Prep Kit (Illumina, Inc., San Diego, CA), according to the manufacturer's instructions. Libraries were sequenced as 101 + 8 + 8 + 101 bp with a dual-indexed run on an Illumina HiSeq2500 with a total of 136–440 million paired-end reads per tumor sample. RNA reads were aligned to the GRCh37 reference genome. Data with %Total Aligned > 0.88 and %Abundant < 0.3 were processed for further analyses. Transcripts per million reads mapped (TPMs) as gene expression values were computed by RSEM-1.3.0, mapped by bowtie2-2.2.3 and annotated by ENSEMBL release 75.[15] For further calculations, we transformed the TPMs by log10 after adding a pseudo value of 1 to avoid an infinite value.

Somatic variant call

Somatic single nucleotide variants (SNVs) were called with VarScan (ver. 2.3.7), MuTect (ver.1.1.4), and Karkinos (ver. 3.0.22) (Genome Science Laboratory, Research Center for Advanced Science and Technology, The University of Tokyo, http://sourceforge.net/projects/karkinos/), whereas somatic insertion-deletions (indels) were detected with VarScan (ver. 2.3.7), SomaticIndelDetector (ver. 1.5-30), and Karkinos (ver. 3.0.22) (Genome Science Laboratory, Research Center for Advanced Science and Technology, The University of Tokyo, http://sourceforge.net/projects/karkinos/).[16-18] SNVs and Indels were taken as genuine alterations when they were detected by at least 2 of the 3 callers, and the corresponding altered alleles were confirmed by RNA-sequencing. In this manner, SNVs and Indels could be evaluated in 63 patients

whose samples passed the quality assessments of exome and RNA-sequencing analyses. Loss of heterozygosity (LOH) in copy number was determined by the number of variant sequence reads compared with the wild-type in the tumor DNA. Tumor samples with a loss of the wild-type allele were defined as those with a variant read frequency of > 0.6.[19] Somatic copy number variations (CNVs) were detected using EXCAVATOR (ver. 2.2) for sequencing results.[20] The BAMs were used to detect somatic copy number aberrations in a tumor by comparing normal and tumor DNAs. The heterogeneous shifting level model (HSLM) algorithm implemented in EXCAVATOR was used for segmentation. HSLM results were further analyzed by GISTIC (version 2.0.22) to determine recurrent altered segments.[21] Segments with log R ratio (LRR) over +0.9 (corresponding to copy number [CN] ≥ 4) and below -1.3 (corresponding to CN = 0) were defined as amplification and homozygous deletion.

Fusion gene detection with RNA-seq

Three different tools were used to detect fusion genes, deFuse (version 0.6.1), TopHat (version 2.1.0), and fusionfusion (version 0.1.0) (Institute of Medical Science, The University of Tokyo, https://github.com/Genomon-Project/fusionfusion).[22,23] Only fusions detected by at least two tools were considered as genuine and used to further analysis.

Detection of structural variants of the 3' UTR of the *CD274* gene

Structural variants of the 3'UTR of the *CD274* (*PD-L1*) were detected using RNA-sequencing data in combination with SQUID (version 1.5), with

discrepancies in the level of expression between the 3'UTR and the entire gene as previously described.[24]

ATL driver genes

Fifty altered genes (*PLCG1, PRKCB, CARD11, CD28, VAV1, RHOA, FYN, IKBKB, RELA, IRF4, CBLB, TNFAIP3, NFKBIA, CSNK1A1, PTPRC, CCR4, CCR7, GPR183, S1PR1, STAT3, JAK3, NOTCH1, ATXN1, PIK3CD, CSNK2A1, CSNK2B, PDE7B, GATA3, TBL1XR1, IRF2BP2, ZEB1, ZNF638, YTHDF2, HNRNPA2B1, ZFP36L2, CD58, B2M, HLA-B, FAS, TET2, DNMT3A, IDH2, EP300, SETD2, KDM6A, TP53, CDKN2A, POT1, KMO, NOXA1*) were determined to be the drivers of ATL in a previous study.[13] Forty four genes with CNVs (*ATXN7L1 CARD11, CD28, IRF4, PRKCQ, CD247, ERC1, PAK2, DLG1, CBLB, TNFAIP3, TRAF3, COPS4, PTPRM, MAN2A1, GPR183, ATXN1, PTPN1, INPP4B, BCL11B, SKI, GATA3, PRDM1, CEBPA, IKZF2, ETV6, TBL1XR1, SYNCRIP, CELF2, CD274, PDCD1, CD58, HLA-A, HLA-B, ARID2, TP53, CDKN2A, NRXN3, IMMP2L, DPYD, FHIT, WWOX, ARHGAP15*) were also identified as drivers of ATL.[13] We pooled these data, excluded the overlapping genes, added an *HLA-C* gene, and thus arrived at a total of 81 genes as ATL drivers. The types of alterations of these genes are shown in Table S1.

