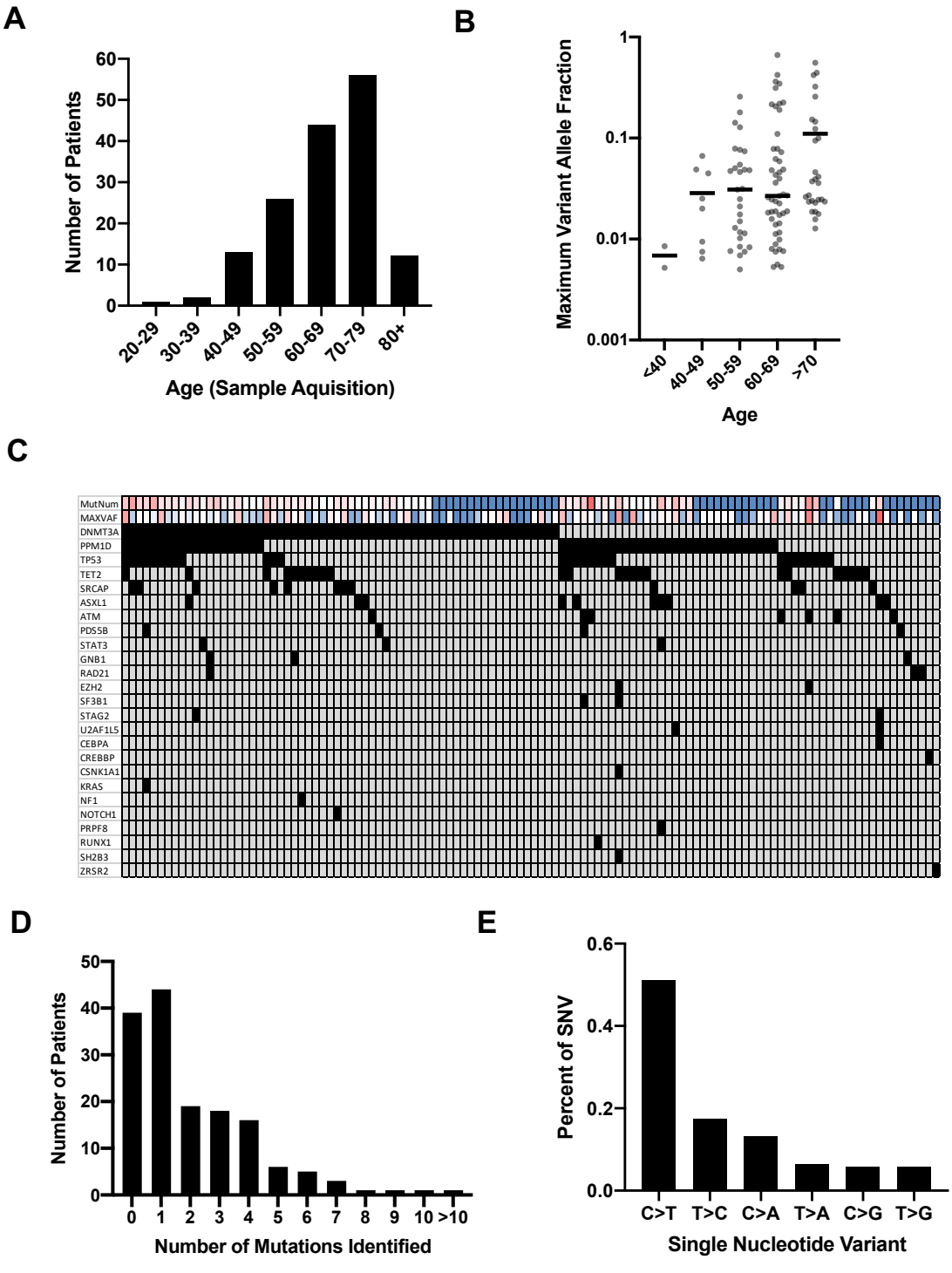
Clonal Hematopoiesis in Patients Receiving Chimeric Antigen Receptor T-Cell Therapy

Supplemental Material

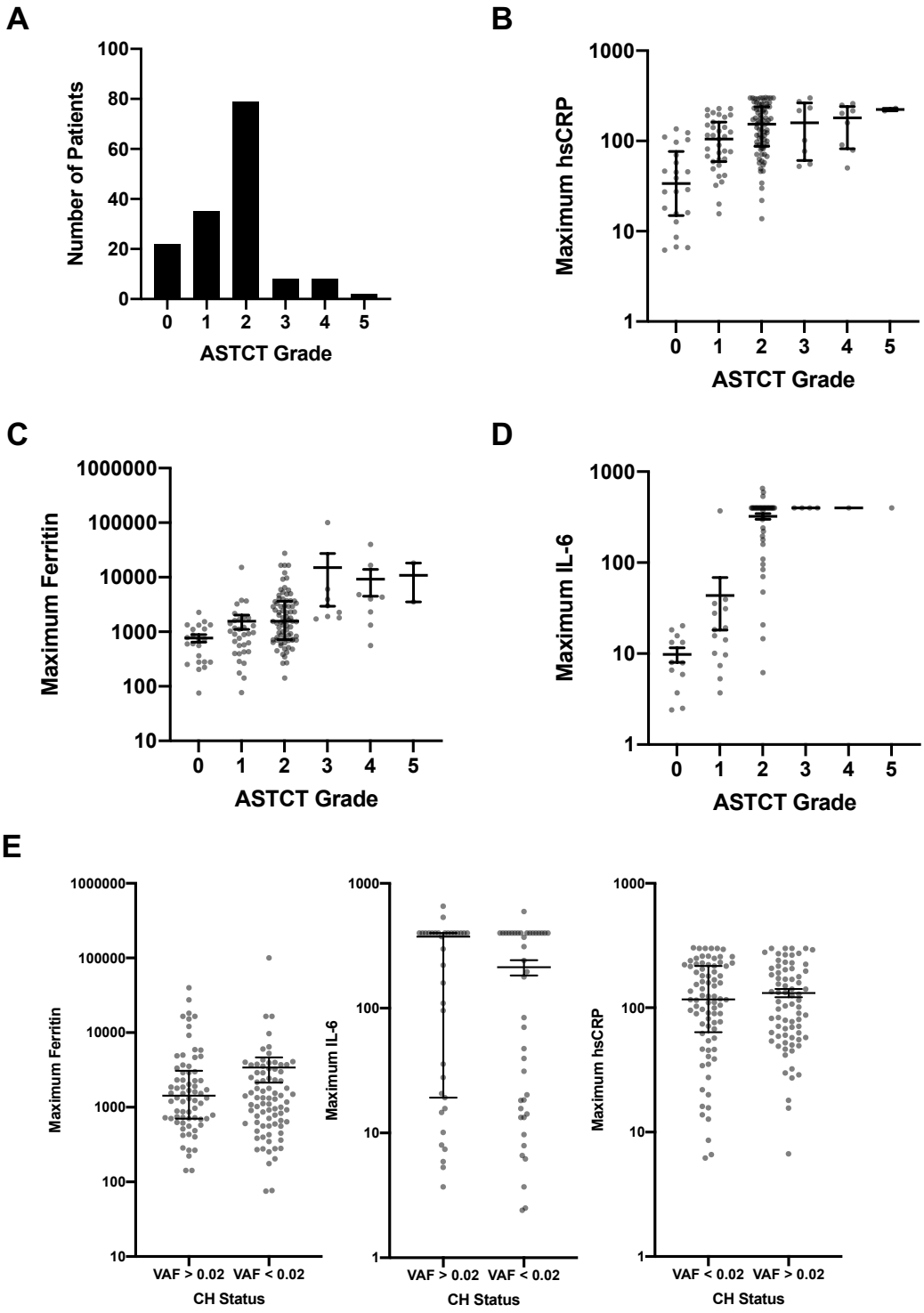
Supplemental Figures

Supplemental Tables

Supplemental Figure 1. Clonal Hematopoiesis Characteristics in CAR T-cell Cohort.
A) The age distribution of patients in the cohort.
B) The maximum variant allele frequency identified in each patient with clonal hematopoiesis plotted for different age groups. The horizontal lines represent the medians in each age strata.
C) A co-mutation plot for all individuals with any clonal hematopoietic mutation identified. Each column is a patient and each row is a gene. The top two rows represent the total number of mutations (MaxNum) and maximum variant allele fraction (MAXVAF) identified in each patient with blue representing fewer and red representing more mutations.
D) Distribution of the number of mutations identified in patients in the cohort.
E) Distribution of the types of single nucleotide variants (SNVs) identified in the cohort.



