

Ruxolitinib-based regimen in children with primary hemophagocytic lymphohistiocytosis

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Supplementary Table 1. Response Definitions

<p>Complete Response—resolution of all clinical signs and symptoms and normalization of all quantifiable symptoms and examinations of HLH, including neutrophil counts, hemoglobin and platelet counts, alanine aminotransferase (ALT), fibrinogen, triglyceride, ferritin, soluble CD25 (sCD25), and interferon-γ (IFN-γ).</p>
<p>Partial Response—a minimal 25% improvement in at least 2 quantifiable symptoms and laboratory parameters, including:</p> <ol style="list-style-type: none">1) 1.5-fold decrease in sCD25 levels;2) 25% decrease in serum ferritin and triglyceride levels;3) 50% decrease in IFN-γ;3) 100% increase in the blood neutrophil count (to $>0.5 \times 10^9/L$ if the initial count was $<0.5 \times 10^9/L$ or $>2.0 \times 10^9/L$ if the initial count was $0.5-2.0 \times 10^9/L$);4) a decrease of at least 50% in patients with an initial ALT > 400 U/L;
<p>No Response—failure to achieve complete response or partial response.</p>

Supplementary Table 2. HLH Treatment History for Previously Treated Patients

	N=12
Prior medications, n (%)	
GCs	12 (100.0)
Etoposide	8 (66.7)
Cyclosporine A	2 (16.7)
Liposomal doxorubicin	1 (8.3)
Intrathecal injection	6 (50.0)
Duration of treatment (days)	55 (19-350)
The best response, n (%)	
CR	7 (58.3)
PR	5 (41.7)
Outcomes for previous HLH treatment, n (%)	
HLH relapse	7 (58.3)
HLH worsening	5 (41.7)

HLH, hemophagocytic lymphohistiocytosis; GCs, glucocorticoids

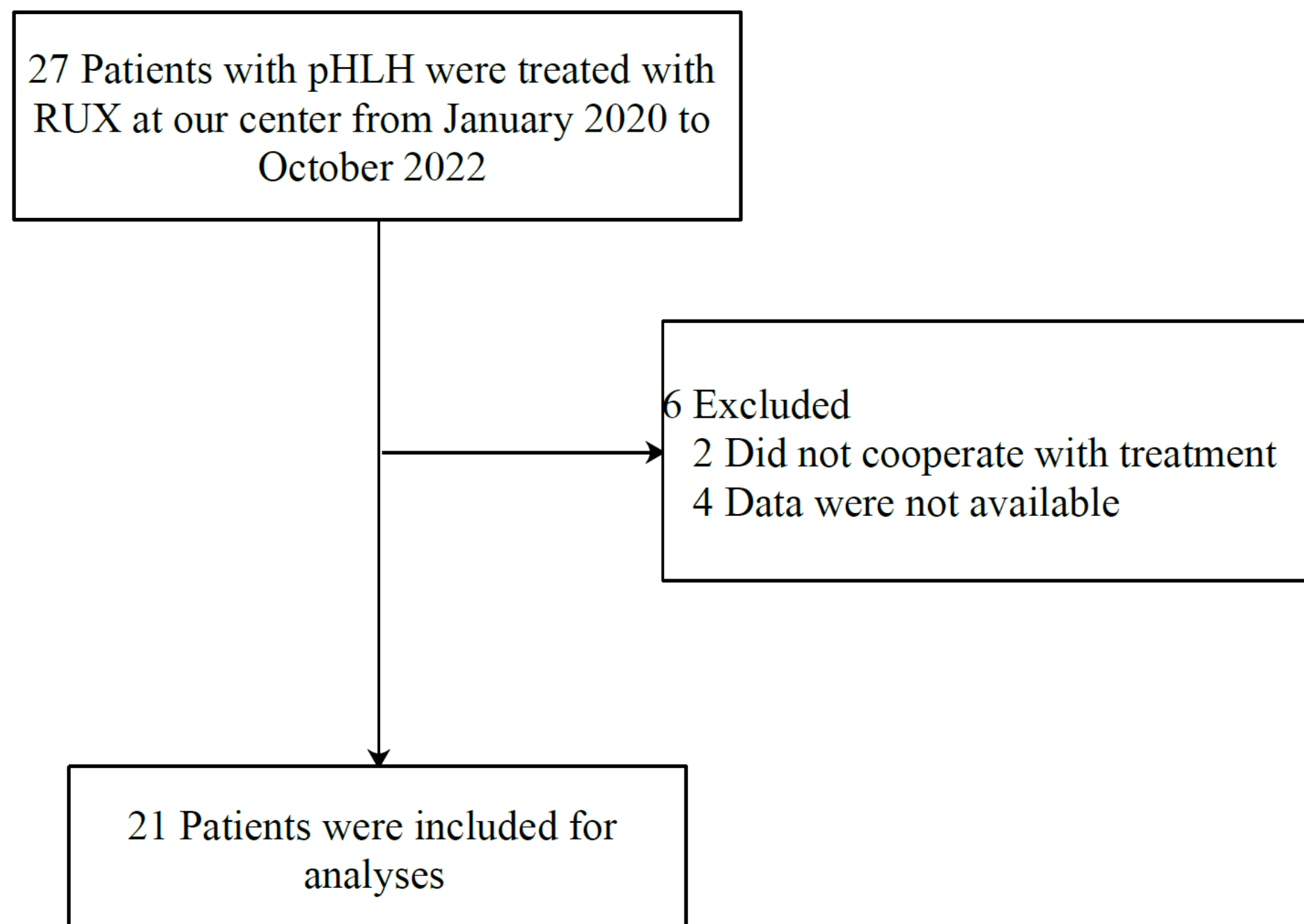
Supplementary Table 3. HLH treatments of the 21 patients

