

Supplemental Appendix

Supplement methods	2
Table S1. Patient distribution by center	3
Table S2. Correlation coefficients between covariates	4
Table S3. Patient characteristics with and without flares	5
Table S4. Multivariate analysis for NRM within 6 months after CR/VGPR treating flares as a time-dependent covariate	7
Table S5. GVHD characteristics at 1st onset and at flare	8
Table S6. Cumulative incidence of GVHD flares within 6 months from CR/VGPR stratified by baseline characteristics	9
Table S7. Effect modifications of steroid taper rates by the AA scores on the risk of flares	11
Table S8. Flare rates within 6 months stratified by three risk factors	12
Figure S1. Associations of treatment response on flares and NRM	13
Figure S2. Association of steroid taper rates on flares	14
Figure S3. Association of biomarkers at the time of flares on NRM	15

Supplement methods

Weekly steroid taper rate

We calculated the weekly steroid taper rate to assess the potential impact of the kinetics of steroid reduction on the risk of flares. We considered CR/VGPR as the starting point (denoted as X_{start}). We used the daily steroid dose calculated at the first occurring event as the ending point: a) day 28 after CR/VGPR, b) steroid discontinuation, c) death, d) the time of flares (denoted as X_{end}). The duration between X_{start} and X_{end} was represented as $Y_{duration}$. The weekly steroid reduction rate was calculated as below.

$$\text{Weekly steroid reduction rate (\%)} = \frac{X_{start} - X_{end}}{Y_{duration}} * 7 * \frac{1}{X_{start}} * 100$$

Separating rapid and slow steroid tapers

We divided the patients into four groups from least reduction to greatest reduction in steroid dose per week, that roughly corresponded to quartiles: Group 1 (<15%), Group 2 ($\geq 15\%$, and <20%), Group 3 ($\geq 20\%$, and <30%), and Group 4 ($\geq 30\%$). There were no high correlation coefficients (> 0.2) between steroid tapering group and baseline characteristics (Table S2). The cumulative incidence of flares at 6 months from CR/VGPR steadily increased from 14% to 33% as the pace of steroid taper increased (Figure S2A). Because there was an interaction between steroid taper rate and the maximum steroid dose before CR/VGPR on GVHD flares (Figure S2B and S2C), we divided patients into slow and rapid taper groups that accounted for the maximum steroid dose before CR/VGPR. Slow tapers included patients who were tapered <20%/week if the maximum steroid dose was ≤ 1 mg/kg or <30%/week if the maximum steroid dose was >1mg/kg. All other patients were included in the rapid taper group.

Table S1. Patient distribution by center

	n=968
University of Regensburg	172
University of Hamburg	129
Ohio State University	106
University of Erlangen	85
Mayo Clinic, Rochester	79
Icahn School of Medicine at Mount Sinai, New York	68
Massachusetts General Hospital, Boston	64
Children's Hospital of Atlanta	40
City of Hope Comprehensive Cancer Center, Duarte	35
University of Pennsylvania	30
University of Michigan	29
Vanderbilt University, Nashville	23
University of Würzburg	22
Columbia University, New York	17
King Chulalongkorn Memorial Hospital, Bangkok	14
Bambino Gesù Childrens Hospital, Rome	10
Childrens Hospital of Los Angeles	9
Hospital for Sick Children, Toronto	9
Goethe University Frankfurt	8
University Hospital Carl Gustav Carus Dresden	8
Freiburg University Medical Center	5
Children's Hospital of Philadelphia	4
Hannover Medical School	2