Supplemental Figure 2. Cytokine Release Syndrome in CAR T-cell Cohort.
A) The distribution of cytokine release syndrome (CRS) grades per the American Society for Transplantation and Cellular Therapy (ASTCT) grading system across the cohort.
B) Maximum high sensitivity C-reactive protein (hsCRP) level in each patient stratified by maximum CRS grade recorded.
C) Maximum ferritin level in each patient stratified by maximum CRS grade recorded.
D) Maximum interleukin-6 (IL-6) level in each patient stratified by maximum CRS grade recorded.
E) Maximum ferritin, IL-6, and hsCRP levels for each patient stratified by absence (variant allele fraction [VAF] < 0.02) or presence (VAF > 0.02) of clonal hematopoiesis.
Shown are median and interquartile range for (B)-(E).



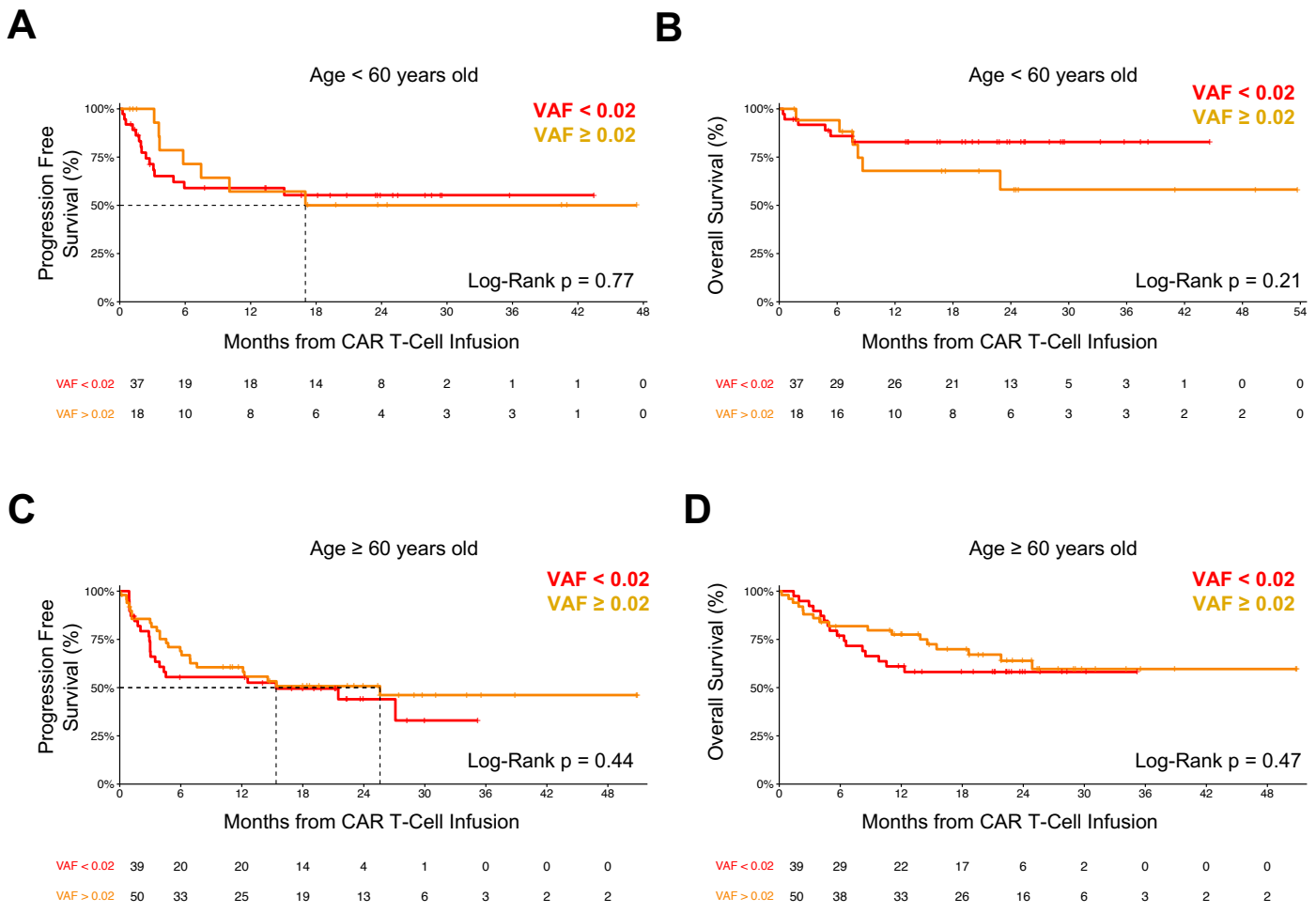
Supplemental Figure 3. Relapse Free and Overall Survival in Cohort Stratified by Age Greater or Less than 60 Years Old.

A) Progression-free survival of patients younger than 60 years old with Non-Hodgkin lymphoma stratified by absence (red) or presence (orange) of clonal hematopoiesis with a variant allele fraction (VAF) greater than or equal to 0.02. A log-rank test was performed to compare survival curves.

B) Overall survival of patients younger than 60 years old with Non-Hodgkin lymphoma stratified by absence (red) or presence (orange) of clonal hematopoiesis with a variant allele fraction (VAF) greater than or equal to 0.02. A log-rank test was performed to compare survival curves.

C) Progression-free survival of patients older than 60 years old with Non-Hodgkin lymphoma stratified by absence (red) or presence (orange) of clonal hematopoiesis with a variant allele fraction (VAF) greater than or equal to 0.02. A log-rank test was performed to compare survival curves.

D) Overall survival of patients older than 60 years old with Non-Hodgkin lymphoma stratified by absence (red) or presence (orange) of clonal hematopoiesis with a variant allele fraction (VAF) greater than or equal to 0.02. A log-rank test was performed to compare survival curves.



Supplemental Table 1. Genes Sequenced for Determination of Clonal Hematopoiesis.

