

Supplemental Online Content

Sorrer ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. *JAMA*. 2011;306(17):1874-1883.

eMethods and List of Previous Publications

eTable 1. Allogeneic HCT Protocols, Clinical Trial Numbers, and Details of Treatment Plans and Diagnoses

eTable 2. Causes of Nonrelapse Mortality

eTable 3. Five-Year Overall Survival Rates Among Patients Aged 60 Years and Older Who Were Given Nonmyeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation as Stratified by Both HCT-Specific Comorbidity Index (HCT-CI) Scores and Relapse Risks

eFigure 1. (A) Kaplan-Meier estimate of progression-free survival of 32% among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and HCT. (B) No statistically significant difference ($p=0.34$, likelihood ratio statistics from Cox regression model) detected in rates of progression-free survival among patients aged 60-64 ($n=218$), 65-69 ($n=121$), and ≥ 70 years ($n=33$).

eFigure 2. Kaplan-Meier estimates of overall survival among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and HCT as stratified by (A) HCT-CI scores of 0 vs. 1-2 vs. ≥ 3 ($p=0.0002$, likelihood ratio statistics from Cox regression model), (B) relapse risk of low vs. standard vs. high ($p=0.0001$, likelihood ratio statistics from Cox regression model), (C) myeloid diagnoses of AML vs. MDS/MPD vs. CML ($p=0.40$, likelihood ratio statistics from Cox regression model), and (D) lymphoid diagnoses of lymphoma vs. CLL vs. MM ($p=0.41$, likelihood ratio statistics from Cox regression model).

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods

The hematopoietic cell transplantation-comorbidity index (HCT-CI)

The HCT-CI included 17 comorbidities:

1. Arrhythmia (score = 1)
2. Cardiac comorbidity (score = 1)
3. Inflammatory bowel disease (score = 1)
4. Diabetes Mellitus (score = 1)
5. Cerebro-vascular accident (score = 1)
6. Psychiatric disturbance (score = 1)
7. Mild hepatic comorbidity (score = 1)
8. Obesity (score = 1)
9. Infection (score = 1)
10. Rheumatologic disease (score = 2)
11. Peptic ulcer (score = 2)
12. Renal comorbidity (score = 2)
13. Moderate pulmonary comorbidity (score = 2)
14. Prior solid malignancy (score = 3)
15. Heart valve disease (score = 3)
16. Severe pulmonary comorbidity (score = 3)
17. Moderate-severe hepatic comorbidity (score = 3)

Definitions of Relapse Risk:

The designation of low, standard, or high relapse risk for each disease and disease stage was as follows:

- Low risk included:
 - low grade non-Hodgkin's lymphoma (NHL), Waldenström macroglobulinemia, and myeloproliferative diseases regardless of disease status;
 - Chronic lymphocytic leukemia (CLL), multiple myeloma, mantle cell lymphoma, and high grade NHL in complete remission (CR);
 - Acute lymphoblastic leukemia (ALL) in first CR.
- Standard risk included:
 - CLL and multiple myeloma not in CR;
 - Acute myeloid leukemia (AML) in CR;
 - Chronic myeloid leukemia (CML) in first chronic phase;
 - Myelodysplastic syndromes (MDS) in refractory anemia or refractory anemia with ringed sideroblasts.
- High risk included:
 - ALL in ≥ 2 CR;
 - Hodgkin lymphoma, secondary MDS, chronic myelomonocytic leukemia, AML evolved from MDS, and renal cell carcinoma regardless of disease status;
 - High grade NHL, AML, and ALL not in CR;
 - MDS in refractory anemia with excess blasts or refractory anemia with excess blasts in transformation;
 - CML in 2nd chronic phase or advanced phase, or blastic crisis.

LIST OF PREVIOUS PUBLICATIONS (Listed chronologically)

1. McSweeney PA, Niederwieser D, Shizuru JA, et al: Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood* 2001;97(11):3390-3400.
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15. Maris MB, Niederwieser D, Sandmaier BM, et al: HLA-matched unrelated donor hematopoietic cell transplantation after nonmyeloablative conditioning for patients with hematologic malignancies. *Blood* 2003;102(6):2021-2030.
16. Mielcarek M, Martin PJ, Leisenring W, et al: Graft-versus-host disease after nonmyeloablative versus conventional hematopoietic stem cell transplantation. *Blood* 2003;102(2):756-762.