HLA genotyping and alteration call

HLA class I genotypes were determined via the OptiType algorithm (ver. 1.2.1) using normal sample exome data.[25] Haplotypes for HLA class II molecules were determined by Alphlard (version 2.1.0).[26] Somatic SNVs, indels,

and CNVs of *HLA-A*, *-B* and *-C* genes were identified with POLYSOLVER (ver. 1.0) and LOHHLA (ver. 20171108).[27,28] For the *B2M* gene, we used the somatic alteration call result described above.

Statistical analyses

Consensus Clustering was employed to identify clusters corresponding to distinct subgroups in the transcriptome with Bioconductor ConsensusClusterPlus.[29,30] We chose k-means clustering algorithm with Euclidean distance and a sub-sampling ratio of 0.8 for 1,000 iterations. Gene set analysis was performed with Ingenuity Pathway Analysis (IPA; version 01-12; QIAGEN, https://www.qiagenbioinformatics.com/products/ingenuitypathway-analysis). Differences between two groups were examined with the Mann–Whitney U test or Fisher´s exact test. Univariate and multivariate Cox proportional hazards regression models were used to identify prognostically relevant alterations, expression, or various biological scores. Before assessing the prognostic association, the expression and biological score data were transformed to binary information; the presence and absence of an alteration was determined based on values above and below a cut-off value, respectively, when the information was given as a numeric. The probability of survival was estimated by the Kaplan–Meier method, and survival times were compared using the log-rank test. Progression-free survival (PFS) was defined as the time from the first dose of mogamulizumab to progression, relapse, or death resulting from any cause, whichever occurred first. Overall survival (OS) was measured from the day of the first dose to death resulting from any cause. The survival estimate

was calculated with all transplanted patients (n = 9) censoring at the day of allogeneic HSCT. All analyses were performed with SPSS Statistics 25 (IBM Corporation, Armonk, NY) or R (version 3.5.2) (http://www.R-project.org). In this study, $P < 0.050$ (two-sided) was considered significant. In the case of multiple pair-wise comparisons, Bonferroni correction was used to adjust statistically significant *P* values.

