LETTER TO THE EDITOR

Clonal hematopoiesis is common in bone marrow of patients with classical Hodgkin lymphoma

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Supplemental Information

Supplemental Table 1. Clinical data of the patients

Supplemental Table 2. NGS panel design

Supplemental Table 3. Detailed data of NGS variants, M-CHIP and L-CHIP

Supplemental Table 1(a). Clinical information.

NS: nodular sclerosis; MC: mixed cellularity; IPS: International Prognosis Score; CR: complete response; PR: partial response; PFS: progression free survival; OS: overall survival; F: favorable outcome (PFS 2 years); U: unfavorable outcome (PFS < 2 years); DoD: death of disease.

Case#	BM#	cHL subtype	Stage	IPS	Response	Relapse	F vs U	DoD	PFS (months)	OS (months)
1	1770	NA	IIB	<3	CR	No	F	Yes	33,73	33,73
2	1580	NS	IIA	<3	CR	No	F	No	123,22	123,22
3	1593	NS	IIIA	<3	CR	No	F	No	121,87	121,87
4	1600	NA	IVA	>3	CR	No	F	Lost	70,59	70,59
5	1605	NA	NA	<3	NA	NA	NA	Lost	0,30	0,30
6	1677	NS	IVA	<3	CR	No	F	No	115,20	115,20
7	1902	MC	IIA	<3	CR	No	F	No	89,39	89,39
8	1901	NS	NA	<3	CR	No	F	No	76,11	76,11
9	2087	NS	IVB	<3	PR	Yes	U	Yes	10,39	48,16
10	2468	NS	NA	<3	CR	No	F	No	44,65	44,65
11	2411	NS	IVA	<3	CR	No	F	No	47,67	47,67
12	2386	NS	NA	<3	PR	Yes	U	No	7,40	30,21
13	2726	NS	IIIB	<3	CR	No	F	No	28,50	28,50
14	2745	MC	IIIB	<3	CR	Yes	U	No	28,14	28,57
15	2765	NS	NA	<3	CR	No	F	No	19,56	19,56
16	2781	NS	IVB	<3	CR	No	F	No	27,12	27,12
17	526	NA	NA	NA	NA	NA	NA	NA	NA	NA
18	549	NS	IVA	<3	CR	Yes	U	Lost	20,02	101,03
19	334	NS	IIA	<3	CR	No	F	No	198,50	198,48
20	368	NS	IIA	<3	CR	No	F	No	204,13	204,13
21	374	NA	NA	<3	CR	No	F	No	197,90	197,92
22	418	NA	IIA	<3	CR	No	F	No	184,60	184,64
23	443	NA	NA	NA	NA	NA	NA	Lost	NA	NA
24	457	NS	IA	<3	CR	Yes	U	No	68,38	173,36
25	518	NA	NA	<3	CR	No	F	No	109,81	109,81
26	524	NS	IIA	<3	CR	Yes	U	No	18,08	120,16
27	525	NA	NA	<3	CR	No	F	No	181,55	181,55
28	543	NA	IIIA	<3	CR	Yes	U	No	82,59	189,37
29	617	NA	NA	>3	CR	Yes	U	No	30,18	177,01
30	722	NA	NA	NA	NA	NA	NA	Lost	136,11	136,11
31	657	NA	NA	<3	CR	No	F	No	180,66	180,66
32	671	NA	IIA	<3	CR	No	F	No	120,00	120,00
33	746	NA	IIA	<3	CR	No	F	No	174,74	174,74
34	753	NA	IVA	<3	CR	No	F	No	128,28	128,28
35	930	NA	IVB	<3	CR	No	F	No	172,87	172,87
36	975	NA	IV	<3	CR	No	F	Yes	55,73	55,73

Supplemental Table 1(b). Clinical information (2): EBV status and inflammation indicators.

EBV status was determined by in situ hybridization for the detection of EBER or immunohistochemistry for LMP1 expression; ESR: erythrocyte sedimentation rate (mm/h); CRP: C-reactive protein, N: normal range (< 5 mg/L). NA: not available.