17. Niederwieser D, Maris M, Shizuru JA, et al: Low-dose total body irradiation (TBI) and fludarabine followed by hematopoietic cell transplantation (HCT) from HLA-matched or mismatched unrelated donors and postgrafting immunosuppression with cyclosporine and mycophenolate mofetil (MMF) can induce durable complete chimerism and sustained remissions in patients with hematological diseases. *Blood* 2003;101 (4):1620-1629.
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eTable 1. Allogeneic HCT Protocols, Clinical Trial Numbers, and Details of Treatment Plans and Diagnoses									
Protocol #	Trials registered at www.clinicaltrials.gov as #	N ^e	Age (range) years	N ^t	Follow-up (range) months	Conditioning regimen	Postgrafting immunosuppression	Donor type	Disease-specific protocol
1209.00*	NCT00003145	8	62 (60-65)	2	86 (86-86)	2 Gy TBI ± fludarabine	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +56 [‡]	MRD	Yes (CML)
1225.00*	NCT00003196	35	63 (60-72)	12	117 (86-131)	2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +35 then taper to +56	MRD	No
1383.00*	NCT00003954	2	65 (64-66)	0	—	Autologous HCT + 2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +80 [§]	MRD	Yes (MM)
1406.00*	NCT00005801	4	65 (63-72)	1	120 (120-120)	2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +35 then taper to +56	MRD	No
1409.00	NCT00005803	1	62 (62-62)	1	87 (87-87)	Autologous HCT + 2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 for MRD Mycophenolate mofetil [¶] : Day 0 to +40 then taper to +96 for URD Cyclosporine: Day -3 to +56 for MRD and day -1 to 100 for URD then taper to +180	MRD URD	Yes (Lymphoma)
1463.00*	NCT00005799	15	62 (60-69)	3	114 (108-117)	Fludarabine + 2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +40 then taper to +96 Cyclosporine: Day -3 to +100 then taper to +180	URD	No
1533.00*	NCT00006251	7	64 (62-72)	0	—	Fludarabine + 2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +35 then taper to +56	MRD	No
1581.00	NCT00036738	5	63 (61-69)	2	25 (22-29)	Imatinib + Fludarabine + 2Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 for MRD Mycophenolate mofetil [¶] : Day 0 to +40 then taper to +96 for URD Cyclosporine: Day -3 to +56 for MRD and day -3 to 100 for URD then taper to +180	MRD URD	Yes (Ph+ ALL or CML-BC)
1591.00*	NCT00040846	19	63 (60-72)	5	21 (17-46)	Fludarabine + 2Gy TBI	Mycophenolate mofetil [†] : Day 0 to +100 then taper to +156 Cyclosporine: Day -3 to +180 then taper to +365	MMRD MMURD	No
1596.00*	NCT00014235	45	64 (60-74)	11	86 (49-104)	Fludarabine + 2Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +56 [‡]	MRD	No
1641.00*	NCT00027820	34	64 (60-69)	11	83 (61-98)	Fludarabine + 2Gy TBI	Mycophenolate mofetil [¶] : Day 0 to +40 then taper to +96 Cyclosporine: Day -3 to +100 then taper to +180	URD	No

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1654.00*	NCT00045435	15	64 (61-72)	6	46 (24-72)	Fludarabine + 2Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +56 then taper to +77	MRD	Yes (AML)
1668.00*	NCT00078858	23	64 (61-74)	8	64 (60-78)	Fludarabine + 2Gy TBI	Mycophenolate mofetil ^{**} : Day 0 to +150 then taper to +180 Cyclosporine: Day -3 to +80 then taper to +150	URD	No
1711.00*	NCT00060424	4	63 (62-67)	0	—	Fludarabine + 2Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +56 then taper to +180	MRD	Yes (CLL, SLL, PLL)
1732.00*	NCT00052546	9	68 (62-71)	2	82 (81-84)	Fludarabine + 2Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 for MRD Mycophenolate mofetil [¶] : Day 0 to +40 then taper to +96 for URD Cyclosporine: Day -3 to +56 for MRD then taper [†] and day -3 to 100 for URD then taper to +180	MRD URD	Yes (MDS/MPD)
1743.00*	NCT00054353	6	64 (60-67)	1	29 (29-29)	Melphalan + Fludarabine + 2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 for MRD Mycophenolate mofetil [¶] : Day 0 to +40 then taper to +96 for URD Cyclosporine: Day -3 to +80 for MRD and day -3 to 100 for URD then taper to +180	MRD URD	Yes (MM)
1813.00	NCT00075478	20	63 (60-73)	11	47 (24-64)	2 Gy TBI vs Fludarabine + 2Gy TBI ^{††}	Mycophenolate mofetil [†] : Day 0 to +27 Cyclosporine: Day -3 to +56 then taper to +180	MRD	No
1840.00	NCT00104858	5	63 (60-65)	3	25 (22-49)	Fludarabine + 2 Gy TBI	Mycophenolate mofetil [†] : Day 0 to +27 for MRD Mycophenolate mofetil [¶] : Day 0 to +40 then taper to +96 for URD Cyclosporine: Day -3 to +56 for MRD and day -3 to 100 for URD then taper to +180	MRD URD	Yes (CLL, SLL, PLL)
1898.00	NCT00089011	25	64 (60-74)	11	46 (15-61)	2 Gy TBI ± Fludarabine ^{††}	Mycophenolate mofetil [†] : Day 0 to +27 Tacrolimus: Day -3 to +56 then taper to +180	MRD	No
1938.00	NCT00105001	68	63 (60-75)	32	37 (16-63)	Fludarabine + 2 Gy TBI	Mycophenolate mofetil + Tacrolimus ± Rapa ^{ss}	URD	No