Patients ID	Age (years)	Predisposing factors	Duration of RUX treatment	Reason for discontinuation of RUX	Additional HLH therapy	Response within the first 8 weeks	HSCT	Status before HSCT	Follow-up (years)	Cause of death
P1	4.72	Unknown	116	-	GCs (initially 2mg/kg/d)	Achieved CR	Yes	CR	1.48(Alive)	-
P2	15.03	Unknown	87	-	GCs (initially 2mg/kg/d)	Achieved PR	Yes	PR	0.48(Alive)	-
P3	3.87	Unknown	69	-	GCs (initially 2mg/kg/d)	Achieved CR; relapse	Yes	CR	0.64(Alive)	-
P4	1.39	Unknown	107	Well-controlled disease; XIAP genetic mutation	GCs (initially 2mg/kg/d)	Achieved CR; relapse	No	-	1.63(Alive)	-
P5	2.09	Unknown	140	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×3 doses)	Achieved CR	Yes	CR	1.76(Alive)	-
P6	2.51	EBV infection	94	Critically ill	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×3 doses)	Achieved CR; relapse	No	-	0.27(Dead)	HLH reactivation; Hernia of brain
P7	1.21	Unknown	239	-	GCs (initially 2mg/kg/d)	Achieved CR; relapse	Yes	CR	1.89(Alive)	-
P8	0.13	Unknown	161	Persistent pneumonia	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×11 doses)	Achieved CR; relapse	Yes	PR	1.61(Dead)	Severe GVHD
P9	3.6	EBV infection	166	Well-controlled disease; XIAP genetic mutation	-	Achieved CR	No	-	2.10(Alive)	-
P10	3.3	EBV infection	181	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×11 doses)	Achieved CR	Yes	CR	2.38(Alive)	-
P11	0.5	Unknown	106	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×8 doses)	Achieved CR	Yes	CR	1.76(Alive)	-
P12	6.27	EBV infection	64	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×3 doses)	Achieved CR; relapse	Yes	PR	2.43(Alive)	-

