Table S1. Patient characteristics		Overall n=3542
Median age at HCT, year [range]		58 [18, 79]
Recipient Age, category	<55	1086 (30.7)
	≥55	2456 (69.3)
Sex mismatch	Other	2958 (83.5)
	Female to Male	584 (16.5)
Primary disease	Acute leukemia	1879 (53.0)
	MDS/MPN	962 (27.2)
	Malignant lymphoma	288 (8.1)
	Other	413 (11.7)
Disease risk	Standard	2882 (81.4)
	High	660 (18.6)
Donor type	HLA matched related	1023 (28.9)
	HLA matched unrelated	1853 (52.3)
	HLA mismatched unrelated	278 (7.8)
	Haploidentical	388 (11.0)
GVHD prophylaxis	CNI and MTX based	1995 (56.3)
	CNI and MMF based	745 (21.0)
	PTCy	629 (17.8)
	Other	173 (4.9)
HCT-CI	0-2	2321 (65.5)
	≥3	1221 (34.5)
In-vivo T-cell depletion	No	2374 (67.0)
	Yes	1168 (33.0)
Donor source	Bone marrow	593 (16.7)
	Peripheral blood	2949 (83.3)
Conditioning	MAC (TBI <8Gy)	1341 (37.9)
	MAC (TBI ≥8Gy)	448 (12.6)
	RIC	1753 (49.5)
CNI discontinuation by day 100	Discontinued	601 (17.0)
	Continued	2941 (83.0)
Median year of HCT [range]		2018 [2014, 2021]

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

Table S2. GVHD characteristics at diagnosis

		Classic n=1601	Late n=256	*P* values
GVHD grades II to IV	I	725 (45.3)	85 (33.2)	<0.001
	II to IV	876 (54.7)	171 (66.8)	
GVHD grades III to IV	I to II	1391 (86.9)	188 (73.4)	<0.001
	III to IV	210 (13.1)	68 (26.6)	
Minnesota risk	Standard	1428 (89.2)	202 (78.9)	<0.001
	High	173 (10.8)	54 (21.1)	
Skin stage 2 to 4	0 to 1	977 (61.0)	160 (62.5)	0.679
	2 to 4	624 (39.0)	96 (37.5)	
Lower GI stage 2 to 4	0 to 1	1419 (88.6)	196 (76.6)	<0.001
	2 to 4	182 (11.4)	60 (23.4)	
Liver GI stage 2 to 4	0 to 1	1571 (98.1)	246 (96.1)	0.058
	2 to 4	30 (1.9)	10 (3.9)	
Upper GI stage	0	1156 (72.2)	180 (70.3)	0.549
	1	445 (27.8)	76 (29.7)	
Median days of onset [range]		30 [5, 99]	148 [100, 314]	
GVHD grades	I	725 (45.3)	85 (33.2)	<0.001
	II	666 (41.6)	103 (40.2)	
	III	174 (10.9)	58 (22.7)	
	IV	36 (2.2)	10 (3.9)	
Skin stage	0	481 (30.0)	103 (40.2)	0.002
	1	496 (31.0)	57 (22.3)	
	2	413 (25.8)	55 (21.5)	
	3	204 (12.7)	41 (16.0)	
	4	7 (0.4)	0 (0.0)	
Lower GI stage	0	1203 (75.1)	160 (62.5)	<0.001
	1	216 (13.5)	36 (14.1)	
	2	95 (5.9)	28 (10.9)	
	3	61 (3.8)	22 (8.6)	
	4	26 (1.6)	10 (3.9)	
Liver stage	0	1553 (97.0)	235 (91.8)	0.001
	1	18 (1.1)	11 (4.3)	
	2	16 (1.0)	6 (2.3)	
	3	10 (0.6)	3 (1.2)	
	4	4 (0.2)	1 (0.4)	

Table S3. GVHD characteristics stratified by sample availability at the time of systemic treatment

