Supplemental Table 1A: Disease characteristics

ID	Age (y)	Gender	HLH type	HLH genetic dgn	HLH therapy	Progr on TX	Emapalumab # of doses	Eculizumab # of doses	sC5b-9 ng/mL	rUPCR mg/mg	Complement genes[#]	Organ injury at TMA diagnosis							HCT	Status
												RRT	Vent	PH	Ser	HTN	CNS	GI		
SUBJECTS WITH DIAGNOSIS OF TMA																				
1	1.3	M	HLH	none	E/Dex ATG	Y	-	-	ND	2.3	*Het-CFHR3/R1*	Y	Y	N	Y	Y	Y	N	Y	alive
2	17	F	HLH	none	E/Dex CSA	Y	-	7	1271	4.5	*Het-CFI*	Y	Y	Y	Y	Y	Y	Y	N	dead[a]
3	0.9	M	HLH	none	AraC, Mpr Abatacept	Y	-	3	325	10.2	None	N	Y	N	Y	Y	Y	N	N	alive
4	0.6	M	HLH-EBV	none	E/Dex Ritux	Y	-	-	388	11.4	*Het-CFHR3/R1*	Y	Y	N	N	Y	Y	Y	N	dead[a]
5	3	F	HLH	ND	E/Dex	Y	-	3	1890	8.5	None	N	Y	N	N	Y	N	N	N	dead
6	0.8	F	FHL2	PRF1	E/Dex	Y	-	3	922	48.5	None	Y	Y	N	N	Y	Y	N	N	dead
7	2	M	HLH	None[&]	E/Dex	Y	21	2	1700	12	*CFHR3, CFHR1 dup, Het-CFI*	Y	Y	Y	N	Y	Y	Y	N	alive
8	1.1	F	Griselli	*RAB27A*	E/Dex	Y	6	6	196	12.5	ND	N	N	N	N	Y	N	N	Y	alive
9	0.7	F	HLH	none	E/Dex	Y	29	9	480	11	*Het-CFHR3/R1 Het-CFB*	N	Y	Y	N	Y	N	Y*	Y	alive
10	3	F	XLP2	*XIAP*	E/Dex	Y[#]	15	-	ND	0.45	*Het-CFHR3/R1 Het-CFHR5*	N	N	n/e	N	Y	N	N	[Y]	alive
11	0.7	M	Griselli	*RAB27A*	E/Dex	Y	10	-	262	0.9	ND	N	N	N	N	Y	N	N	Y	alive
12	4	M	FHL4	*STX11*	E/Dex	Y	11	6	680	6.5	ND	N	Y	N	Y	Y	Y	Y	Y	alive
13	23	F	HLH-EBV	none	E/Dex Ritux	Y	4	-	1315	0.9	ND	Y	Y	Y	Y	Y	Y	N	N	dead
14	9	F	HLH-EBV	none	E/Dex Ritux	Y	3	-	1737	11.8	ND	Y	Y	N	Y	Y	Y	Y*	N	dead
15	0.6	F	FHL5	*STXBP2*	E/Dex Alemtuz	Y	12	9	450	8.04	ND	N	Y	N	N	Y	Y	Y	Y	alive
16	4	M	FHL5	*STXBP2*	E/Dex	Y	13	11	358	13.9	ND	N	N	N	N	Y	Y	N	Y	alive
SUBJECTS WITHOUT DIAGNOSIS OF TMA																				
17	1.1	M	HLH-EBV	none	E/Dex Ritux	Y[C]	18	n/a	162	0.5	ND	N	N	N	N	N	Y	N	Y	alive
18	2.5	F	FHL5	*STXBP2*	E/Dex	Y[#]	13	n/a	ND	0.45	ND	N	Y	Y	Y	N	N	N	[Y]	dead
19	3.8	M	FHL3	*UNC13D*	E/Dex CSA	Y[C]	34	n/a	186	0.6	ND	N	N	N	N	N	Y	N	Y	alive
20	2.2	F	HLH	none	E/pred anakinra	Y[C]	22	n/a	160	1.12	ND	N	Y	N	N	N	Y	N	Y	alive
21	9	M	Griselli	*RAB27A*	E/Dex CSA	Y[C]	2	n/a	ND	0.2	ND	N	Y	N	N	N	Y	N	N	dead
22	0.3	F	FHL5	*STXBP2*	E/Dex	Y	13	n/a	234	5.1	ND	N	N	N	N	N	N	N	Y	alive
23	<0.1	F	FHL3	*UNC13D*	E/Dex	Y	1	n/a	ND	0.3	ND	N	Y	N	N	N	Y	N	N	dead