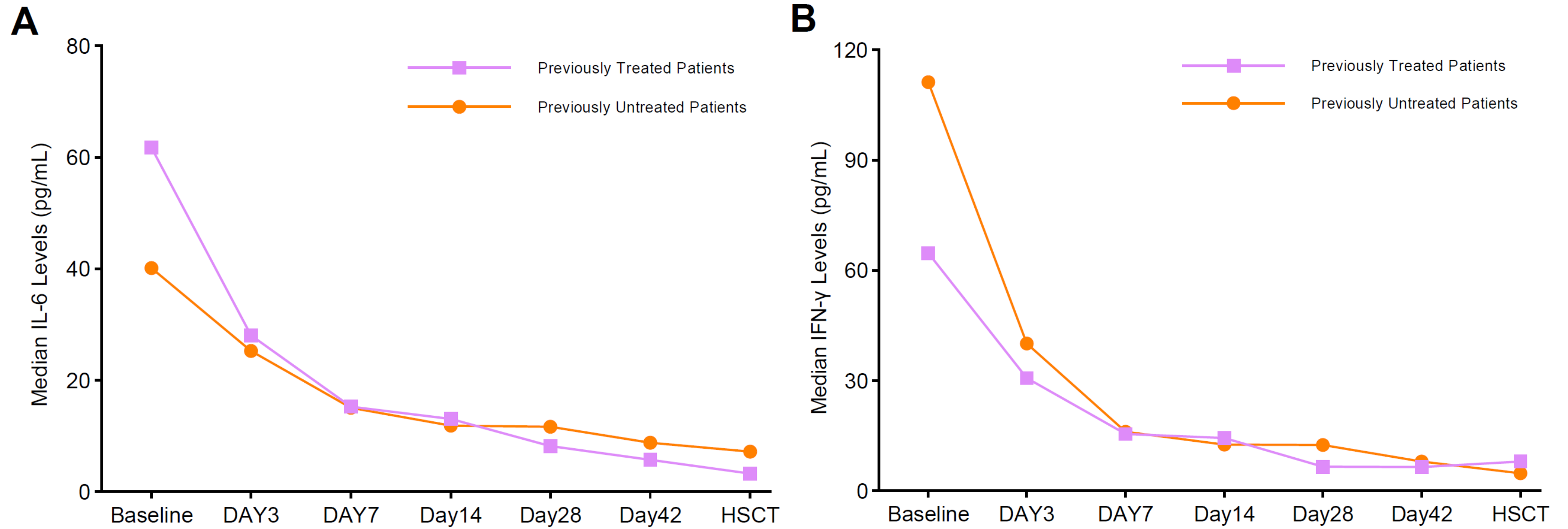
P13	5.45	Unknown	50	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×6 doses)	Achieved CR	Yes	CR	2.56(Alive)	-
P14	4.96	EBV infection	62	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×3 doses) Liposomal doxorubicin (25 mg/m2×1 doses) Pegaspargase (2000 U/m2×3 doses)	Achieved CR; relapse	Yes	CR	0.38(Alive)	-
P15	0.47	Unknown	38	-	GCs (initially 2mg/kg/d)	Achieved CR	Yes	CR	1.23(Dead)	Severe GVHD
P16	0.15	Unknown	93	-	GCs (initially 2mg/kg/d)	Achieved CR	Yes	CR	2.02(Alive)	-
P17	7.78	Unknown	116	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×10 doses)	Achieved CR	Yes	CR	1.32(Alive)	-
P18	0.68	Unknown	99	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×7 doses)	Achieved CR	Yes	CR	1.23(Alive)	-
P19	10.12	EBV infection	99	Pulmonary tuberculosis	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×11 doses)	Achieved CR; relapse	Yes	Active	0.85(Alive)	-
P20	2.44	Unknown	92	-	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×8 doses)	Achieved CR	Yes	CR	0.82(Alive)	-
P21	3.1	EBV infection	94	Critically ill	GCs (initially 2mg/kg/d) Etoposide (100 mg/m2/dose×11 doses)	Achieved PR	No	-	0.32(Dead)	HLH reactivation; multi-organ failure

RUX, Ruxolitinib; EBV, Epstein-Barr virus; GCs, Glucocorticoids; GVHD, graft-versus-host disease