		Classic			Late		
		Sample available	Sample non-available		Sample available	Sample non-available	
		n=1041	n=204	*P* values	n=89	n=104	*P* values
GVHD grades II to IV	I	327 (31.4)	74 (36.3)	0.190	13 (14.6)	21 (20.2)	0.347
	II to IV	714 (68.6)	130 (63.7)		76 (85.4)	83 (79.8)	
GVHD grades III to IV	I to II	852 (81.8)	173 (84.8)	0.366	51 (57.3)	72 (69.2)	0.099
	III to IV	189 (18.2)	31 (15.2)		38 (42.7)	32 (30.8)	
Minnesota risk	Standard	883 (84.8)	175 (85.8)	0.830	55 (61.8)	80 (76.9)	0.028
	High	158 (15.2)	29 (14.2)		34 (38.2)	24 (23.1)	
Skin stage 2 to 4	0 to 1	546 (52.4)	110 (53.9)	0.759	50 (56.2)	57 (54.8)	0.885
	2 to 4	495 (47.6)	94 (46.1)		39 (43.8)	47 (45.2)	
Lower GI stage 2 to 4	0 to 1	875 (84.1)	181 (88.7)	0.109	54 (60.7)	76 (73.1)	0.090
	2 to 4	166 (15.9)	23 (11.3)		35 (39.3)	28 (26.9)	
Liver GI stage 2 to 4	0 to 1	1015 (97.5)	196 (96.1)	0.243	84 (94.4)	99 (95.2)	1
	2 to 4	26 (2.5)	8 (3.9)		5 (5.6)	5 (4.8)	
Upper GI stage	0	725 (69.6)	143 (70.1)	0.934	52 (58.4)	72 (69.2)	0.133
	1	316 (30.4)	61 (29.9)		37 (41.6)	32 (30.8)	

Table S4. GVHD characteristics stratified by sample availability after 1 week of treatment

		Classic			Late		
		Sample available	Sample non-available		Sample available	Sample non-available	
		n=687	n=558	*P* values	n=83	n=110	*P* values
GVHD grades II to IV	I	233 (33.9)	168 (30.1)	0.161	11 (13.3)	23 (20.9)	0.186
	II to IV	454 (66.1)	390 (69.9)		72 (86.7)	87 (79.1)	
GVHD grades III to IV	I to II	575 (83.7)	450 (80.6)	0.179	48 (57.8)	75 (68.2)	0.174
	III to IV	112 (16.3)	108 (19.4)		35 (42.2)	35 (31.8)	
Minnesota risk	Standard	594 (86.5)	464 (83.2)	0.111	53 (63.9)	82 (74.5)	0.116
	High	93 (13.5)	94 (16.8)		30 (36.1)	28 (25.5)	
Skin stage 2 to 4	0 to 1	341 (49.6)	315 (56.5)	0.019	50 (60.2)	57 (51.8)	0.306
	2 to 4	346 (50.4)	243 (43.5)		33 (39.8)	53 (48.2)	
Lower GI stage 2 to 4	0 to 1	590 (85.9)	466 (83.5)	0.266	51 (61.4)	79 (71.8)	0.163
	2 to 4	97 (14.1)	92 (16.5)		32 (38.6)	31 (28.2)	
Liver GI stage 2 to 4	0 to 1	677 (98.5)	534 (95.7)	0.003	79 (95.2)	104 (94.5)	1
	2 to 4	10 (1.5)	24 (4.3)		4 (4.8)	6 (5.5)	
Upper GI stage	0	492 (71.6)	376 (67.4)	0.107	46 (55.4)	78 (70.9)	0.034
	1	195 (28.4)	182 (32.6)		37 (44.6)	32 (29.1)	