Supplementary Table S1. Driver genes in ATL

Gene	Types of alterations	Gene	Types of alterations	Gene	Types of alterations
ARHGAP15	CNV	*FAS*	SNV, Indel	*PIK3CD*	SNV, Indel
ARID2	SNV, Indel, CNV	*FHIT*	CNV	*PLCG1*	SNV, Indel
ATXN1	SNV, Indel, CNV	*FYN*	SNV, Indel	*POT1*	SNV, Indel
ATXN7L1	SNV, CNV	*GATA3*	SNV, Indel, CNV	*PRDM1*	SNV, Indel, CNV
B2M	SNV, Indel	*GPR183*	SNV, Indel, CNV	*PRKCB*	SNV, Indel
BCL11B	SNV, CNV	*HLA-A*	SNV, Indel, CNV	*PRKCQ*	CNV
CARD11	SNV, Indel, CNV	*HLA-B*	SNV, Indel, CNV	*PTPN1*	CNV
CBLB	SNV, Indel, CNV	*HLA-C*	SNV, Indel, CNV	*PTPRC*	SNV
CCR4	SNV, Indel	*HNRNPA2B1*	SNV, Indel	*PTPRM*	CNV
CCR7	SNV, Indel	*IDH2*	SNV	*RELA*	SNV
CD247	CNV	*IKBKB*	SNV	*RHOA*	SNV
CD274	CNV, SV	*IKZF2*	CNV	*S1PR1*	SNV, Indel
CD28	SNV, CNV, Fusion	*IMMP2L*	CNV	*SETD2*	SNV, Indel
CD58	SNV, Indel, CNV	*INPP4B*	CNV	*SKI*	SNV, CNV
CDKN2A	SNV, CNV	*IRF2BP2*	SNV, Indel	*STAT3*	SNV, Indel
CEBPA	SNV, Indel, CNV	*IRF4*	SNV, CNV	*SYNCRIP*	CNV
CELF2	CNV	*JAK3*	SNV, Indel	*TBL1XR1*	SNV, Indel, CNV
COPS4	CNV	*KDM6A*	SNV, Indel	*TET2*	SNV, Indel
CSNK1A1	SNV	*KMO*	SNV	*TNFAIP3*	SNV, Indel, CNV
CSNK2A1	SNV	*MAN2A1*	CNV	*TP53*	SNV, Indel, CNV
CSNK2B	SNV, Indel	*NFKBIA*	SNV, Indel	*TRAF3*	SNV, CNV
DLG1	CNV	*NOTCH1*	SNV, Indel	*VAV1*	SNV
DNMT3A	SNV	*NOXA1*	SNV	*WWOX*	CNV
DPYD	CNV	*NRXN3*	CNV	*YTHDF2*	SNV, Indel
EP300	SNV, Indel	*PAK2*	CNV	*ZEB1*	SNV, Indel
ERC1	CNV	*PDCD1*	SNV, CNV	*ZFP36L2*	SNV
ETV6	CNV	*PDE7B*	SNV, Indel	*ZNF638*	SNV, Indel

CNV, copy number variation; Indel, insertion-deletion; SNV, single nucleotide variant; SV, structural variations

Supplementary Table S2. Patient demographics and clinical characteristics (n = 64)		
Characteristics		**number (%)**
Sex		
female		**31 (48)**
male		**33 (52)**
Age, years		
mean	**66**	
median	**68**	
range	**36-86**	
ATL clinical subtype		
acute		**46 (72)**
lymphoma		**7 (11)**
chronic		**11 (17)**
Previous systemic chemotherapy		
no		**26 (41)**
yes		**38 (59)**
ECOG PS		
0		**16 (25)**
1		**32 (50)**
2		**12 (19)**
3		**4 (6)**
Serum sIL-2R (U/mL)[$]		
mean	**16,332**	
median	**6,040**	
range	**629-227,000**	
LDH/ULN		
mean	**1.7**	
median	**1.2**	
range	**0.4-6.3**	

ATL, adult T-cell leukemia/lymphoma; ECOG, Eastern Cooperative oncology Group; PS, performance status; sIL-2R, soluble interleukin-2 receptor; ULN, upper limit of normal, [$]A patient's data was missing.

Supplementary Table S3. Frequencies and types of somatic alterations identified in driver genes