ASXL1	CSNK1A5	IDH2	PIGA	SRSF2
ATM	CSNK1A6	IKZF1	PIGT	STAG1
ATRX	CSNK1A7	JAK2	PPM1D	STAG2
B2M	CSNK1A8	JAK3	PRPF40B	STAT3
BCOR	CSNK1A9	KIT	PRPF8	STAT5B
BCORL1	CTCF	KRAS	PTEN	TERC
BRAF	CUX1	LUC7L2	PTPN11	TERT
BRCC3	DDX41	MIR142	RAD21	TET2
CALR	DNMT3A	MPL	RIT1	TP53
CBL	EP300	MRE11A	RPL11	U2AF1
CBLB	ETNK1	MYC	RPS7	U2AF2
CEBPA	ETV6	MYD88	RUNX1	VPS45
CREBBP	EZH2	MYH9	SETBP1	WT1
CSF1R	FANCL	NF1	SETD2	YLPM1
CSF3R	FLT3	NOTCH1	SF1	ZBTB33
CSNK1A1	FP SNP	NOTCH2	SF3A1	ZNF318
CSNK1A10	GATA1	NPM1	SF3B1	ZRSR2
CSNK1A11	GATA2	NRAS	SH2B3	
CSNK1A2	GNAS	PDS5B	SMC1A	
CSNK1A3	GNB1	PHF6	SMC3	
CSNK1A4	IDH1	PHIP	SRCAP	

Supplemental Table 2. Cohort Characteristics

Total Patients and CAR T-Cell Treatment (n)	**154**
Non-Hodgkin Lymphoma	144
Multiple Myeloma	10
Age (median, range)	**63 (24-83)**
Gender (n,%)	
Male	91 (59)
Female	63 (41)
Best Overall Response (n,%)	
Complete Remission	100 (65)
Partial Remission	32 (21)
Stable Disease	5 (3)
Progressive Disease	17 (11)
Prior Lines of Treatment (n,%)	
1-2	71 (46)
3-5	67 (44)
6-10	16 (10)
Prior Stem Cell Transplant (n,%)	
Autologous	41 (27)
Allogeneic	5 (3)
CRS Grade (n,%)	
0	22 (14)
1-2	114 (74)
3-4	16 (10)
5	2 (1)
Treatment for CRS (n,%)	
Tocilizumab	83 (54)
Steroids	59 (38)

Supplemental Table 3. Clonal Hematopoietic Mutations Identified in Cohort.

chrom	pos_start	pos_end	ref	var	gene	cdna	aa	result	reads1	reads2	var_freq
20	31022277	31022277	C	T	ASXL1	c.C1762T	p.Q588X	stopgain	742	18	0.0237
20	31023217	31023217	T	-	ASXL1	c.2702delT	p.I901fs	frameshift deletion	1276	98	0.0713
20	31022441	31022441	-	G	ASXL1	c.1927dupG	p.G642fs	frameshift insertion	1077	178	0.1418
20	31022533	31022533	-	C	ASXL1	c.2019dupC	p.G673fs	frameshift insertion	1149	15	0.0129
20	31022441	31022441	-	G	ASXL1	c.1927dupG	p.G642fs	frameshift insertion	931	35	0.0362
20	31022637	31022637	C	T	ASXL1	c.C2122T	p.Q708X	stopgain	1186	10	0.0084
20	31022441	31022441	-	G	ASXL1	c.1927dupG	p.G642fs	frameshift insertion	1366	10	0.0073
20	31022441	31022441	-	G	ASXL1	c.1927dupG	p.G642fs	frameshift insertion	652	369	0.3607
20	31022441	31022441	-	G	ASXL1	c.1927dupG	p.G642fs	frameshift insertion	1412	75	0.0504
20	31022936	31022936	T	-	ASXL1	c.2421delT	p.V807fs	frameshift deletion	1073	23	0.021
11	108198405	108198405	T	C	ATM	c.T7009C	p.C2337R	nonsynonymous SNV	931	8	0.0085
11	108199860	108199860	T	C	ATM	c.T7202C	p.I2401T	nonsynonymous SNV	669	60	0.0823
11	108236087	108236087	G	A	ATM	c.G9023A	p.R3008H	nonsynonymous SNV	962	5	0.0052
11	108173740	108173740	T	G	ATM	c.T5480G	p.L1827X	stopgain	750	5	0.0066
11	108150301	108150301	C	-	ATM	c.3368delC	p.A1123fs	frameshift deletion	708	5	0.007
11	108218036	108218036	A	T	ATM	c.A8615T	p.H2872L	nonsynonymous SNV	472	7	0.0146
11	108155084	108155084	A	T	ATM	c.A3877T	p.N1293Y	nonsynonymous SNV	924	7	0.0075
11	108172460	108172460	A	G	ATM	c.A5263G	p.M1755V	nonsynonymous SNV	478	11	0.0225
11	108224493	108224493	G	A	ATM	c.G8672A	p.G2891D	nonsynonymous SNV	620	7	0.0112
11	108236087	108236087	G	A	ATM	c.G9023A	p.R3008H	nonsynonymous SNV	735	5	0.0068
19	33792838	33792838	-	T	CEBPA	c.125dupA	p.K42fs	frameshift insertion	1113	47	0.0405
19	33792390	33792390	-	C	CEBPA	c.573dupG	p.Q192fs	frameshift insertion	992	243	0.1968
16	3808050	3808050	C	-	CREBBP	c.3370-1G>-		splicing	228	11	0.046
5	148899890	148899890	T	G	CSNK1A1	c.A152C	p.D51A	nonsynonymous SNV	261	12	0.044
2	25458628	25458628	G	-	DNMT3A	c.2545delC	p.P849fs	frameshift deletion	642	67	0.0945
2	25469555	25469555	-	C	DNMT3A	c.1212dupG	p.P405fs	frameshift insertion	851	11	0.0128
2	25467188	25467188	C	T	DNMT3A	c.G1687A	p.V563M	nonsynonymous SNV	653	190	0.2254
2	25467105	25467105	A	-	DNMT3A	c.1770delT	p.G590fs	frameshift deletion	1193	5	0.0042
2	25467119	25467119	A	C	DNMT3A	c.T1756G	p.C586G	nonsynonymous SNV	1103	88	0.0739
2	25464577	25464577	C	T	DNMT3A	c.1481-1G>A		splicing	568	6	0.0105
2	25462006	25462006	T	C	DNMT3A	c.A2401G	p.M801V	nonsynonymous SNV	1109	13	0.0116
2	25463566	25463566	C	T	DNMT3A	c.G2116A	p.G706R	nonsynonymous SNV	1359	38	0.0272