Figure S1

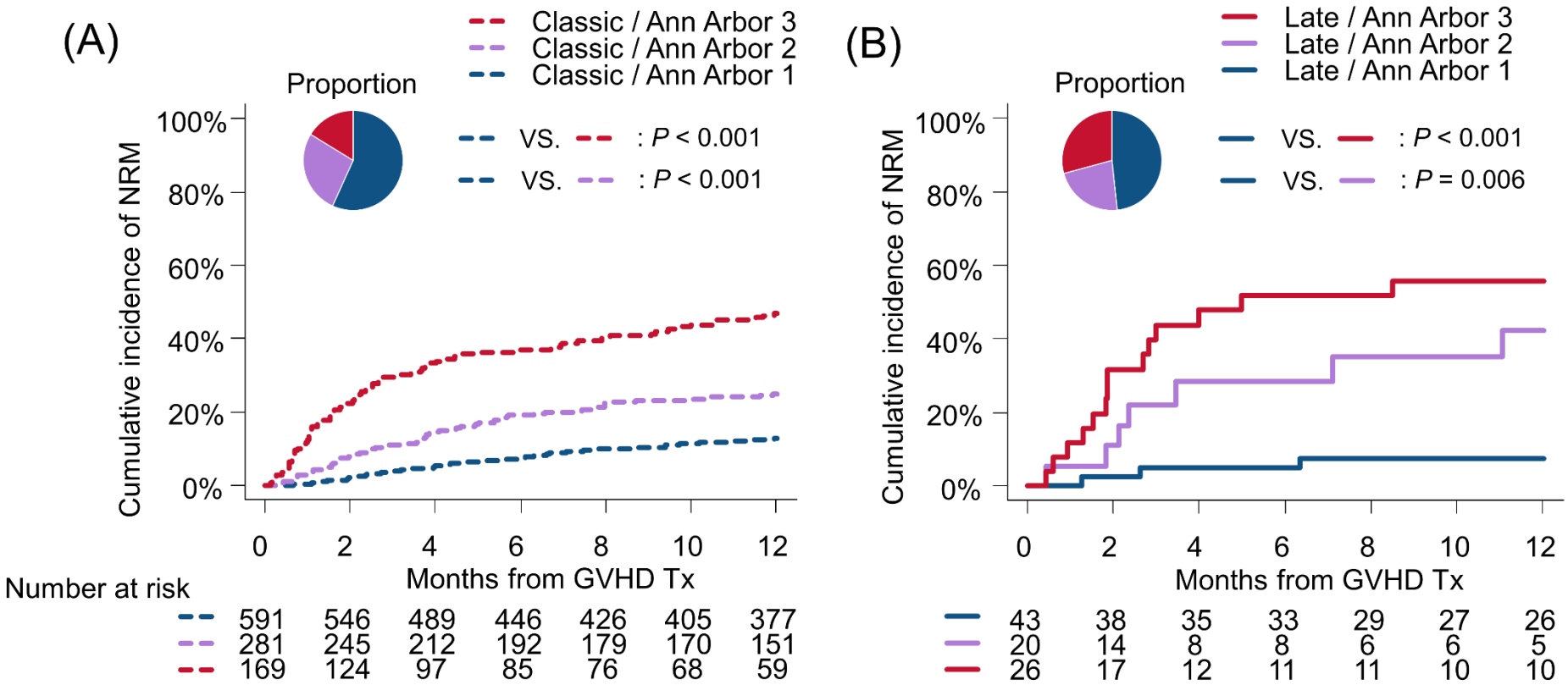

Figure S1. Association of biomarkers on NRM at treatment

(A) The proportion of patients on each risk group in classic acute GVHD at onset of treatment were AA1 56.8% (591/1041), AA2 27.0% (281/1041), and AA3 16.2% (169/1041). The cumulative incidences of NRM at 6 months were 7.4% (95% CI, 5.5-9.8) in AA1, 19.3% (95% CI, 14.9-24.2) in AA2, and 37.0% (95% CI, 29.7-44.3) in AA3 (AA1 vs. AA2, $p < 0.001$; AA1 vs. AA3, $p < 0.001$ with Bonferroni adjustment). (B) The proportion of patients on each risk group in late acute GVHD at treatment were AA1 48.3% (43/89), AA2 22.5% (20/89), and AA3 29.2% (26/89). The cumulative incidences of NRM at 6 months were 4.9% (95% CI, 0.9-14.7) in AA1, 28.3% (95% CI, 9.7-50.5) in AA2, and 51.8% (95% CI, 30.4-69.6) in AA3 (AA1 vs. AA2, $p = 0.006$; AA1 vs. AA3, $p < 0.001$ with Bonferroni adjustment).