Table S2. Correlation coefficients between covariates

	Recipient age	Sex mismatch	Donor type	GVHD prophylaxis	HCT-CI	Use of ATG or alemtuzumab	Conditioning	Max GVHD grades before CR/VGPR	Timing of CR/VGPR	Max steroid dose before CR/VGPR	GVHD treatment before CR/VGPR	Treatment response	Steroid taper rates*	Steroid taper rates**	Correlation coefficients
AA at CR/VGPR	0.096	0.017	0.088	0.066	0.061	0.089	0.057	0.189	0.046	0.233	0.111	0.063	0.013	0.100	
Recipient age		0.102	0.219	0.070	0.193	0.088	0.308	0.070	0.039	0.199	0.045	0.035	0.114	0.126	> 0.3
Sex mismatch			0.225	0.063	0.102	0.038	0.067	0.003	0.021	0.030	0.053	0.011	0.006	0.040	> 0.5
Donor type				0.521	0.219	0.394	0.136	0.081	0.042	0.087	0.056	0.084	0.110	0.114	
GVHD prophylaxis					0.07	0.378	0.093	0.121	0.048	0.057	0.061	0.039	0.077	0.074	
HCT-CI						0.073	0.091	0.058	0.005	0.017	0.044	0.065	0.054	0.080	
Use of ATG or alemtuzumab							0.112	0.065	0.086	0.051	0.065	0.057	0.128	0.177	
Conditioning								0.027	0.111	0.089	0.052	0.039	0.111	0.082	
Max GVHD grades before CR/VGPR									0.146	0.301	0.231	0.127	0.056	0.076	
Timing of CR/VGPR										0.091	0.284	0.005	0.055	0.104	
Max steroid dose before CR/VGPR											0.176	0.127	0.216	0.224	
GVHD treatment before CR/VGPR												0.008	0.047	0.093	
Treatment response													0.021	0.110	

*Rapid tapers were defined as the weekly steroid decrease rate $\geq 30\%$ / week if max steroid dose before CR/VGPR ≥ 1 mg/kg or $\geq 20\%$ / week if max steroid dose before CR/VGPR < 1 mg/kg

**Weekly steroid decrease rate were divided into four groups: Group 1 ($<15\%$), Group 2 ($\geq 15\%$, and $<20\%$), Group 3 ($\geq 20\%$, and $<30\%$), and Group 4 ($\geq 30\%$)

Table S3. Patient characteristics with and without flares

		Without flares n = 758 (%)	With flares n = 210 (%)
Median age at HCT, year [range]		54 [0, 79]	56 [0, 78]
Recipient Age, category	<18	83 (10.9)	23 (11.0)
	18-54	299 (39.4)	78 (37.1)
	≥55	376 (49.6)	109 (51.9)
Primary disease	Acute leukemia	420 (55.4)	104 (49.5)
	MDS/MPN	171 (22.6)	67 (31.9)
	Lymphoma	69 (9.1)	16 (7.6)
	Other	98 (12.9)	23 (11.0)
Sex Mismatch	Female to male	112 (14.8)	41 (19.5)
	Others	646 (85.2)	169 (80.5)
Donor type	HLA matched related	137 (18.1)	35 (16.7)
	HLA matched unrelated	428 (56.5)	112 (53.3)
	HLA mismatched unrelated	73 (9.6)	31 (14.8)
	Haploidentical	93 (12.3)	23 (11.0)
	Umbilical cord blood	27 (3.6)	9 (4.3)
GVHD prophylaxis	CNI based	576 (76.0)	162 (77.1)
	PTCy based	150 (19.8)	38 (18.1)
	Others	32 (4.2)	10 (4.8)
HCT-CI	0-2	518 (68.3)	134 (63.8)
	≥3	240 (31.7)	76 (36.2)
Use of ATG or alemtuzumab	No	438 (57.8)	115 (54.8)
	Yes	320 (42.2)	95 (45.2)
Donor source	Bone marrow	164 (21.6)	38 (18.1)