2	25463568	25463568	A	G	DNMT3A	c.T2114C	p.I705T	nonsynonymous SNV	1118	9	0.008
2	25467199	25467199	C	-	DNMT3A	c.1676delG	p.C559fs	frameshift deletion	998	14	0.0138
2	25467128	25467128	A	T	DNMT3A	c.T1747A	p.C583S	nonsynonymous SNV	1356	34	0.0245
2	25463321	25463321	T	C	DNMT3A	c.1718-2A>G		splicing	971	7	0.0072
2	25463292	25463293	0	-	DNMT3A	c.2200_2201del	p.F734fs	frameshift deletion	1356	36	0.0259
2	25459830	25459830	C	T	DNMT3A	c.G2453A	p.C818Y	nonsynonymous SNV	905	41	0.0433
2	25457242	25457242	C	T	DNMT3A	c.G2645A	p.R882H	nonsynonymous SNV	1114	40	0.0347
2	25467083	25467083	G	A	DNMT3A	c.C1792T	p.R598X	stopgain	1032	226	0.1797
2	25458595	25458595	A	G	DNMT3A	c.T2578C	p.W860R	nonsynonymous SNV	740	5	0.0067
2	25469646	25469646	C	A	DNMT3A	c.667-1G>T		splicing	979	20	0.02
2	25463171	25463171	C	G	DNMT3A	c.G2322C	p.E774D	nonsynonymous SNV	527	134	0.2027
2	25470556	25470556	C	T	DNMT3A	c.G918A	p.W306X	stopgain	939	244	0.2063
2	25470555	25470555	G	-	DNMT3A	c.919delC	p.P307fs	frameshift deletion	1198	13	0.0107
2	25457176	25457176	G	A	DNMT3A	c.C2711T	p.P904L	nonsynonymous SNV	1131	6	0.0053
2	25470560	25470560	C	G	DNMT3A	c.G914C	p.W305S	nonsynonymous SNV	1148	6	0.0052
2	25469049	25469049	-	T	DNMT3A	c.1408dupA	p.I470fs	frameshift insertion	779	14	0.0177
2	25462086	25462086	T	C	DNMT3A	c.1867-2A>G		splicing	671	24	0.0345
2	25471061	25471061	C	-	DNMT3A	c.700delG	p.G234fs	frameshift deletion	1282	68	0.0504
2	25457281	25457281	C	T	DNMT3A	c.G2606A	p.G869D	nonsynonymous SNV	581	11	0.0186
2	25463593	25463593	C	A	DNMT3A	c.G2089T	p.E697X	stopgain	909	7	0.0076
2	25463287	25463287	G	A	DNMT3A	c.C2206T	p.R736C	nonsynonymous SNV	1105	27	0.0239
2	25462065	25462065	T	G	DNMT3A	c.A2342C	p.D781A	nonsynonymous SNV	806	23	0.0277
2	25462068	25462068	A	G	DNMT3A	c.T2339C	p.I780T	nonsynonymous SNV	1001	7	0.0069
2	25463566	25463566	C	-	DNMT3A	c.2116delG	p.G706fs	frameshift deletion	1192	9	0.0075
2	25457243	25457243	G	A	DNMT3A	c.C2644T	p.R882C	nonsynonymous SNV	794	451	0.3622
2	25458619	25458619	T	C	DNMT3A	c.A2554G	p.M852V	nonsynonymous SNV	1176	9	0.0076
2	25464532	25464532	T	G	DNMT3A	c.A1981C	p.I661L	nonsynonymous SNV	1392	7	0.005
2	25461998	25461998	C	T	DNMT3A	c.1952+1G>A		splicing	854	6	0.007
2	25458691	25458691	T	-	DNMT3A	c.2482delA	p.S828fs	frameshift deletion	664	5	0.0075
2	25470011	25470011	A	G	DNMT3A	c.T1031C	p.L344P	nonsynonymous SNV	771	39	0.0481
2	25457243	25457243	G	A	DNMT3A	c.C2644T	p.R882C	nonsynonymous SNV	1061	6	0.0056
2	25464450	25464450	C	T	DNMT3A	c.G2063A	p.R688H	nonsynonymous SNV	882	10	0.0112
2	25468910	25468910	G	A	DNMT3A	c.C1453T	p.Q485X	stopgain	918	7	0.0076
2	25464525	25464525	G	T	DNMT3A	c.C1988A	p.S663X	stopgain	1127	9	0.0079
2	25459804	25459804	C	T	DNMT3A	c.2022+1G>A		splicing	900	52	0.0546
2	25463182	25463182	G	A	DNMT3A	c.C2311T	p.R771X	stopgain	739	11	0.0147
2	25469990	25469990	C	-	DNMT3A	c.1052delG	p.C351fs	frameshift deletion	911	42	0.0441
2	25458628	25458628	G	-	DNMT3A	c.2545delC	p.P849fs	frameshift deletion	847	10	0.0117
2	25464490	25464490	C	T	DNMT3A	c.G2023A	p.V675M	nonsynonymous SNV	1184	7	0.0059
2	25470585	25470585	A	G	DNMT3A	c.T889C	p.W297R	nonsynonymous SNV	1317	57	0.0415
2	25469083	25469083	T	-	DNMT3A	c.1375delA	p.K459fs	frameshift deletion	1267	49	0.0372
2	25457162	25457162	A	C	DNMT3A	c.T2725G	p.F909V	nonsynonymous SNV	1025	15	0.0144
2	25463541	25463541	G	C	DNMT3A	c.C2141G	p.S714C	nonsynonymous SNV	1154	27	0.0229
2	25463289	25463289	T	C	DNMT3A	c.A2204G	p.Y735C	nonsynonymous SNV	1074	6	0.0056
2	25469982	25469982	A	-	DNMT3A	c.1060delT	p.F354fs	frameshift deletion	1003	19	0.0186
2	25463172	25463172	T	C	DNMT3A	c.A2321G	p.E774G	nonsynonymous SNV	832	7	0.0083
2	25470560	25470560	C	T	DNMT3A	c.G914A	p.W305X	stopgain	969	25	0.0252
2	25470532	25470532	C	T	DNMT3A	c.G942A	p.W314X	stopgain	1201	176	0.1278
2	25463289	25463289	T	C	DNMT3A	c.A2204G	p.Y735C	nonsynonymous SNV	965	5	0.0052
2	25469161	25469161	T	-	DNMT3A	c.1297delA	p.K433fs	frameshift deletion	860	35	0.0391