Figure S2

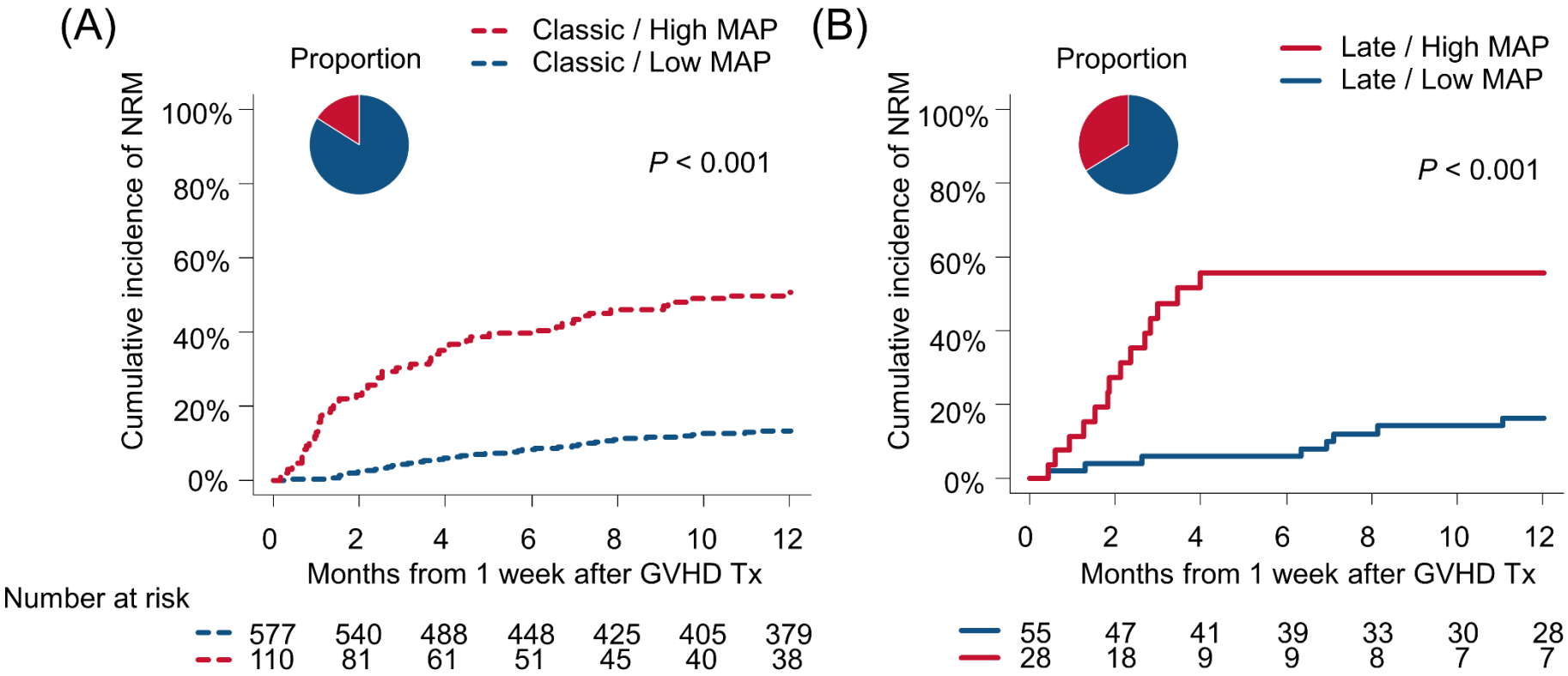

Figure S2. Association of biomarkers on NRM after one week of treatment

(A) After one week of treatment, the proportion of patients on each risk group in classic acute GVHD were Low MAP 84.0% (577/687) and High MAP 16.0% (110/687). The cumulative incidences of NRM at 6 months were 8.3% (95% CI, 6.2-10.7) and 40.4% (95% CI, 31.1-49.5) in Low and High MAP groups, respectively ($p < 0.001$). (B) The proportion of patients on each risk group in late acute GVHD were 66.3% (55/83) and 33.7% (28/83) for Low and High MAP groups, respectively. The cumulative incidences of NRM at 6 months were 5.7% (95% CI, 1.5-14.4) and 55.5% (95% CI, 33.6-72.8), respectively ($p < 0.001$).