Gene	total number of alterations	types of alterations and number							
		Missense SNV	Truncation	Inframe indel	LOH by CN loss	Amplification	Homozygous deletion	Fusion	Others or mixed
PLCG1	26	23	1	2	0	0	0	0	0
TP53	22	10	5	1	0	0	4	0	2
HLA-A	18	6	7	0	4	0	1	0	0
TBL1XR1	17	11	4	1	0	0	0	0	1
CCR4	14	0	14	0	0	0	0	0	0
VAV1	14	13	0	0	0	0	0	0	1
HLA-B	13	2	5	0	5	0	1	0	0
PRKCB	13	13	0	0	0	0	0	0	0
STAT3	13	13	0	0	0	0	0	0	0
CARD11	10	9	0	0	0	1	0	0	0
CD28	10	1	0	0	0	6	0	2	1
CDKN2A	9	0	1	0	0	0	8	0	0
IRF4	9	4	0	0	0	5	0	0	0
ARID2	8	1	3	0	0	0	1	2	1
HLA-C	8	0	1	0	6	0	1	0	0
CCR7	7	0	7	0	0	0	0	0	0
FAS	7	2	4	0	0	0	0	0	1
NOTCH1	7	1	6	0	0	0	0	0	0
RHOA	7	7	0	0	0	0	0	0	0
BCL11B	6	1	0	0	0	5	0	0	0
CD274	6	0	0	0	0	3	0	0	3
GATA3	6	0	3	0	0	2	0	0	1
POT1	6	4	2	0	0	0	0	0	0
CD58	5	0	3	0	0	0	1	0	1
CBLB	5	1	0	0	0	1	1	0	2
IRF2BP2	4	4	0	0	0	0	0	0	0
SKI	4	1	0	0	0	3	0	0	0
TET2	4	1	3	0	0	0	0	0	0
TRAF3	4	0	1	0	0	3	0	0	0
YTHDF2	4	1	3	0	0	0	0	0	0
ATXN1	3	1	1	0	0	0	0	1	0
ATXN7L1	3	0	0	0	0	3	0	0	0
CSNK2A1	3	2	1	0	0	0	0	0	0
IMMP2L	3	0	0	0	0	3	0	0	0
CD247	2	0	0	0	0	2	0	0	0
DLG1	2	0	0	0	0	2	0	0	0
EP300	2	1	1	0	0	0	0	0	0
FYN	2	2	0	0	0	0	0	0	0
GPR183	2	0	0	0	0	0	2	0	0
HNRNPA2B1	2	1	1	0	0	0	0	0	0
IKZF2	2	1	1	0	0	0	0	0	0
MAN2A1	2	1	0	0	0	0	1	0	0
PAK2	2	0	0	0	0	2	0	0	0
PRDM1	2	0	2	0	0	0	0	0	0
PRKCQ	2	0	0	0	0	2	0	0	0
PTPRC	2	2	0	0	0	0	0	0	0
SETD2	2	1	0	0	0	0	0	0	1
ZFP36L2	2	2	0	0	0	0	0	0	0
ARHGAP15	1	0	1	0	0	0	0	0	0
B2M	1	0	0	0	0	0	1	0	0
CEBPA	1	0	1	0	0	0	0	0	0
CELF2	1	0	0	0	0	1	0	0	0
CSNK1A1	1	1	0	0	0	0	0	0	0
CSNK2B	1	0	1	0	0	0	0	0	0
ERC1	1	0	0	0	0	0	0	0	1
ETV6	1	0	0	0	0	1	0	0	0
FHIT	1	0	0	0	0	1	0	0	0
JAK3	1	1	0	0	0	0	0	0	0
NFKBIA	1	0	1	0	0	0	0	0	0
NRXN3	1	1	0	0	0	0	0	0	0
PIK3CD1	1	0	1	0	0	0	0	0	0
PDCD1	1	1	0	0	0	0	0	0	0
PTPN1	1	0	0	0	0	1	0	0	0
PTPRM	1	1	0	0	0	0	0	0	0
S1PR1	1	0	1	0	0	0	0	0	0
ZEB1	1	0	0	0	0	0	1	0	0

SNV, single nucleotide variant; LOH, loss of heterozygosity; CN, copy number

Supplementary Table S4.
Clinical response to mogamulizumab according to driver gene alterations

	Clinical response to mogamulizumab		
Characteristics	**CR**	**PR/SD/PD**	***P* value***
number (%)	42 (67)	21 (33)	
***CCR4* alterations**			**0.024**
presence	13 (93)	1 (7)	
absence	29 (59)	20 (41)	
***CCR7* alterations**			**0.036**
presence	2 (29)	5 (71)	
absence	40 (71)	16 (29)	

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease, $P < 0.05/30$ (two-sided) was considered to be statistically significant after Bonferroni correction.

Supplementary Table S5. Association between the transcriptome subtype and gene alterations