	Peripheral blood	567 (74.8)	163 (77.6)
	Umbilical cord blood	27 (3.6)	9 (4.3)
Conditioning	MAC (TBI <8Gy)	330 (43.5)	91 (43.3)
	MAC (TBI ≥8Gy)	129 (17.0)	27 (12.9)
	RIC	299 (39.4)	92 (43.8)
Median year of HCT [range]		2018 [2014, 2021]	2018 [2014, 2021]
Max grades before CR/VGPR	Grades I-II	623 (82.2)	165 (78.6)
	Grades III-IV	135 (17.8)	45 (21.4)
Timing of achievement of CR/VGPR	Late response (>14 days)	146 (19.3)	26 (12.4)
	Early response (≤14 days)	612 (80.7)	184 (87.6)
Max steroid dose before CR/VGPR	<1mg/kg	372 (49.1)	88 (41.9)
	≥1mg/kg	386 (50.9)	122 (58.1)
GVHD treatment before CR/VGPR	Steroid alone	682 (90.0)	182 (86.7)
	Steroid + ruxolitinib	18 (2.4)	4 (1.9)
	Steroid + other*	58 (7.7)	24 (11.4)
Treatment response	CR	536 (70.7)	146 (69.5)
	VGPR	222 (29.3)	64 (30.5)

MDS/MPN, myelodysplastic syndromes/myeloproliferative neoplasms; CNI, calcineurin inhibitor; PTCy, post-transplant cyclophosphamide; ATG, anti-thymocyte globulin; HCT-CI, hematopoietic cell transplantation-specific comorbidity index; MAC, myeloablative conditioning; TBI, total body irradiation; RIC, reduced intensity conditioning.

*Excludes ruxolitinib

Table S4. Multivariate analysis for NRM within 6 months after CR/VGPR treating flares as a time-dependent covariate

		HR(95% CI)	<i>P</i> values
Development of flares*		4.79(3.15-7.28)	<0.001
Recipient Age, category	18-54	1	Ref
	<18	0.77(0.34-1.74)	0.534
	≥55	1.39(0.65-2.99)	0.402
HCT-CI	0-2	1	Ref
	≥3	1.89(1.25-2.86)	0.003
Max grade before CR/VGPR	Grades I-II	1	Ref
	Grades III-IV	1.32(0.82-2.13)	0.248
Timing of achievement of CR/VGPR	Late response (>14 days)	1	Ref
	Early response (≤14 days)	0.63(0.38-1.04)	0.069
Max steroid dose before CR/VGPR	<1mg/kg	1	Ref
	≥1mg/kg	1.32(0.82-2.13)	0.248
GVHD treatment before CR/VGPR	Steroid alone	1	Ref
	Steroid + ruxolitinib	1.15(0.35-3.80)	0.822
	Steroid + other**	1.80(1.01-3.22)	0.047
Treatment response	CR	1	Ref
	VGPR	0.76(0.45-1.27)	0.288

* Time-dependent covariate

**Excludes ruxolitinib

Table S5. GVHD characteristics at 1st onset and at flare

		1st onset GVHD		
		Whole patients	Flare patients	Flare onset
		n = 968 (%)	n = 210 (%)	n = 210 (%)
GVHD grades	I	313 (32)	74 (35.2)	43 (21)
	II	497 (51)	98 (46.7)	80 (38)
	III	132 (14)	28 (13.3)	58 (28)
	IV	26 (3)	10 (4.8)	29 (14)
Skin stage	0	300 (31)	59 (28.1)	102 (49)
	1	173 (18)	41 (19.5)	30 (14)
	2	285 (29)	67 (31.9)	43 (21)
	3	206 (21)	41 (19.5)	33 (16)
	4	4 (1)	2 (1.0)	2 (1)
LGI stage	0	662 (68)	141 (67.1)	94 (45)
	1	162 (17)	33 (15.7)	39 (19)
	2	78 (8)	20 (9.5)	32 (15)
	3	44 (5)	8 (3.8)	21 (10)
	4	22 (2)	8 (3.8)	24 (11)
UGI stage	0	682 (71)	150 (71.4)	162 (77)
	1	286 (30)	60 (28.6)	48 (23)
Liver stage	0	942 (97)	205 (97.6)	194 (92)
	1	12 (1)	3 (1.4)	7 (3)
	2	11 (1)	2 (1.0)	7 (3)
	3	2 (1)	0 (0.0)	0 (0)
	4	1 (1)	0 (0.0)	2 (1)