Figure S3

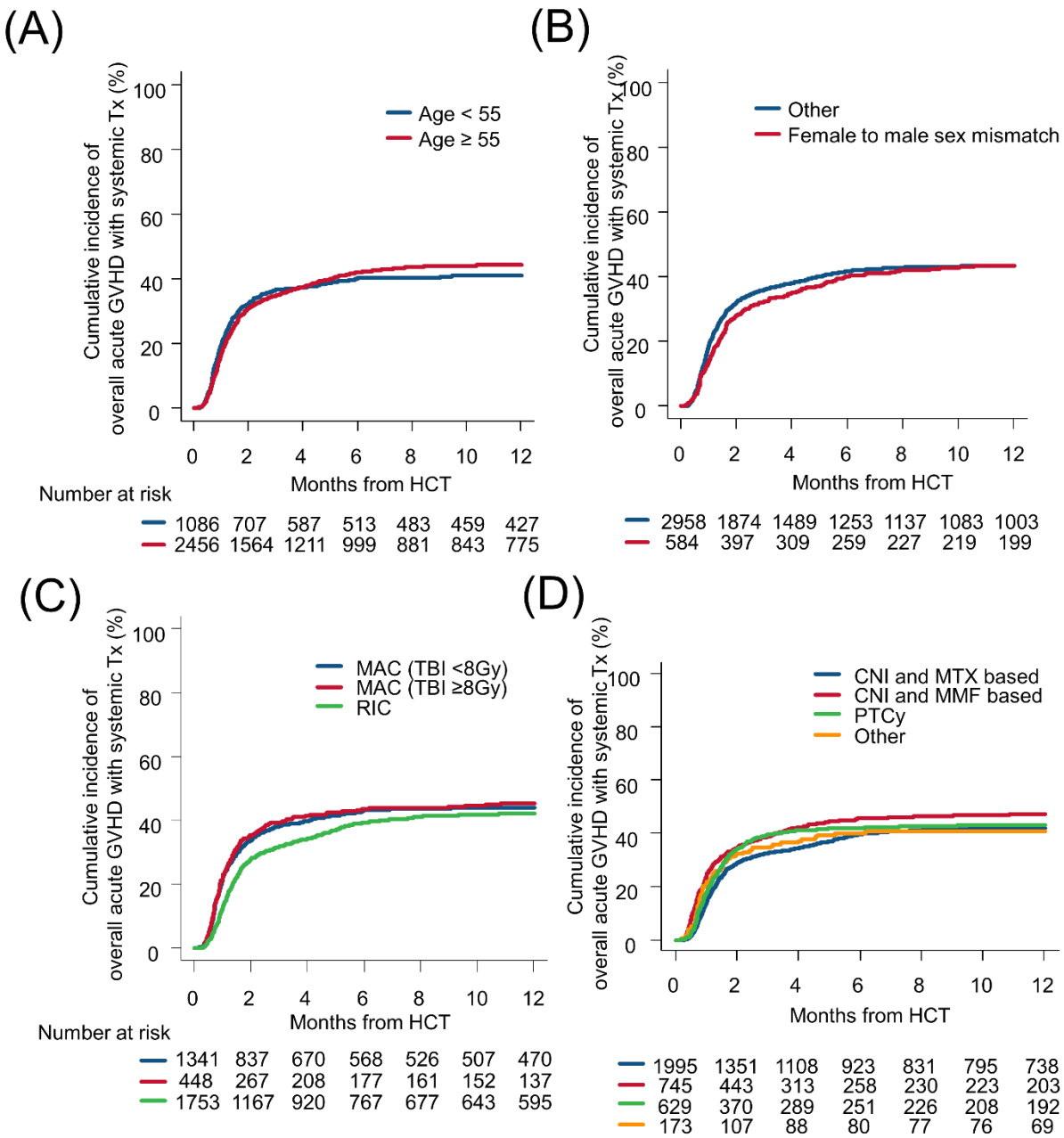
(A)
Cumulative incidence of overall acute GVHD with systemic Tx (%)
Age < 55
Age ≥ 55
Months from HCT
Number at risk
1086 707 587 513 483 459 427
2456 1564 1211 999 881 843 775
(B)
Cumulative incidence of overall acute GVHD with systemic Tx (%)
Other
Female to male sex mismatch
Months from HCT
2958 1874 1489 1253 1137 1083 1003
584 397 309 259 227 219 199
(C)
Cumulative incidence of overall acute GVHD with systemic Tx (%)
MAC (TBI <8Gy)
MAC (TBI ≥8Gy)
RIC
Months from HCT
Number at risk
1341 837 670 568 526 507 470
448 267 208 177 161 152 137
1753 1167 920 767 677 643 595
(D)
Cumulative incidence of overall acute GVHD with systemic Tx (%)
CNI and MTX based
CNI and MMF based
PTCy
Other
Months from HCT
1995 1351 1108 923 831 795 738
745 443 313 258 230 223 203
629 370 289 251 226 208 192
173 107 88 80 77 76 69