Supplemental Table 3. Clonal Hematopoietic Mutations Identified in Cohort (continued).

chrom	pos_start	pos_end	ref	var	gene	cdna	aa	result	reads1	reads2	var_freq
2	25462000	25462000	T	C	DNMT3A	c.A2407G	p.R803G	nonsynonymous SNV	885	5	0.0056
2	25467168	25467168	C	-	DNMT3A	c.1707delG	p.P569fs	frameshift deletion	1118	70	0.0589
2	25464568	25464568	C	T	DNMT3A	c.G1945A	p.V649M	nonsynonymous SNV	991	8	0.008
2	25469089	25469089	G	-	DNMT3A	c.1369delC	p.P457fs	frameshift deletion	1795	16	0.0088
2	25469028	25469028	C	T	DNMT3A	c.973+1G>A		splicing	1338	12	0.0089
2	25463188	25463188	T	G	DNMT3A	c.A2305C	p.I769L	nonsynonymous SNV	888	17	0.0188
2	25463289	25463289	T	C	DNMT3A	c.A2204G	p.Y735C	nonsynonymous SNV	1060	12	0.0112
2	25463553	25463553	C	T	DNMT3A	c.G2129A	p.C710Y	nonsynonymous SNV	939	34	0.0349
2	25463230	25463230	A	T	DNMT3A	c.T2263A	p.F755I	nonsynonymous SNV	879	246	0.2187
2	25463583	25463583	G	A	DNMT3A	c.C2099T	p.P700L	nonsynonymous SNV	795	7	0.0087
2	25470464	25470464	G	A	DNMT3A	c.C1010T	p.S337L	nonsynonymous SNV	700	8	0.0113
2	25463509	25463509	C	A	DNMT3A	c.G2173T	p.E725X	stopgain	888	5	0.0056
2	25470463	25470463	T	-	DNMT3A	c.1011delA	p.S337fs	frameshift deletion	929	6	0.0064
2	25464432	25464432	T	A	DNMT3A	c.A2081T	p.H694L	nonsynonymous SNV	886	8	0.0089
2	25467163	25467163	G	T	DNMT3A	c.C1712A	p.A571D	nonsynonymous SNV	1158	10	0.0086
2	25463563	25463563	C	T	DNMT3A	c.G2119A	p.G707S	nonsynonymous SNV	1072	9	0.0083
2	25464460	25464460	C	T	DNMT3A	c.G2053A	p.G685R	nonsynonymous SNV	1164	25	0.021
2	25470011	25470011	A	G	DNMT3A	c.T1031C	p.L344P	nonsynonymous SNV	1125	20	0.0175
2	25462023	25462023	C	A	DNMT3A	c.G2384T	p.W795L	nonsynonymous SNV	1042	50	0.0458
2	25463205	25463205	A	-	DNMT3A	c.2288delT	p.V763fs	frameshift deletion	842	291	0.2568
2	25467477	25467477	G	C	DNMT3A	c.C1599G	p.Y533X	stopgain	954	14	0.0145
2	25457290	25457290	C	T	DNMT3A	c.2142-1G>A		splicing	698	6	0.0085
2	25457265	25457265	A	C	DNMT3A	c.T2622G	p.Y874X	stopgain	924	5	0.0054
2	25467497	25467497	G	A	DNMT3A	c.C1579T	p.Q527X	stopgain	959	12	0.0124
2	25463588	25463588	C	T	DNMT3A	c.G2094A	p.W698X	stopgain	887	5	0.0056
2	25457177	25457177	G	T	DNMT3A	c.C2710A	p.P904T	nonsynonymous SNV	917	8	0.0086
2	25468153	25468153	A	-	DNMT3A	c.1523delT	p.L508fs	frameshift deletion	714	247	0.257
2	25466797	25466797	C	T	DNMT3A	c.G1906A	p.V636M	nonsynonymous SNV	1057	13	0.0121
7	148507485	148507485	C	G	EZH2	c.G1969C	p.D657H	nonsynonymous SNV	302	13	0.0413
7	148515187	148515187	G	-	EZH2	c.1022delC	p.A341fs	frameshift deletion	850	15	0.0173
1	1747227	1747227	C	A	GNB1	c.G171T	p.K57N	nonsynonymous SNV	1237	8	0.0064
1	1747229	1747229	T	C	GNB1	c.A169G	p.K57E	nonsynonymous SNV	1075	9	0.0083
1	1747227	1747227	C	A	GNB1	c.G171T	p.K57N	nonsynonymous SNV	1242	7	0.0056
12	25380268	25380268	A	C	KRAS	c.T190G	p.Y64D	nonsynonymous SNV	852	5	0.0058
17	29556485	29556485	T	A	NF1	c.2850+2T>A		splicing	563	6	0.0105
9	139399282	139399282	C	T	NOTCH1	c.G4861A	p.G1621S	nonsynonymous SNV	1259	17	0.0133
13	33306277	33306277	-	C	PDS5B	c.2164dupC	p.G721fs	frameshift insertion	261	5	0.0188
13	33347346	33347346	C	T	PDS5B	c.C4192T	p.Q1398X	stopgain	826	80	0.0883
13	33281071	33281071	T	-	PDS5B	c.1857delT	p.S619fs	frameshift deletion	452	5	0.0109
13	33275577	33275577	T	C	PDS5B	c.1856+2T>C		splicing	169	7	0.0398
17	58740638	58740671	0	-	PPM1D	c.1543_1576del	p.M515fs	frameshift deletion	893	59	0.062
17	58740713	58740713	G	-	PPM1D	c.1618delG	p.E540fs	frameshift deletion	589	11	0.0183
17	58740376	58740376	G	A	PPM1D	c.G1281A	p.W427X	stopgain	553	14	0.0247
17	58740680	58740680	A	-	PPM1D	c.1585delA	p.T529fs	frameshift deletion	1051	5	0.0047
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	1199	7	0.0058
17	58740623	58740623	C	T	PPM1D	c.C1528T	p.Q510X	stopgain	1079	8	0.0073
17	58740757	58740758	0	-	PPM1D	c.1662_1663del	p.G554fs	frameshift deletion	1174	17	0.0143
17	58740674	58740674	G	T	PPM1D	c.G1579T	p.E527X	stopgain	1119	10	0.0089
17	58740438	58740438	A	-	PPM1D	c.1343delA	p.N448fs	frameshift deletion	732	6	0.0081
17	58740375	58740375	G	A	PPM1D	c.G1280A	p.W427X	stopgain	569	7	0.0122
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	733	8	0.0108
17	58740505	58740505	-	C	PPM1D	c.1411dupC	p.D470fs	frameshift insertion	642	116	0.1528
17	58740365	58740365	G	T	PPM1D	c.G1270T	p.E424X	stopgain	565	5	0.0088
17	58740374	58740374	T	-	PPM1D	c.1279delT	p.W427fs	frameshift deletion	700	5	0.0071
17	58740698	58740698	A	T	PPM1D	c.A1603T	p.K535X	stopgain	732	5	0.0068
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	854	12	0.0139
17	58740479	58740479	C	T	PPM1D	c.C1384T	p.Q462X	stopgain	828	13	0.0155
17	58740623	58740623	-	A	PPM1D	c.1529dupA	p.Q510fs	frameshift insertion	780	15	0.0188
17	58740618	58740618	T	-	PPM1D	c.1523delT	p.M508fs	frameshift deletion	1186	44	0.0358
17	58740697	58740697	-	A	PPM1D	c.1603dupA	p.F534fs	frameshift insertion	1122	6	0.0053
17	58740713	58740713	G	-	PPM1D	c.1618delG	p.E540fs	frameshift deletion	951	18	0.0186
17	58740536	58740536	G	-	PPM1D	c.1441delG	p.A481fs	frameshift deletion	1161	10	0.0085
17	58740532	58740532	T	-	PPM1D	c.1437delT	p.A479fs	frameshift deletion	1403	8	0.0057
17	58740720	58740720	A	-	PPM1D	c.1625delA	p.N542fs	frameshift deletion	1487	13	0.0087
17	58740486	58740486	T	-	PPM1D	c.1391delT	p.V464fs	frameshift deletion	1428	16	0.0111
17	58740690	58740690	C	-	PPM1D	c.1595delC	p.T532fs	frameshift deletion	1423	18	0.0125
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	1546	19	0.0121
17	58740697	58740697	T	-	PPM1D	c.1602delT	p.F534fs	frameshift deletion	1302	7	0.0053
17	58740438	58740439	0	-	PPM1D	c.1343_1344del	p.N448fs	frameshift deletion	1215	36	0.0288
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	1384	41	0.0288
17	58740546	58740546	T	A	PPM1D	c.T1451A	p.L484X	stopgain	1068	15	0.0139
17	58740529	58740529	C	A	PPM1D	c.C1434A	p.C478X	stopgain	824	21	0.0249
17	58740713	58740713	G	-	PPM1D	c.1618delG	p.E540fs	frameshift deletion	1353	11	0.0081
17	58740623	58740623	C	T	PPM1D	c.C1528T	p.Q510X	stopgain	1305	19	0.0143
17	58740438	58740438	A	-	PPM1D	c.1343delA	p.N448fs	frameshift deletion	1240	26	0.0205
17	58740694	58740694	C	-	PPM1D	c.1599delC	p.N533fs	frameshift deletion	1281	41	0.031
17	58740649	58740649	T	-	PPM1D	c.1554delT	p.P518fs	frameshift deletion	1253	54	0.0413
17	58740701	58740701	A	-	PPM1D	c.1606delA	p.R536fs	frameshift deletion	1077	253	0.1902
17	58740530	58740530	-	C	PPM1D	c.1436dupC	p.A479fs	frameshift insertion	1172	8	0.0068
17	58740665	58740665	C	T	PPM1D	c.C1570T	p.Q524X	stopgain	811	429	0.346
17	58740486	58740486	-	AGTC	PPM1D	c.1391_1392insAGTC	p.V464fs	frameshift insertion	1581	10	0.0063
17	58740823	58740823	-	A	PPM1D	c.1729dupA	p.V576fs	frameshift insertion	1148	7	0.0061
17	58740816	58740817	0	-	PPM1D	c.1721_1722del	p.N574fs	frameshift deletion	953	48	0.048
17	58740836	58740836	C	T	PPM1D	c.C1741T	p.R581X	stopgain	1167	6	0.0051
17	58740446	58740446	G	T	PPM1D	c.G1351T	p.E451X	stopgain	510	40	0.0727