HLH: clinically diagnosed hemophagocytic lymphohistiocytosis, FHL: familiar hemophagocytic lymphohistiocytosis, HLH-EBV: HLH-associated with Epstein- Barr virus, XLP2, X-linked lymphoproliferative disease type 2, M; male, F; female, E; etoposide, Dex: dexamethasone, Ritux: rituximab, CSA: cyclosporine, AraC: cytarabine, : alemtuzumab, Pred: prednisolone, Progr on Tx: progressed on therapy, Y; yes, N; no, ND; not done/not tested; n/e not examined, n/a: not applicable, RRT: renal replacement therapy, Vent: respiratory support via mechanical ventilation, PH: pulmonary hypertension, Ser; serositis, HTN: severe hypertension (>2

antihypertensive medication or continues infusion), CNS: central nervous system symptoms, GI- lower intestinal bleeding, HCT: hematopoietic cell transplantation, [Y] – indicated history of prior HCT with subsequent HLH relapse, #relapsed post first HCT, [C]CNS progression on therapy (received additional IT methotrexate), [a] autopsies with the evidence on TMA in the kidney. [&] 1 heterozygous variant of uncertain significance in BLOC1S6 (c.330C>G(p.H110Q). [#] Complement gene variant information is listed in Supplemental Table 1B.

Supplemental Table 1B: Complement variants identified in tested subjects with TMA

ID	GENE NAME (w/ Reference Sequence)	VARIANT (predicted effect)	INTERPRETATION
1	*CFHR3/CFHR1*[#]	heterozygous deletion	Unknown if in heterozygous state confers any additional risk for aHUS. This variant in heterozygous state has been reported in hematopoietic stem cell transplant (HCT) recipients with transplant-associated thrombotic microangiopathy (TA-TMA) (Jodele et al, Blood. 2016 Feb 25;127(8):989-96; Jodele et el, Blood. 2013 Sep 19;122(12):2003-7)
2	*CFI*	c.1246A>C(p.I416L), heterozygous deletion	A likely pathogenic variant in CFI that is predicted to increase the risk of developing aHUS
4	*CFHR3/CFHR1*[#]	Heterozygous deletion	Unknown if in heterozygous state confers any additional risk for aHUS. This variant in heterozygous state has been reported in hematopoietic stem cell transplant (HCT) recipients with transplant-associated thrombotic microangiopathy (TA-TMA) (Jodele et al, Blood. 2016 Feb 25;127(8):989-96; Jodele et el, Blood. 2013 Sep 19;122(12):2003-7)
7	*CFHR3* *CFHR1*	Partial duplication Partial duplication	A partial gene duplication involving exons 1-3 of CFHR3 gene and exons 3-6 of CFHR1 gene, which is of uncertain clinical significance.
	CFI (NM_000204.3)	c.1217G>A(p.R406H), heterozygous deletion	VUCS unable to predict, reported in association with macular degeneration
9	*CFHR3*	Heterozygous deletion	The presence of this deletion neither confirms nor rules out the diagnosis of atypical hemolytic uremic syndrome (aHUS).
	CFB (NM_001710.5)	c.1697A>C(p.E566A), heterozygous deletion	VUCS, unable to predict
	CFHR1 (NM_002113.2)	c.310C>T(p.H104Y), heterozygous deletion	VUCS, unable to predict
10	*CFHR3/CFHR1*[#]	heterozygous deletion	Unknown if in heterozygous state confers any additional risk for aHUS. This variant in heterozygous state has been reported in hematopoietic stem cell transplant (HCT) recipients with transplant-associated thrombotic microangiopathy (TA-TMA) (Jodele et al, Blood. 2016 Feb 25;127(8):989-96; Jodele et el, Blood. 2013 Sep 19;122(12):2003-7)
	CFHR5	c.486_487insAA(p.E163fs), heterozygous deletion	heterozygous for a frameshift mutation in *CFHR5* is associated with aHUS

Genes sequenced: *C3, CFB, CFH, CFHR1, CFHR3, CFHR5, CFI, DGKE, MCP, THBD.*

[#]*CFHR3/CFHR1* deletion analysis is performed by multiple ligation-dependent probe amplification (MLPA) analysis.

VUCS = Variant of Uncertain Clinical Significance.