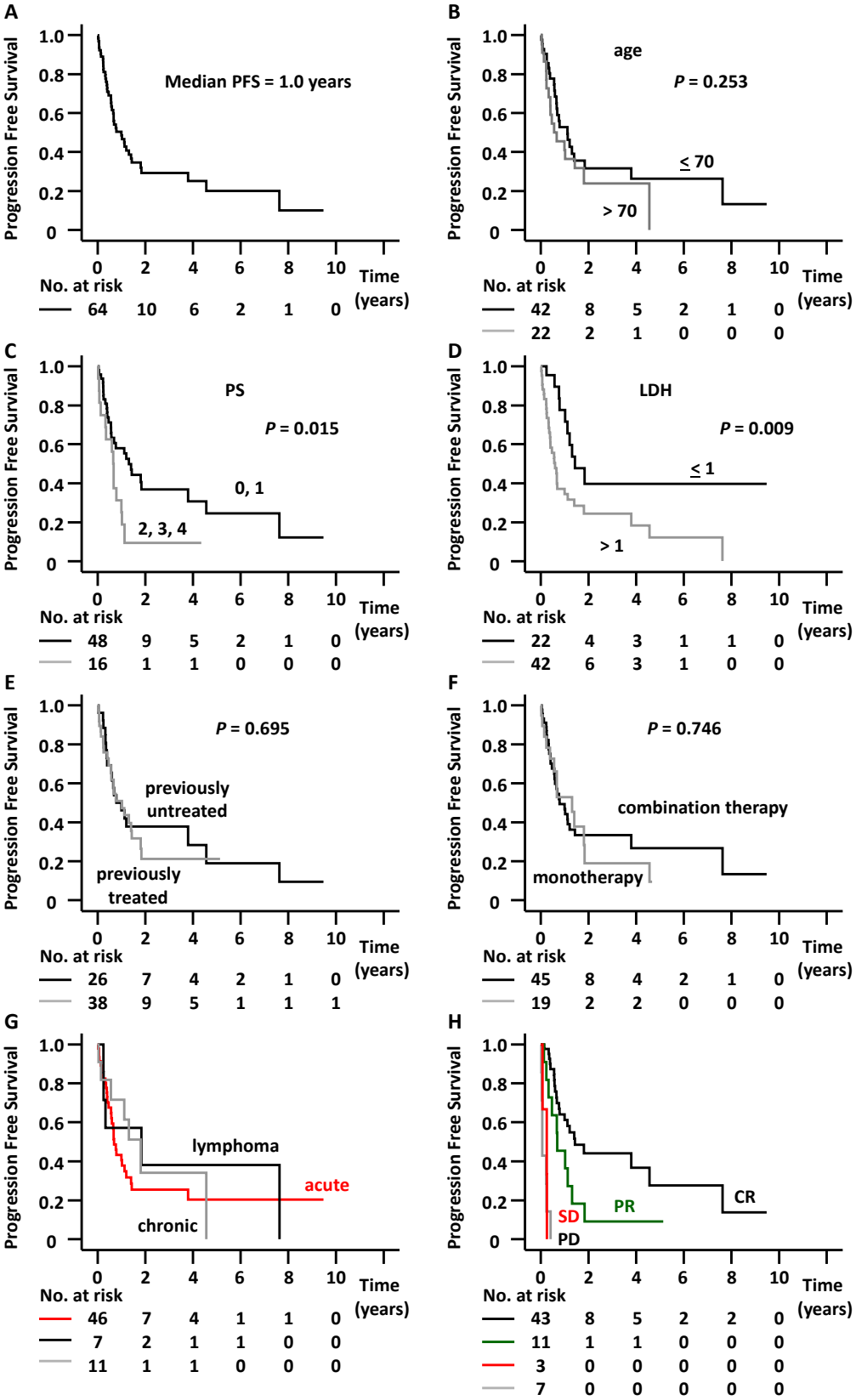
	TBL1XR1 alterations			*STAT3* alterations			*SKI* alterations			*TRAF3* alterations		
Characteristics	**-**	**+**	***P***	**-**	**+**	***P***	**-**	**+**	***P***	**-**	**+**	***P***
Number (%)	46 (73)	17 (27)		50 (79)	13 (21)		59 (94)	4 (6)		59 (94)	4 (6)	
TS-A	18 (95)	1 (5)	0.045	17 (89)	2 (11)	0.035	19 (100)	0 (0)	0.027	19 (100)	0 (0)	0.027
TS-B	11 (61)	7 (39)		16 (89)	2 (11)		17 (94)	1 (6)		17 (94)	1 (6)	
TS-C	3 (60)	2 (40)		5 (100)	0 (0)		3 (60)	2 (40)		3 (60)	2 (40)	
TS-D	14 (67)	7 (33)		12 (57)	9 (43)		20 (95)	1 (5)		20 (95)	1 (5)	

TS, transcriptome subtypes; *P < 0.05/49 (two-sided) was considered to be statistically significant after Bonferroni correction.