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1959.00	NCT00118352	1	61 (61-61)	0	—	Fludarabine + 2Gy TBI	Mycophenolate mofetil [†] : Day 0 to +100 then taper to +180 Cyclosporine: Day -3 to +180 then taper to +365	MMRD [‡] MMURD [‡]	No
2056.00	NCT00397813	21	66 (61-72)	7	26 (20-31)	Fludarabine + 3-4 Gy TBI ^{¶¶}	Mycophenolate mofetil [†] : Day 0 to +27 for MRD Mycophenolate mofetil [†] : Day 0 to +40 then taper to +96 for URD Cyclosporine: Day -3 to +56 for MRD and day -3 to 100 for URD then taper to +180	MRD URD	Yes (MDS/MPD)

Abbreviations: ALL indicates acute lymphocytic leukemia; AML, acute myeloid leukemia; BC, blastic crisis; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; HCT, hematopoietic cell transplantation; MDS, myelodysplastic syndromes; MM, multiple myeloma; MMRD, HLA-mismatched related donor; MMURD, HLA-mismatched unrelated donor; MPD, myeloproliferative disorders; MRD, HLA-matched related donor; Ph, Philadelphia chromosome; PLL, prolymphocytic leukemia; Rapa, rapamycin; SLL, small lymphocytic lymphoma; TBI, total body irradiation; URD, HLA-matched or single allele-mismatch unrelated donor.

* Protocols closed to accrual.

† Mycophenolate mofetil given every 12 hours.

‡ Taper till either day +77 for high-risk diseases or day +180 for low-risk diseases.

§ Taper till either day +108 for high-disease burden after autologous HCT or day +180 for low-disease burden.

¶ Mycophenolate mofetil given every 8 hours.

‖ Related or unrelated donors who are matched for HLA-DRB1 and DQB1 alleles (must be defined by high resolution typing), and who are mismatched for: (i) any single serologically detectable HLA-A or B or C antigen ± 1 allele or (ii) any combination of two HLA-A, -B, or -C alleles (if prospectively typed at molecular level).

**Mycophenolate mofetil given every 8 hours till day +30 then every 12 hours till day +150.

†† Phase III three-arm randomized study: Arm 1: mycophenolate mofetil was tapered between days 40-96, while cyclosporine was tapered between days 100-180. Arm 2: mycophenolate mofetil was tapered between days 150-180, while cyclosporine was tapered between days 100-150. Arm 3: mycophenolate mofetil was tapered between days 150-180, while cyclosporine was tapered between days 100-150. Sirolimus was given once daily until day 80 in the 3 arms.

‡‡ 2 Gy TBI only for patients with prior Auto HCT < 6 months.

§§ Phase II three-arm randomized study.

¶¶ TBI dose escalation study.

€ Total number of patients enrolled in each protocol.

£ Number of patients alive at last follow up.

eTable 2. Causes of Nonrelapse Mortality		
Cause	# of Patients (n=104)	Median survival, months
Infections	28	9
GVHD + infections	19	8.5
GVHD	15	6
MOF ± infections	14	4
GVHD + MOF/pulmonary	9	6
Second Cancer*	6	62
Acute cardiac event or congestive heart failure	3	5
Intracranial hemorrhage	2	11.5
Adult respiratory distress syndrome	2	2
Pulmonary embolism	1	3
Sinusoidal obstructive syndrome	1	0.2
Others†	4	23

Abbreviations: GVHD indicates graft-versus-host-disease; MOF, multi-organ failure.