Table S6. Cumulative incidence of GVHD flares within 6 months from CR/VGPR stratified by baseline characteristics

		Cumulative incidence (95% CI)	<i>P</i> values
Recipient Age, category	<18	21.1% (13.8-29.4)	0.823
	18-54	20.5% (16.5-24.8)	
	≥55	22.5% (18.9-26.4)	
Sex Mismatch	Female to male	20.6% (17.9-23.5)	0.100
	Others	26.4% (19.6-33.6)	
Donor type	HLA matched related	20.0% (14.4-26.4)	0.299
	HLA matched unrelated	20.6% (17.2-24.2)	
	HLA mismatched unrelated	29.0% (20.5-37.9)	
	Haploidentical	20.4% (13.5-28.3)	
	Umbilical cord blood	26.6% (13.0-42.3)	
GVHD prophylaxis	CNI based	21.6% (18.7-24.7)	0.826
	PTCy based	20.6% (15.1-26.7)	
	Others	24.3% (12.5-38.3)	
HCT-CI	0-2	20.5% (17.5-23.7)	0.263
	≥3	23.8% (19.2-28.7)	
Use of ATG or alemtuzumab	No	21.0% (17.7-24.6)	0.589
	Yes	22.3% (18.4-26.5)	
Conditioning	MAC (TBI <8Gy)	21.5% (17.7-25.6)	0.229
	MAC (TBI ≥8Gy)	16.9% (11.4-23.2)	
	RIC	23.6% (19.4-28.0)	
Max grade before CR/VGPR	Grades I-II	21.0% (18.2-24.0)	0.429
	Grades III-IV	24.2% (18.0-30.9)	

Timing of achievement of CR/VGPR	Late response (>14 days)	14.3% (9.5-20.1)	0.016
	Early response (\leq 14 days)	23.1% (20.2-26.1)	
Max steroid dose before CR/VGPR	<1mg/kg	19.2% (15.7-22.9)	0.082
	\geq 1mg/kg	23.8% (20.1-27.6)	
GVHD treatment before CR/VGPR	Steroid alone	21.1% (18.4-23.9)	0.344
	Steroid + ruxolitinib	15.1% (3.5-34.4)	
	Steroid + other	28.2% (18.6-38.5)	
Treatment response	CR	21.3% (18.3-24.5)	0.833
	VGPR	22.1% (17.4-27.1)	

Table S7. Effect modifications of steroid taper rates by the AA scores on the risk of flares