Supplementary Table S6. Multivariate analysis including HLA-genotypes for OS in patients with ATL

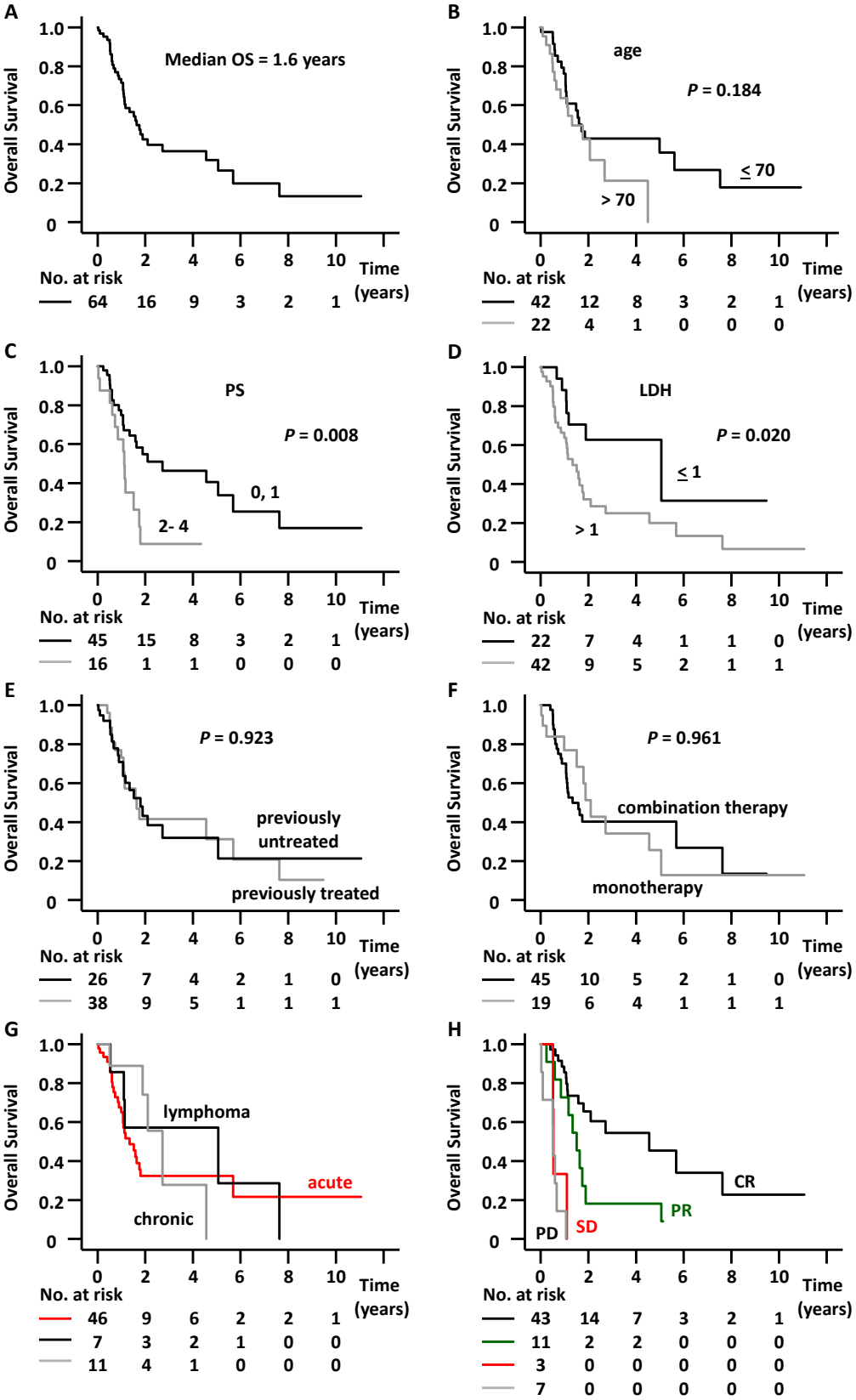
Variables	n*	HR	(95% CI)	*P* value
HLA-A				
*26:03 (-)	59	1.000		Reference
*26:03 (+)	5	1.356	(0.404-4.546)	0.622
HLA-B				
*40:02 (-)	48	1.000		Reference
*40:02 (+)	16	1.978	(0.756-5.176)	0.165
HLA-C				
*03:04 (-)	44	1.000		Reference
*03:04 (+)	20	1.227	(0.514-2.932)	0.645
HLA-DPB1				
*05:01 (-)	19	1.000		Reference
*05:01 (+)	45	0.409	(0.182-0.921)	0.031
ECOG PS				
0, 1	48	1.000		Reference
2, 3, 4	16	2.454	(1.044-5.769)	0.039
LDH				
≤ ULN	22	1.000		Reference
> ULN	42	2.046	(0.852-4.916)	0.109