Supplemental Table 3. Clonal Hematopoietic Mutations Identified in Cohort (continued).

chrom	pos_start	pos_end	ref	var	gene	cdna	aa	result	reads1	reads2	var_freq
17	58740453	58740453	C	A	PPM1D	c.C1358A	p.S453X	stopgain	963	6	0.0062
17	58740731	58740731	C	-	PPM1D	c.1636delC	p.L546X	stopgain	941	46	0.0466
17	58740376	58740376	G	A	PPM1D	c.G1281A	p.W427X	stopgain	846	7	0.0082
17	58740623	58740623	C	T	PPM1D	c.C1528T	p.Q510X	stopgain	1198	9	0.0073
17	58740697	58740697	T	-	PPM1D	c.1602delT	p.F534fs	frameshift deletion	1164	10	0.0085
17	58740694	58740694	-	T	PPM1D	c.1600dupT	p.N533fs	frameshift insertion	1170	10	0.0085
17	58740623	58740623	C	-	PPM1D	c.1528delC	p.Q510fs	frameshift deletion	1198	19	0.0154
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	1233	27	0.0214
17	58740809	58740809	C	T	PPM1D	c.C1714T	p.R572X	stopgain	1265	27	0.0209
17	58740665	58740665	C	T	PPM1D	c.C1570T	p.Q524X	stopgain	1046	9	0.0085
17	58740674	58740674	G	T	PPM1D	c.G1579T	p.E527X	stopgain	1041	8	0.0076
17	58740603	58740603	C	G	PPM1D	c.C1508G	p.S503X	stopgain	659	56	0.0783
17	58740509	58740509	G	T	PPM1D	c.G1414T	p.E472X	stopgain	943	15	0.0157
17	58740731	58740731	C	-	PPM1D	c.1636delC	p.L546X	stopgain	1099	23	0.0205
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	1053	10	0.0094
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	811	5	0.0061
17	58740665	58740665	C	T	PPM1D	c.C1570T	p.Q524X	stopgain	687	11	0.0158
17	58740836	58740836	C	T	PPM1D	c.C1741T	p.R581X	stopgain	1039	7	0.0067
17	58740380	58740380	A	-	PPM1D	c.1285delA	p.R429fs	frameshift deletion	789	19	0.0235
17	58740602	58740602	T	-	PPM1D	c.1507delT	p.S503fs	frameshift deletion	1157	12	0.0103
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	1228	40	0.0315
17	58740710	58740710	G	T	PPM1D	c.G1615T	p.E539X	stopgain	944	13	0.0136
17	58740533	58740533	-	T	PPM1D	c.1438_1439insT	p.K480fs	frameshift insertion	515	29	0.0533
17	58740633	58740633	T	A	PPM1D	c.T1538A	p.L513X	stopgain	1151	63	0.0519
17	58740731	58740731	C	-	PPM1D	c.1636delC	p.L546X	stopgain	978	9	0.0091
17	58740704	58740704	A	-	PPM1D	c.1609delA	p.T537fs	frameshift deletion	788	27	0.0331
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	980	83	0.0781
17	58740438	58740438	A	-	PPM1D	c.1343delA	p.N448fs	frameshift deletion	1125	8	0.0071
17	58740720	58740720	-	T	PPM1D	c.1626dupT	p.N542fs	frameshift insertion	1507	8	0.0053
17	58740529	58740529	C	A	PPM1D	c.C1434A	p.C478X	stopgain	1109	13	0.0116
17	58740623	58740623	-	A	PPM1D	c.1529dupA	p.Q510fs	frameshift insertion	1231	23	0.0183
17	58740809	58740809	C	T	PPM1D	c.C1714T	p.R572X	stopgain	629	5	0.0079
17	58740749	58740749	C	T	PPM1D	c.C1654T	p.R552X	stopgain	1388	11	0.0079
17	58740376	58740376	G	A	PPM1D	c.G1281A	p.W427X	stopgain	431	314	0.4215
17	58740633	58740633	T	A	PPM1D	c.T1538A	p.L513X	stopgain	1382	10	0.0072
17	58740518	58740518	G	T	PPM1D	c.G1423T	p.E475X	stopgain	1306	93	0.0665
17	58740665	58740665	C	T	PPM1D	c.C1570T	p.Q524X	stopgain	892	5	0.0056
17	58740380	58740380	A	-	PPM1D	c.1285delA	p.R429fs	frameshift deletion	702	36	0.0488
17	58740492	58740492	-	A	PPM1D	c.1398dupA	p.I466fs	frameshift insertion	769	36	0.0447
17	58740493	58740493	A	-	PPM1D	c.1398delA	p.I466fs	frameshift deletion	1135	58	0.0486
17	58740731	58740731	C	-	PPM1D	c.1636delC	p.L546X	stopgain	908	44	0.0462
17	58740726	58740726	-	C	PPM1D	c.1632dupC	p.G544fs	frameshift insertion	960	23	0.0234
17	58740809	58740809	C	T	PPM1D	c.C1714T	p.R572X	stopgain	1031	53	0.0489
17	58740680	58740680	A	-	PPM1D	c.1585delA	p.T529fs	frameshift deletion	938	6	0.0064
17	58740809	58740809	C	T	PPM1D	c.C1714T	p.R572X	stopgain	1243	12	0.0096
17	58740543	58740544	0	-	PPM1D	c.1448_1449del	p.T483fs	frameshift deletion	838	32	0.0368
17	1559855	1559855	T	C	PRPF8	c.A5624G	p.H1875R	nonsynonymous SNV	940	78	0.0766
8	117864787	117864787	C	T	RAD21	c.1321+1G>A		splicing	628	20	0.0309
8	117874078	117874078	A	C	RAD21	c.374+2T>G		splicing	502	5	0.0099
8	117864237	117864237	G	A	RAD21	c.C1420T	p.Q474X	stopgain	1122	7	0.0062
21	36252961	36252961	G	C	RUNX1	c.C401G	p.A134G	nonsynonymous SNV	1315	6	0.0045
2	198267489	198267489	T	C	SF3B1	c.A1868G	p.Y623C	nonsynonymous SNV	1149	92	0.0741
2	198267359	198267359	C	A	SF3B1	c.G1998T	p.K666N	nonsynonymous SNV	291	231	0.4425
12	111856644	111856644	G	-	SH2B3	c.695delG	p.G232fs	frameshift deletion	601	34	0.0535
16	30727486	30727486	C	T	SRCAP	c.C2593T	p.Q865X	stopgain	801	5	0.0062
16	30749027	30749027	C	T	SRCAP	c.C7666T	p.Q2556X	stopgain	879	10	0.0112
16	30749773	30749773	C	-	SRCAP	c.8412delC	p.P2804fs	frameshift deletion	889	6	0.0067
16	30718563	30718563	G	-	SRCAP	c.366delG	p.K122fs	frameshift deletion	986	40	0.039
16	30732782	30732782	C	-	SRCAP	c.3526delC	p.Q1176fs	frameshift deletion	916	6	0.0065
16	30735086	30735086	T	-	SRCAP	c.4341delT	p.L1447fs	frameshift deletion	1224	10	0.0081
16	30735667	30735668	0	-	SRCAP	c.4922_4923del	p.S1641fs	frameshift deletion	1027	9	0.0087
16	30745315	30745315	G	-	SRCAP	c.6595delG	p.A2199fs	frameshift deletion	835	5	0.006
16	30745902	30745903	0	-	SRCAP	c.6695_6696del	p.T2232fs	frameshift deletion	1023	7	0.0068
16	30747633	30747633	A	-	SRCAP	c.6842delA	p.E2281fs	frameshift deletion	1363	11	0.008
16	30731610	30731610	-	C	SRCAP	c.2946dupC	p.D982fs	frameshift insertion	1119	15	0.0132
16	30721057	30721057	G	-	SRCAP	c.856+1G>-		splicing	832	21	0.0246
16	30735621	30735621	C	T	SRCAP	c.C4876T	p.Q1626X	stopgain	1830	21	0.0113
16	30735975	30735975	C	T	SRCAP	c.C5230T	p.Q1744X	stopgain	1554	29	0.0183
16	30736222	30736222	C	A	SRCAP	c.C5477A	p.S1826X	stopgain	1115	9	0.008
16	30747710	30747710	G	T	SRCAP	c.G6919T	p.E2307X	stopgain	950	5	0.0052
X	123164976	123164976	G	A	STAG2	c.288+1G>A		splicing	373	11	0.0286
X	123197716	123197716	C	T	STAG2	c.C1840T	p.R614X	stopgain	73	145	0.6651
17	40474428	40474428	T	C	STAT3	c.A1973G	p.K658R	nonsynonymous SNV	1303	7	0.0053
17	40475058	40475058	C	G	STAT3	c.G1852C	p.G618R	nonsynonymous SNV	1179	6	0.0051
17	40475070	40475070	T	G	STAT3	c.A1840C	p.S614R	nonsynonymous SNV	1258	28	0.0218
17	40474420	40474420	C	A	STAT3	c.G1981T	p.D661Y	nonsynonymous SNV	1189	6	0.005
4	106164021	106164021	T	-	TET2	c.3531delT	p.I1177fs	frameshift deletion	651	7	0.0106
4	106193748	106193748	C	T	TET2	c.C4210T	p.R1404X	stopgain	428	118	0.2161
4	106180823	106180823	C	T	TET2	c.C3851T	p.S1284F	nonsynonymous SNV	1233	8	0.0064
4	106197285	106197285	T	C	TET2	c.T5618C	p.I1873T	nonsynonymous SNV	1211	14	0.0114
4	106196976	106196976	C	-	TET2	c.5309delC	p.P1770fs	frameshift deletion	987	14	0.014
4	106157149	106157149	C	T	TET2	c.C2050T	p.Q684X	stopgain	1245	7	0.0056
4	106196324	106196324	C	T	TET2	c.C4657T	p.Q1553X	stopgain	1328	10	0.0075
4	106196748	106196748	-	A	TET2	c.5082dupA	p.L1694fs	frameshift insertion	668	57	0.0786
4	106190869	106190869	A	G	TET2	c.A4147G	p.R1383G	nonsynonymous SNV	1009	7	0.0069