Case#	BM#	Age (y)	cHL subtype	EBV status	ESR (mm/h)	CRP (mg/L)
1	1770	7	NA	-	<10	NA
2	1580	31	NS	-	26	N
3	1593	44	NS	-	11	NA
4	1600	79	NA	-	96	NA
5	1605	18	NA	+	<10	NA
6	1677	22	NS	-	57	22,5
7	1902	38	MC	+	10	N
8	1901	44	NS	-	<10	N
9	2087	33	NS	-	10,5	N
10	2468	24	NS	-	<10	N
11	2411	25	NS	-	<10	37
12	2386	56	NS	-	37	87,9
13	2726	24	NS	-	<10	N
14	2745	41	MC	+	13	12,9
15	2765	36	NS	-	<10	23,3
16	2781	30	NS	-	40	45
17	526	33	NA	NA	NA	NA
18	549	70	NS	NA	26	36,3
19	334	29	NS	-	NA	NA
20	368	28	NS	+	NA	NA
21	374	27	NA	-	<10	N
22	418	53	NA	-	<10	N
23	443	84	NA	-	NA	NA
24	457	64	NS	-	22	N
25	518	19	NA	NA	<10	N
26	524	37	NS	-	NA	NA
27	525	34	NA	NA	12	N
28	543	50	NA	-	<10	N
29	617	45	NA	-	24	35
30	722	76	NA	-	10	NA
31	657	39	NA	-	65	44,2
32	671	37	NA	-	12,5	38
33	746	38	NA	NA	<10	N
34	753	40	NA	-	66	NA
35	930	33	NA	-	<10	N
36	975	79	NA	-	<10	N

Supplemental Table 2. NGS panel design, including the commonest M-CHIP driver mutations.

Pathway/function	Genes
DNA methylation	*DNMT3A, TET2, IDH1, IDH2*
Chromatin modification	*ASXL1, EZH2, KDM6A, SETBP1*
RNA Splicing	*SF3B1, U2AF1, SRSF2, PRPF8, ZRSR2*
Transcriptional regulation	*RUNX1, CUX1, ETV6, GATA2, BCOR, BCOR1, IRF1, PHF6*
Signaling	*NRAS, KRAS, CBL, GNAS, PTEN, PTPN11, JAK2, MPL, FLT3, NF1, CALR, KIT*
Cell cycle	*TP53, PPM1D, CDKN2A, NPM1*

Supplemental Table 3(a). NGS results. VAF: variant allele frequency.