Figure S3. Timing of overall acute GVHD that required systemic treatment at 3 months and 12 months after HCT

(A) The median onset of overall acute GVHD with treatment was day 30 in younger patients (<55) and day 36 in older patients (≥ 55) ($p < 0.001$). The cumulative incidences of overall acute GVHD with treatment at 3 months were 36.5% (95% CI, 33.7-39.4) in younger patients and 34.7% (95% CI, 32.9-36.6) in older patients ($p = 0.311$); the cumulative incidences of overall acute GVHD with treatment at 12 months were 41.0% (95% CI, 38.1-43.9) in younger patients and 44.3% (95% CI, 42.3-46.3) in older patients ($p = 0.065$). (B) The median onset of overall acute GVHD with treatment was day 42 in female to male sex mismatch HCT and day 33 in other ($p < 0.001$). The cumulative incidences of overall acute GVHD with treatment at 3 months were 32.2% (95% CI, 28.5-36.1) in female to male sex mismatch HCT and 35.9% (95% CI, 34.2-37.6) in other ($p = 0.088$); the cumulative incidences of overall acute GVHD with treatment at 12 months were 43.3% (95% CI, 39.2-47.3) in female to male sex mismatch HCT and 43.3% (95% CI, 41.5-45.1) in other ($p = 0.999$). (C) The median onset of overall acute GVHD with treatment was day 30 in non-TBI based MAC regimen and day 40 in RIC regimen ($p < 0.001$). The cumulative incidences of overall acute GVHD with treatment at 3 months were 38.4% (95% CI, 35.8-41.0) in non-TBI based MAC regimen and 31.8% (95% CI, 29.7-34.0) in RIC regimen ($p < 0.001$); the cumulative incidences of overall acute GVHD with treatment at 12 months were 44.2% (95% CI, 41.5-46.8) in non-TBI based MAC regimen and 42.1% (95% CI, 39.8-44.5) in RIC regimen ($p = 0.265$). (D) The median onset of overall acute GVHD with treatment was day 38 in CNI and MTX based prophylaxis and day 34 in PTCy prophylaxis ($p < 0.001$). The cumulative incidences of overall acute GVHD with treatment at 3 months were 32.6% (95% CI, 30.6-34.7) in CNI and MTX based prophylaxis and 39.5% (95% CI, 35.7-43.3) in PTCy prophylaxis ($p = 0.002$); the cumulative incidences of overall acute GVHD with treatment at 12 months were 42.1% (95% CI, 39.9-44.3) in CNI and MTX based prophylaxis and 43.2% (95% CI, 39.3-47.1) in PTCy prophylaxis ($p = 0.620$).