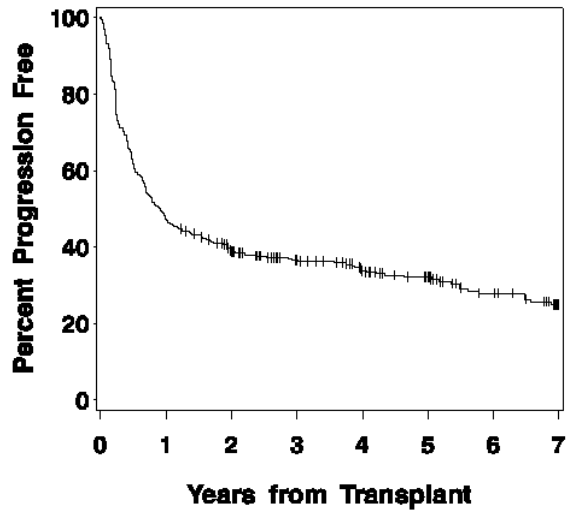
* Includes cancers of esophagus, stomach, colon, pancreas, lung, and endometrium.

† One patient died from aspiration pneumonia as a complication of a surgical procedure done to reverse an ileostomy. One patient died from severe autoimmune hemolytic anemia. One patient died from multiple vacuolated lesions, involving brainstem and vicinity of basal ganglia, of unknown etiology. One patient died of unknown cause.

eTable 3. Five-Year Overall Survival Rates Among Patients Aged 60 Years and Older Who Were Given Nonmyeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation as Stratified by Both HCT-Specific Comorbidity Index (HCT-CI) Scores⁸ and Relapse Risks.⁷

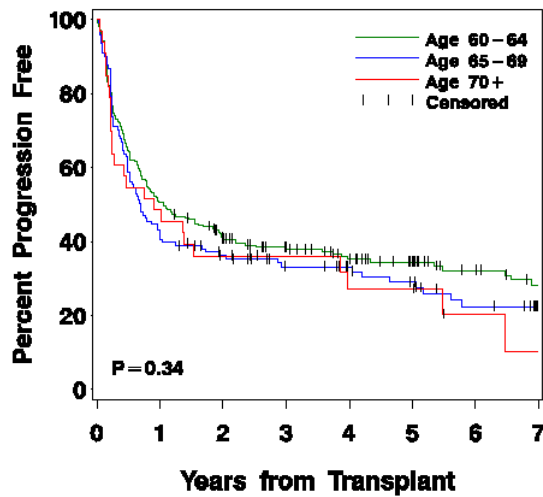
N, Overall survival at 5-years (95% CI)		HCT-CI scores		
		0	1 – 2	≥3
Relapse risks	Low	14, 69% (44%-95%)	24, 56% (33%-79%)	27, 56% (37%-74%)
	Standard	40, 45% (29%-61%)	56, 44% (31%-57%)	82, 23% (12%-34%)
	High	26, 41% (21%-62%)	35, 15% (2%-28%)	62, 23% (11%-35%)

eFigure 1. (A) Kaplan-Meier estimate of progression-free survival of 32% among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and HCT. (B) No statistically significant difference ($p=0.34$, likelihood ratio statistics from Cox regression model) detected in rates of progression-free survival among patients aged 60-64 ($n=218$), 65-69 ($n=121$), and ≥ 70 years ($n=33$).



Suppl. Fig. 1(A) Number of patients at risk for progression-free survival

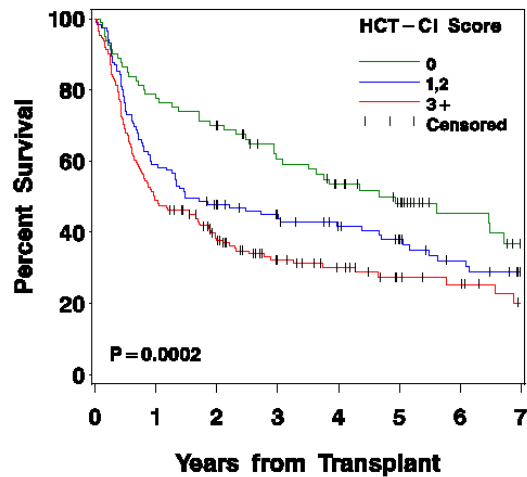
	Years							
	0	1	2	3	4	5	6	7
All patients	372	175	132	104	83	64	42	26



Suppl. Fig. 1 (B) Number of patients at risk for progression-free survival as stratified by age groups