Case#	BMA#	Genes	Locus	Genotype	VAF %	Amino Acid Change	Transcript	Coding	Variant Effect
1	1770	*KRAS*	chr12:25398255	G/T	3.81	p.Gln22Lys	NM_033360.4	c.64C>A	missense
	1910	*KRAS*	chr12:25398255	G/T	10.57	p.Gln22Lys	NM_033360.4	c.64C>A	missense
4	1600	*BCOR*	chrX:39923655	C/T	5.21	p.Glu1146Lys	NM_001123385.2	c.3436G>A	missense
		JAK2	chr9:5066718	C/T	3.46	p.Gln419Ter	NM_004972.4	c.1255C>T	nonsense
9	2087	*CBL*	chr11:119149371	ATGA/A	2.65	p.Asp460del	NM_005188.4	c.1380_1382delTGA	nonframeshiftDeletion
		KRAS	chr12:25380206	T/C	3.88	p.Ile84Met	NM_033360.4	c.252A>G	missense
18	549	*TET2*	chr4:106158108	GAAAAAG/AAAAAAG	1.72	p.Trp1003Ter	NM_001127208.3	c.3009G>A	nonsense
		TET2	chr4:106164914	G/A	5.19	p.Arg1261His	NM_001127208.3	c.3782G>A	missense
19	334	*DNMT3A*	chr2:25523008	CGGGGGG/CAGGGGG	2.12	p.Pro59Leu	NM_022552.5	c.176C>T	missense
		TET2	chr4:106162540	G/A	3.50	p.Gly1152Arg	NM_001127208.3	c.3454G>A	missense
20	368	*RUNX1*	chr21:36164790	G/A	2.31	p.Ser362Leu	NM_001754.5	c.1085C>T	missense
		ZRSR2	chrX:15808605	G/A	3.04	p.Ala95Thr	NM_005089.4	c.-14G>A	missense
		DNMT3A	chr2:25523008	CGGGGG/CGGGG	2.14	p.Pro59ArgfsTer13	NM_022552.5	c.176delC	frameshiftDeletion
22	418	*CBL*	chr11:119149371	ATGA/A	2.67	p.Asp460del	NM_005188.4	c.1380_1382delTGA	nonframeshiftDeletion
23	443	*TET2*	chr4:106157695	C/T	28.40	p.Gln866Ter	NM_001127208.3	c.2596C>T	nonsense
		CDKN2A	chr9:21971105	C/T	4.73	p.Ala85Thr	NM_001195132.2	c.253G>A	missense
		CDKN2A	chr9:21971156	C/T	4.12	p.Ala68Thr	NM_001195132.2	c.202G>A	missense
		ZRSR2	chrX:15821824	G/A	3.40	p.Glu73Lys	NM_005089.4	c.217G>A	missense
24	*457*	*CDKN2A*	*chr9:21971057*	*C/A*	*5.41*	*p.Gly101Trp*	*NM_001195132.2*	*c.301G>T*	*missense*
	1629	*NRAS*	*chr1:115256568*	*C/T*	*5.61*	*p.Gly48Asp*	*NM_002524.5*	*c.143G>A*	*missense*
25	518	*TET2*	chr4:106157474	C/T	3.34	p.Ser792Leu	NM_001127208.3	c.2375C>T	missense
		TET2	chr4:106196291	C/T	4.72	p.Gln1542Ter	NM_001127208.3	c.4624C>T	nonsense
		SETBP1	chr18:42532058	G/A	2.96	p.Arg918Gln	NM_015559.3	c.2753G>A	missense
26	524	*NPM1*	chr5:170814990	G/A	4.76	p.Arg13Lys	NM_002520.7	c.38G>A	missense
28	543	*ZRSR2*	chrX:15841195	AGGGA/AGGAA	2.46	p.Asp428Asn	NM_001127208.3	c.1282G>A	missense
32	671	*TP53*	chr17:7578283	G/A	3.56	p.Ala189Val	NM_000546.6	c.566C>T	missense
		DNMT3A	chr2:25470581	C/T	5.42	p.Gly298Glu	NM_022552.5	c.893G>A	missense
34	753	*ZRSR2*	chrX:15833894	G/A	4.76	p.Asp218Asn	NM_005089.4	c.652G>A	missense
		CUX1	chr7:101877495	G/A	3.36	p.Met1199Ile	NM_181552.4	c.3597G>A	missense
		EZH2	chr7:148514459	G/A	4.64	p.Pro422Leu	NM_004456.5	c.1265C>T	missense
		MPL	chr1:43805023	C/T	3.55	p.Ala158Val	NM_005373.3	c.473C>T	missense
		DNMT3A	chr2:25497942	CC/CT	5.08	p.Arg169Gln	NM_022552.5	c.506G>A	missense
		TET2	chr4:106196296	ACCCCAGCAGCAGCAG/ACCCCAGCAGCAG	3.01	p.Gln1548del	NM_001127208.3	c.4643_4645delAGC	nonframeshiftDeletion
	767	*TET2*	chr4:106158064	C/T	4.15	p.Pro989Ser	NM_001127208.3	c.2965C>T	missense
36	975	*TET2*	chr4:106158064	C/T	3.04	p.Pro989Ser	NM_001127208.3	c.2965C>T	missense
		TET2	chr4:106196303	C/T	5.65	p.Gln1546Ter	NM_001127208.3	c.4636C>T	nonsense
		TET2	chr4:106196621	C/T	1.93	p.Gln1652Ter	NM_001127208.3	c.4954C>T	nonsense
		CUX1	chr7:101844916	ACCCCCCG/ACCCCCG	2.13	p.Pro782ArgfsTer26	NM_181552.4	c.2345delC	frameshiftDeletion

Supplemental Table 3(b). NGS results, indicative of L-CHIP, cHL panel. VAF: variant allele frequency.

Case#	BMA#	Genes	Locus	Genotype	VAF %	Amino Acid Change	Transcript	Coding	Variant Effect
23	443	*CREBBP*	*chr16:3779434*	*A/G*	*4.55*	*p.Met1872Val*	*NM_004380.3*	*c.5614A>G*	*missense*
		NOTCH1	*chr9:139413186*	*A/G*	*3.79*	*p.Tyr319Cys*	*NM_017617.5*	*c.956A>G*	*missense*
		RET	*chr10:43607603*	*G/A*	*3.14*	*p.Glu527Lys*	*NM_020975.6*	*c.1579G>A*	*missense*