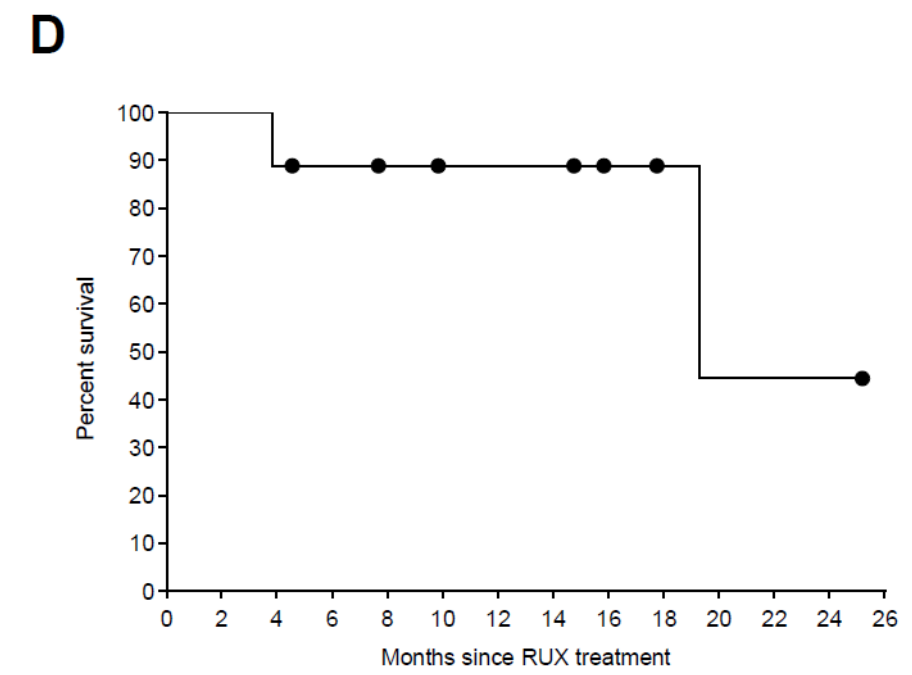
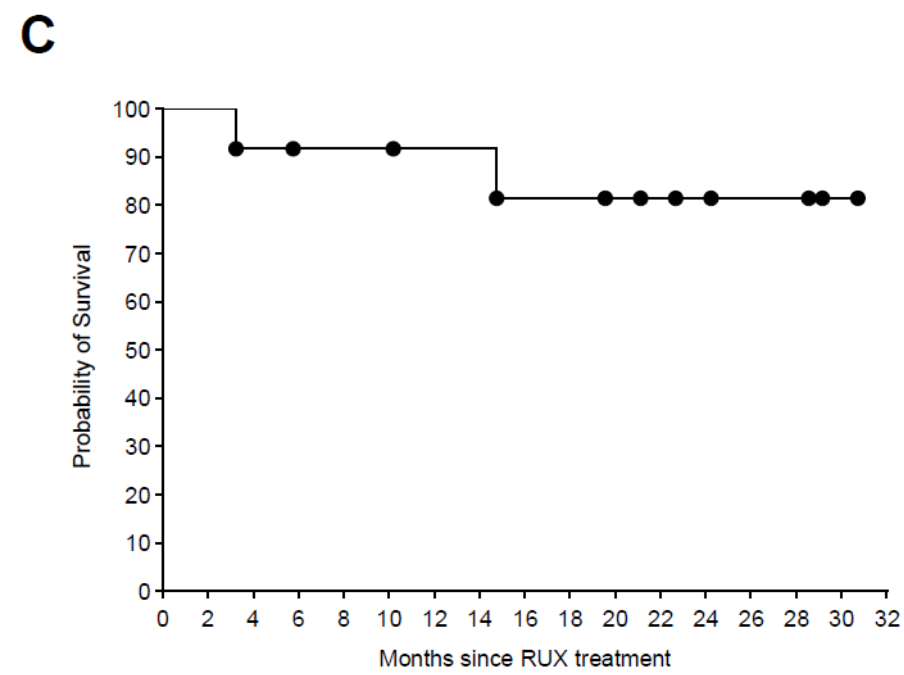
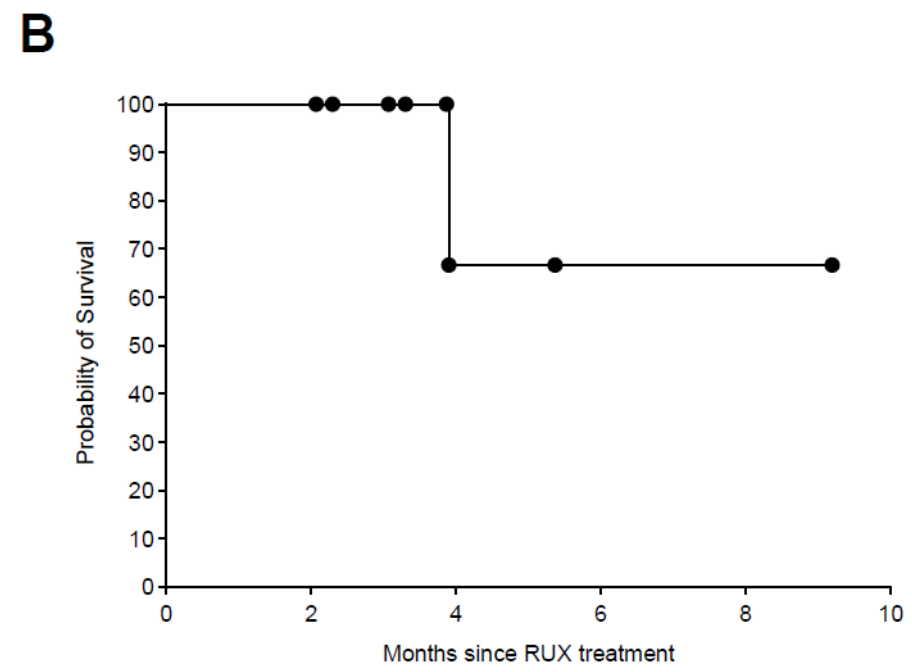
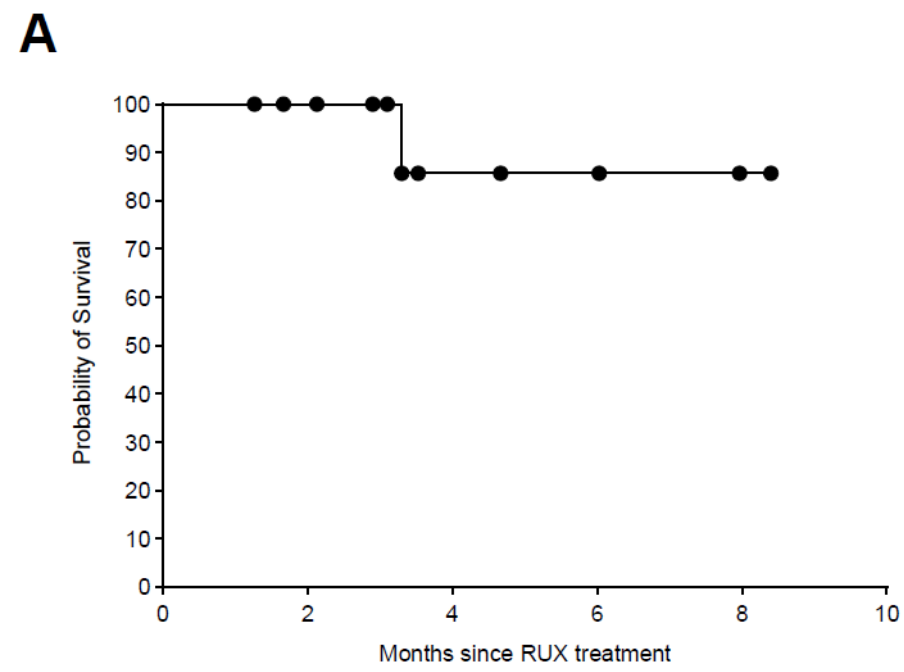
Supplementary Figure 1. Flow Diagram.



Supplementary Figure 2. Serum levels of IL-6 and IFN- γ . (A) Interleukin-6 (IL-6) levels in serum during treatment. (B) IFN- γ levels in serum during treatment. (We collected and analyzed data on cytokine levels at days 7, 14, 28, and 42 during treatment, as well as levels within 3 days before HSCT. Notably, 4 patients did not receive HSCT, so median cytokine levels at HSCT were calculated using data of the 17 patients who received HSCT.)



Supplementary Figure 3. Kaplan–Meier Estimates of Survival. (A) Survival until HSCT of previously treated patients. (B) Survival until HSCT of previously untreated patients. (C) Overall survival of previously treated patients. (D) Overall survival of previously untreated patients.



Supplementary Figure 4. Patients treated by RUX-based regimen received reduced cumulative dose of glucocorticoids. (A) Previously treated patients. (B) Previously untreated patients. (For comparison purposes, glucocorticoids doses were converted to dexamethasone-equivalents using standard conversions.)