OS, overall survival; CI, confidence interval; n, number; HR, hazard ratio; ECOG PS, Eastern Cooperative oncology Group performance status; ULN, upper limit of normal


A
Progression Free Survival
Median PFS = 1.0 years
No. at risk
64 10 6 2 1 0
Time (years)
B
age
P = 0.253
≤ 70
> 70
No. at risk
42 8 5 2 1 0
22 2 1 0 0 0
C
PS
P = 0.015
0, 1
2, 3, 4
No. at risk
48 9 5 2 1 0
16 1 1 0 0 0
D
LDH
P = 0.009
≤ 1
> 1
No. at risk
22 4 3 1 1 0
42 6 3 1 0 0
E
P = 0.695
previously untreated
previously treated
No. at risk
26 7 4 2 1 0
38 9 5 1 1 1
F
P = 0.746
combination therapy
monotherapy
No. at risk
45 8 4 2 1 0
19 2 2 0 0 0
G
lymphoma
acute
chronic
No. at risk
46 7 4 1 1 0
7 2 1 1 0 0
11 1 1 0 0 0
H
CR
PR
SD
PD
No. at risk
43 8 5 2 2 0
11 1 1 0 0 0
3 0 0 0 0 0
7 0 0 0 0 0

sFIGURE S1

Supplementary Figure S1. Progression free survival (PFS) of ATL patients according to their clinical parameters (A) PFS of all patients enrolled in the present study. **(B)** PFS of patients > 70 and ≤ 70 years of age. **(C)** PFS according to ECOG PS status (0,1 vs 2-4). **(D)** PFS according to serum LDH levels (≤ upper limit of normal [ULN] vs. > ULN). **(E)** PFS comparison between previously untreated or treated patients. **(F)** PFS comparison between patients who received mogamulizumab monotherapy or combination therapy. **(G)** PFS according to clinical subtype (acute, lymphoma, and chronic). Median PFS of patients with acute, lymphoma, and chronic subtypes was 0.7, 1.8, and 1.8 years, respectively. There were no significant differences in PFS between patients with acute and lymphoma subtypes (P = 0.586), those with acute and chronic subtypes (P = 0.405), or those with lymphoma and chronic subtypes (P = 0.669). **(H)** PFS according to clinical response to mogamulizumab-containing treatment (CR, PR, SD, and PD).



Supplementary Figure S2

Supplementary Figure S2. Overall survival (OS) of ATL patients according to their clinical parameters (A) OS of all patients enrolled in the present study. **(B)** OS of patients > 70 and ≤ 70 years of age. **(C)** OS according to ECOG PS status (0,1 vs 2-4). **(D)** OS according to serum LDH levels (≤ upper limit of normal [ULN] vs > ULN). **(E)** OS compared between previously untreated or treated patients. **(F)** OS compared between patients who received mogamulizumab monotherapy or combination therapy. **(G)** OS according to clinical subtype (acute, lymphoma, and chronic). Median OS of patients with acute, lymphoma, and chronic subtypes was 1.3, 5.1, and 2.7 years, respectively. There were no significant differences in OS between patients with acute and lymphoma subtypes (P = 0.650), those with acute and chronic subtypes (P = 0.297), or those with lymphoma and chronic subtypes (P = 0.641). **(H)** OS according to clinical response to mogamulizumab-containing treatment (CR, PR, SD, vs. PD).