Supplemental Table 3. Clonal Hematopoietic Mutations Identified in Cohort (continued).

chrom	pos_start	pos_end	ref	var	gene	cdna	aa	result	reads1	reads2	var_freq
4	106190860	106190860	C	T	TET2	c.C4138T	p.H1380Y	nonsynonymous SNV	808	170	0.1738
4	106180774	106180774	A	T	TET2	c.3804-2A>T		splicing	737	13	0.0173
4	106156651	106156651	-	TT	TET2	c.1552_1553insTT	p.I518fs	frameshift insertion	747	341	0.3131
4	106197002	106197002	G	-	TET2	c.5335delG	p.A1779fs	frameshift deletion	447	12	0.0261
4	106157620	106157620	G	-	TET2	c.2521delG	p.V841fs	frameshift deletion	991	78	0.073
4	106156025	106156025	-	A	TET2	c.927dupA	p.A309fs	frameshift insertion	1053	130	0.1099
4	106164769	106164769	G	A	TET2	c.G3637A	p.V1213M	nonsynonymous SNV	1076	7	0.0065
4	106155938	106155938	-	T	TET2	c.840dupT	p.S280fs	frameshift insertion	1489	14	0.0093
4	106164794	106164794	G	A	TET2	c.G3662A	p.C1221Y	nonsynonymous SNV	1186	70	0.0557
4	106194066	106194066	C	T	TET2	c.C4528T	p.Q1510X	stopgain	652	93	0.1248
4	106197208	106197208	G	A	TET2	c.G5541A	p.W1847X	stopgain	718	519	0.4196
4	106197244	106197244	T	-	TET2	c.5577delT	p.I1859fs	frameshift deletion	1260	9	0.0071
4	106157139	106157139	A	-	TET2	c.2040delA	p.R680fs	frameshift deletion	611	44	0.0672
4	106190795	106190795	G	C	TET2	c.G4073C	p.C1358S	nonsynonymous SNV	781	6	0.0076
4	106197366	106197366	T	C	TET2	c.T5699C	p.V1900A	nonsynonymous SNV	1446	22	0.015
4	106156932	106156932	G	-	TET2	c.1833delG	p.M611fs	frameshift deletion	851	10	0.0116
4	106197248	106197248	G	T	TET2	c.G5581T	p.G1861X	stopgain	1267	37	0.0284
4	106156747	106156747	C	T	TET2	c.C1648T	p.R550X	stopgain	1070	6	0.0056
4	106157371	106157371	C	T	TET2	c.C2272T	p.Q758X	stopgain	778	10	0.0127
4	106197013	106197017	0	-	TET2	c.5346_5350del	p.L1782fs	frameshift deletion	1152	12	0.0103
17	7578235	7578235	T	C	TP53	c.A614G	p.Y205C	nonsynonymous SNV	654	59	0.0827
17	7578457	7578457	C	T	TP53	c.G473A	p.R158H	nonsynonymous SNV	677	84	0.1104
17	7578191	7578191	A	G	TP53	c.T658C	p.Y220H	nonsynonymous SNV	427	102	0.1928
17	7577548	7577548	C	T	TP53	c.G733A	p.G245S	nonsynonymous SNV	1089	20	0.018
17	7578518	7578518	C	T	TP53	c.G412A	p.A138T	nonsynonymous SNV	830	5	0.006
17	7577539	7577539	G	A	TP53	c.C742T	p.R248W	nonsynonymous SNV	753	19	0.0246
17	7578406	7578406	C	T	TP53	c.G524A	p.R175H	nonsynonymous SNV	1356	150	0.0996
17	7577094	7577094	G	A	TP53	c.C844T	p.R282W	nonsynonymous SNV	917	5	0.0054
17	7577543	7577543	C	T	TP53	c.G738A	p.M246I	nonsynonymous SNV	950	8	0.0084
17	7577115	7577115	A	C	TP53	c.T823G	p.C275G	nonsynonymous SNV	1461	11	0.0075
17	7578403	7578403	C	A	TP53	c.G527T	p.C176F	nonsynonymous SNV	1672	13	0.0077
17	7577568	7577568	C	T	TP53	c.G713A	p.C238Y	nonsynonymous SNV	648	5	0.0077
17	7578475	7578475	G	C	TP53	c.C455G	p.P152R	nonsynonymous SNV	906	6	0.0066
17	7577094	7577094	G	A	TP53	c.C844T	p.R282W	nonsynonymous SNV	963	11	0.0113
17	7577120	7577120	C	T	TP53	c.G818A	p.R273H	nonsynonymous SNV	981	25	0.0249
17	7577138	7577138	C	G	TP53	c.G800C	p.R267P	nonsynonymous SNV	1190	59	0.0472
17	7578236	7578236	A	G	TP53	c.T613C	p.Y205H	nonsynonymous SNV	997	5	0.005
17	7577121	7577121	G	T	TP53	c.C817A	p.R273S	nonsynonymous SNV	1048	8	0.0076
17	7578191	7578191	A	T	TP53	c.T658A	p.Y220N	nonsynonymous SNV	738	8	0.0107
17	7578190	7578190	T	C	TP53	c.A659G	p.Y220C	nonsynonymous SNV	720	20	0.027
17	7577120	7577120	C	T	TP53	c.G818A	p.R273H	nonsynonymous SNV	1180	19	0.0158
17	7577532	7577532	G	A	TP53	c.C749T	p.P250L	nonsynonymous SNV	948	19	0.0196
17	7577022	7577022	G	A	TP53	c.C916T	p.R306X	stopgain	1063	14	0.013
17	7577559	7577559	G	A	TP53	c.C722T	p.S241F	nonsynonymous SNV	767	29	0.0364
17	7576865	7576865	A	T	TP53	c.T981A	p.Y327X	stopgain	676	95	0.1232
17	7577120	7577120	C	T	TP53	c.G818A	p.R273H	nonsynonymous SNV	985	27	0.0267
17	7577505	7577505	T	A	TP53	c.A776T	p.D259V	nonsynonymous SNV	643	6	0.0092
17	7578535	7578535	T	C	TP53	c.A395G	p.K132R	nonsynonymous SNV	1023	7	0.0068
17	7577124	7577124	C	A	TP53	c.G814T	p.V272L	nonsynonymous SNV	934	9	0.0095
17	7578550	7578550	G	A	TP53	c.C380T	p.S127F	nonsynonymous SNV	860	24	0.0271
17	7578442	7578442	T	C	TP53	c.A488G	p.Y163C	nonsynonymous SNV	1248	35	0.0273
17	7577574	7577574	T	C	TP53	c.A707G	p.Y236C	nonsynonymous SNV	689	54	0.0727
17	7577108	7577108	C	A	TP53	c.G830T	p.C277F	nonsynonymous SNV	909	154	0.1449
17	7578406	7578406	C	T	TP53	c.G524A	p.R175H	nonsynonymous SNV	1499	8	0.0053
17	7577098	7577100	0	-	TP53	c.838_840del	p.280_280del	nonframeshift deletion	1286	18	0.0138
17	7577580	7577580	T	C	TP53	c.A701G	p.Y234C	nonsynonymous SNV	925	8	0.0086
17	7577550	7577550	C	T	TP53	c.G731A	p.G244D	nonsynonymous SNV	796	12	0.0149
17	7577559	7577559	G	A	TP53	c.C722T	p.S241F	nonsynonymous SNV	1206	10	0.0082
17	7578442	7578442	T	C	TP53	c.A488G	p.Y163C	nonsynonymous SNV	1910	10	0.0052
17	7578503	7578503	C	T	TP53	c.G427A	p.V143M	nonsynonymous SNV	1749	14	0.0079
17	7578449	7578449	C	T	TP53	c.G481A	p.A161T	nonsynonymous SNV	1445	9	0.0062
17	7577114	7577114	C	T	TP53	c.G824A	p.C275Y	nonsynonymous SNV	1055	10	0.0094
17	7578191	7578191	A	G	TP53	c.T658C	p.Y220H	nonsynonymous SNV	721	13	0.0177
17	7574034	7574034	C	G	TP53	c.877-1G>C		splicing	727	17	0.0228
17	7578479	7578479	G	A	TP53	c.C451T	p.P151S	nonsynonymous SNV	1340	45	0.0325
17	7578190	7578190	T	C	TP53	c.A659G	p.Y220C	nonsynonymous SNV	674	60	0.0817
17	7579447	7579447	A	-	TP53	c.240delT	p.P80fs	frameshift deletion	1294	119	0.0842
17	7577570	7577570	C	T	TP53	c.G711A	p.M237I	nonsynonymous SNV	305	385	0.558
17	7577082	7577082	C	T	TP53	c.G856A	p.E286K	nonsynonymous SNV	1296	18	0.0137
17	7579717	7579717	G	C	TP53	c.C79G	p.P27A	nonsynonymous SNV	553	5	0.009
17	7578555	7578555	C	T	TP53	c.259-1G>A		splicing	625	299	0.3236
21	44514777	44514777	T	C	U2AF1L5	c.A470G	p.Q157R	nonsynonymous SNV	1047	11	0.0104
21	44514777	44514777	T	G	U2AF1L5	c.A470C	p.Q157P	nonsynonymous SNV	464	276	0.373
X	15841102	15841102	G	T	ZRSR2	c.G1186T	p.E396X	stopgain	585	6	0.0102