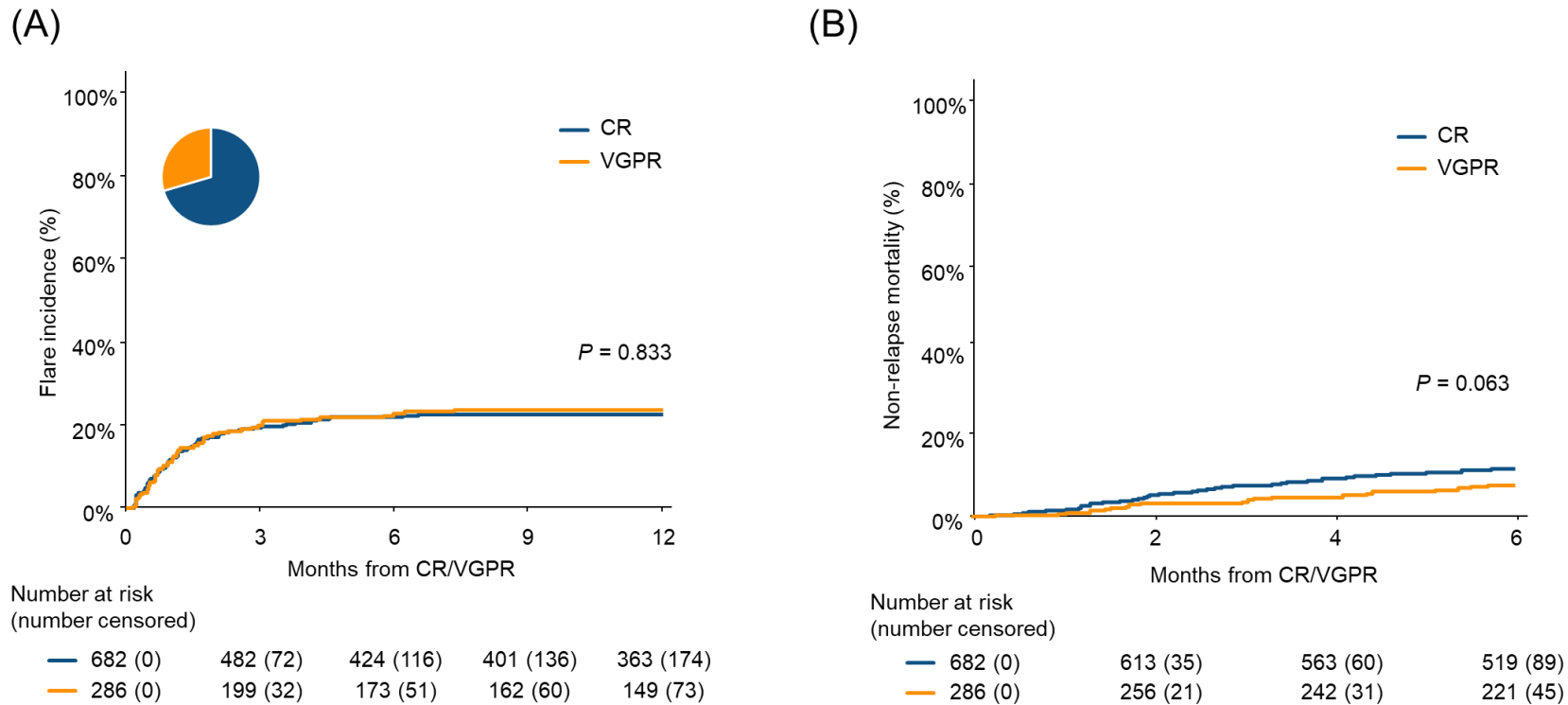
	Cumulative incidence at 6 months (95% CI)	<i>P</i> values	Adjusted HR* (95% CI)	<i>P</i> values	Additive interaction HR(95% CI)*	Additive interaction <i>P</i> values*
AA1 (n = 534)						
Slow tapers	11.9%(8.7-15.7)	0.001	1	Ref	1	Ref
Rapid tapers	22.1%(16.6-28.1)		2.25(1.43-3.55)	<0.001	2.09(0.40-3.78)	0.008
AA2/3 (n = 434)						
Slow tapers	22.3%(17.4-27.5)	<0.001	1	Ref		
Rapid tapers	39.8%(32.1-37.4)		3.24(1.99-5.28)	<0.001		

*Adjusted for maximum GVHD grade, treatment, and maximum steroid dose before CR/VGPR, time to CR/VGPR, age, sex mismatch, donor type, GVHD prophylaxis, HCT-CI, use of ATG or alemtuzumab, and conditioning regimen.