Supplemental Table 4. Association between Clonal Hematopoiesis and Toxicity After CAR T-Cell Therapy.
A) ASTCT cytokine release syndrome (CRS) grade stratified by age and CHIP status across entire cohort.
B) Clinical evidence of neurotoxicity stratified by age and CHIP status across in non-Hodgkin Lymphoma (NHL) patients.

A

			ASTCT CRS Score		
	CH Status	**Total Patients**	**Grade < 2 # (%)**	**Grade ≥ 2 # (%)**	**p-value***
All Patients	VAF < 0.02	80	32 (40.0)	48 (60.0)	0.5
	VAF ≥ 0.02	74	25 (33.8)	49 (66.2)	
Age < 60	VAF < 0.02	40	21 (52.5)	19 (47.5)	0.032
	VAF ≥ 0.02	22	5 (22.7)	17 (77.3)	
Age ≥ 60	VAF < 0.02	40	11 (27.5)	29 (72.5)	0.37
	VAF ≥ 0.02	52	20 (38.5)	32 (61.5)	

*** p-values were calculated using a Fisher's exact test**

B

			Neurotoxicity		
	CH Status	**Total Patients**	No # (%)	Yes # (%)	p-value*
All NHL Patients	VAF < 0.02	76	43 (56.6)	33 (43.4)	0.066
	VAF > 0.02	67	27 (40.3)	40 (59.7)	
NHL Age < 60	VAF < 0.02	37	23 (62.2)	14 (37.8)	0.56
	VAF > 0.02	18	9 (50.0)	9 (50.0)	
NHL Age > 60	VAF < 0.02	39	20 (51.3)	19 (48.7)	0.20
	VAF > 0.02	49	18 (36.7)	31 (63.3)	

*** p-values were calculated using a Fisher's exact test**

Supplemental Methods

DNA Sequencing and Variant Calling

Following hybridization of sheared genomic DNA, we generated libraries tagged with duplex unique molecular identifiers using a custom bait set from Twist Bioscience (San Francisco, CA) targeting 101 genes recurrently mutated in CH (**Supplemental Table 1**). The bait set targeted regions of the genes previously shown to harbor recurrent, pathogenic variants (all regions targeted by the bait set will be made available upon request). Following UMI deduplication and alignment, we performed variant calling using Varscan version 2.2.3 and annotation using Annovar (April 2017 build). We classified variants as CH based on accepted criteria for pathogenicity and included variants with at least 5 supporting consensus reads in final analysis.[16,17]

Statistical Methods

Exploratory endpoints included serum levels of high sensitivity C-reactive protein (hsCRP), ferritin, and interleukin-6 (IL-6) between groups with and without CH VAF > 0.02, stratified by age above or below 60. PFS and OS comparisons were performed using the log-rank test, comparisons of rates of best overall response, CRS, and frequency of CH between this and previously published cohorts were performed using Fisher's exact tests, and comparisons of continuous variables between groups (such as cytokine levels) were performed using Mann-Whitney U tests. Differences between groups were considered statistically significant at p-values < 0.05. All analyses were performed and the results plotted using R (v4.0.0) or PRISM (v9.0.0)