Table S8. Flare rates within 6 months stratified by three risk factors

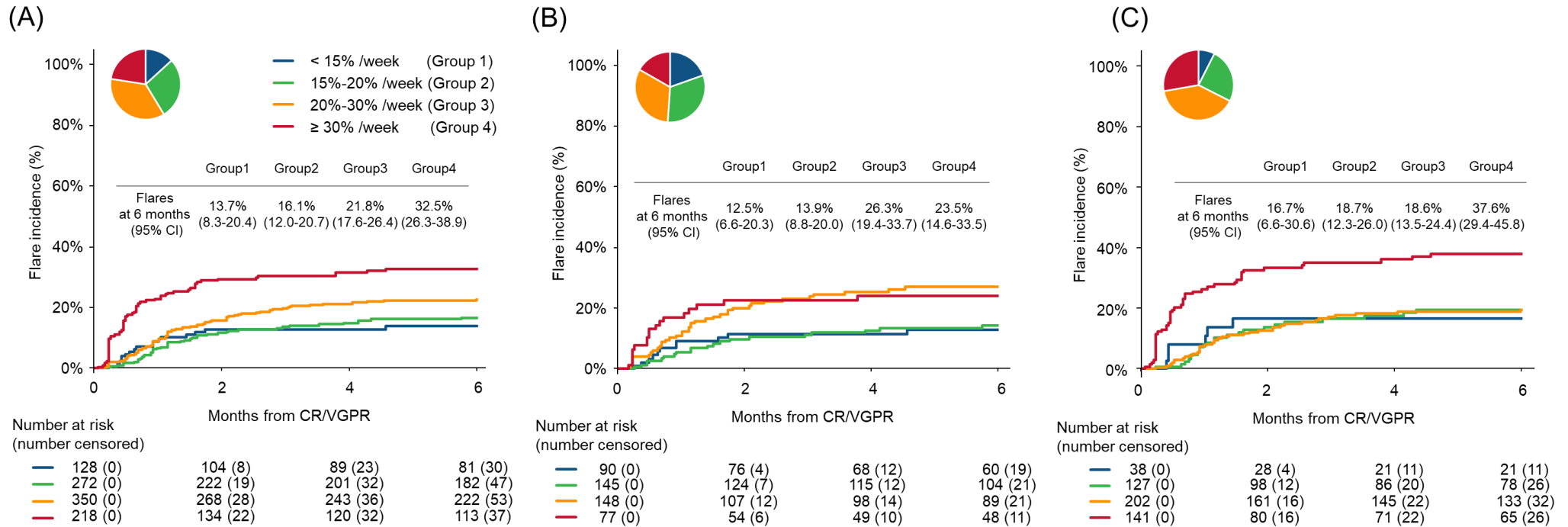
	AA1	AA2/3
Late response & Slow tapers	2%, n=51	21.1%, n=46
Late response & Rapid tapers	10.0%, n=41	30.3%, n=34
Early response & Slow tapers	13.7%, n=280	22.5%, n=224
Early response & Rapid tapers	25.2%, n=162	42.4%, n=130

Figure S1. Associations of treatment response on flares and NRM



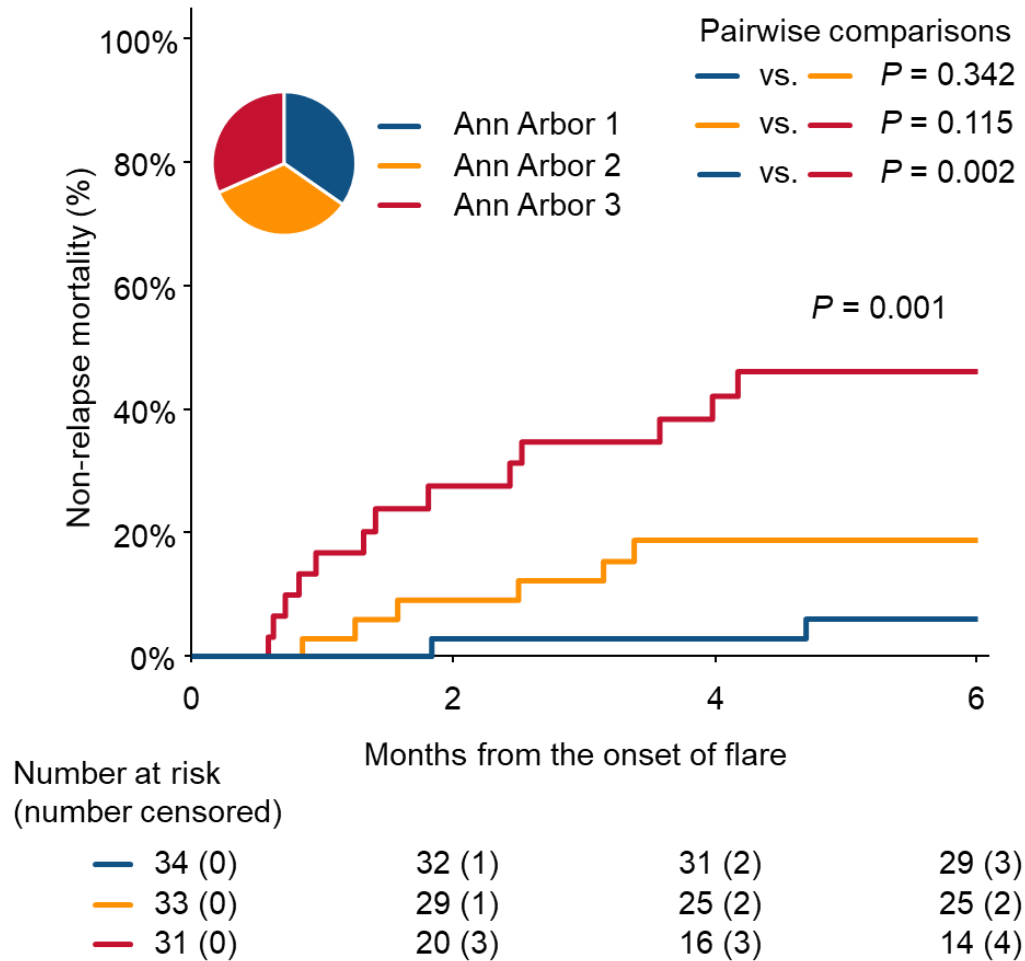
(A) The cumulative incidence of flares after CR/VGPR in patients who achieved CR or VGPR; the cumulative incidence at 6 month was 21.3% (95% CI, 18.3% to 24.5%) in patients with CR and 22.1% (95% CI, 17.4% to 27.1%) in patients with VGPR. The pie chart shows the percentage of patients with CR (blue) and VGPR (yellow). (B) The cumulative incidence of NRM after CR/VGPR in patients who achieved CR or VGPR; the cumulative incidence at 6 month was 11.0% (95% CI, 8.8% to 13.5%) in patients with CR and 7.1% (95% CI, 4.5% to 10.5%) in patients with VGPR. The pie charts represent the percentage of CR (blue) and VGPR (yellow).

Figure S2. Association of steroid taper rates on flares



(A) The cumulative incidence of flares stratified by the weekly steroid reduction rate. The weekly steroid reduction rate was divided into four groups: Group 1 (<15%), Group 2 (≥15%, and <20%), Group 3 (≥20%, and <30%), and Group 4 (≥30%). (B) The cumulative incidence of flares stratified by the weekly steroid reduction rate in patients with maximum steroid dose before CR/VGPR <1 mg/kg. (C) The cumulative incidence of flares stratified by the weekly steroid reduction rate in patients with maximum steroid dose before CR/VGPR ≥1 mg/kg. The pie charts represent the percentage of each steroid reduction group.

Figure S3. Association of biomarkers at the time of flares on NRM



The cumulative incidence of NRM stratified by the AA score at the time of flares; the cumulative incidence at 6 month was 6.0% (95% CI, 1.0% to 17.6%) in AA1, 18.5% (95% CI, 7.4% to 33.6%) in AA2, and 42.2% (95% CI, 24.4% to 59.0%) in AA3. The pie chart shows the percentage of AA1 (blue), AA2 (yellow), and AA3 (red). P values for pairwise comparisons were adjusted using a Bonferroni method.