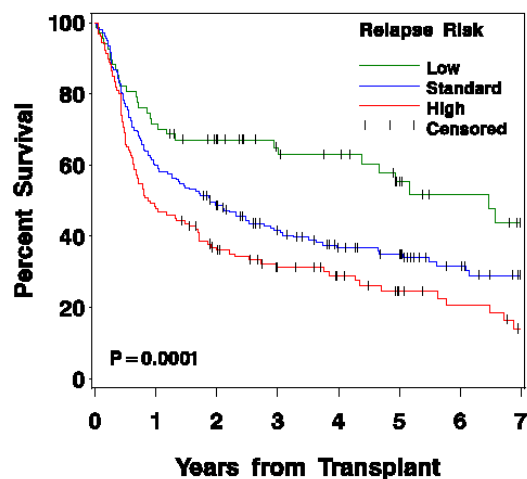
Age group, years	Years							
	0	1	2	3	4	5	6	7
60-64	218	110	82	66	52	38	27	20
65-69	121	49	39	30	25	20	13	5
≥ 70	33	16	11	8	6	6	2	1

eFigure 2. Kaplan-Meier estimates of overall survival among 372 patients aged 60 years or older, who were treated with nonmyeloablative conditioning and HCT as stratified by (A) HCT-CI scores of 0 vs. 1-2 vs. ≥ 3 ($p=0.0002$, likelihood ratio statistics from Cox regression model), (B) relapse risk of low vs. standard vs. high ($p=0.0001$, likelihood ratio statistics from Cox regression model), (C) myeloid diagnoses of AML vs. MDS/MPD vs. CML ($p=0.40$, likelihood ratio statistics from Cox regression model), and (D) lymphoid diagnoses of lymphoma vs. CLL vs. MM ($p=0.41$, likelihood ratio statistics from Cox regression model).



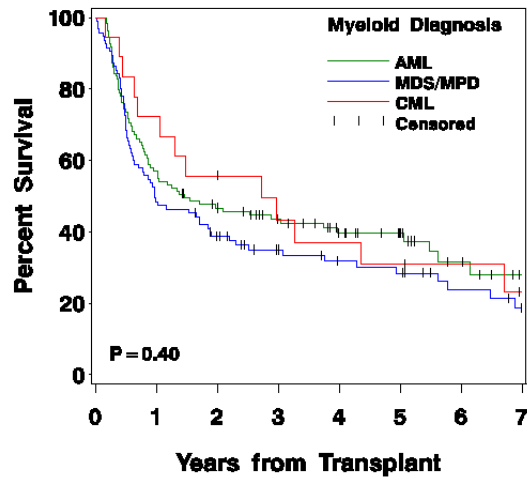
Suppl. Fig. 2 (A) Number of patients at risk for overall survival as stratified by HCT-CI scores

Age group, years	Years							
	0	1	2	3	4	5	6	7
0	80	62	55	43	34	26	16	10
1-2	115	68	53	44	36	29	20	13
≥ 3	171	84	55	34	25	16	13	7



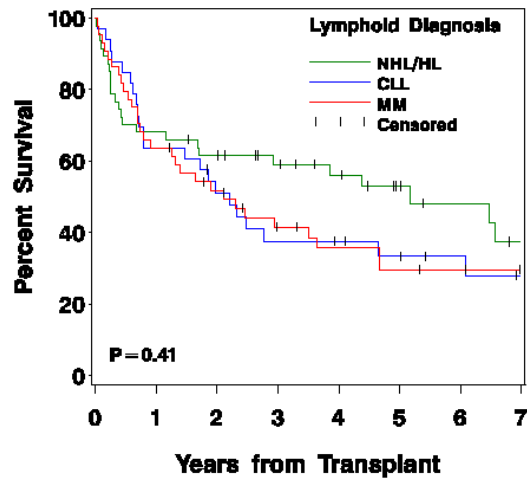
Suppl. Fig. 2 (B) Number of patients at risk for overall survival as stratified by relapse-risk groups

Age group, years	Years							
	0	1	2	3	4	5	6	7
Low	67	48	40	30	27	19	13	8
Standard	179	107	83	62	47	39	26	17
High	126	60	41	30	22	14	10	5



Suppl. Fig. 2 (C) Number of patients at risk for overall survival as stratified by myeloid diagnosis

Age group, years	Years							
	0	1	2	3	4	5	6	7
AML	109	62	48	37	27	19	10	4
MDS	95	46	33	24	19	17	10	6
CML	18	13	10	7	6	5	4	2



Suppl. Fig. 2 (D) Number of patients at risk for overall survival as stratified by lymphoid diagnosis

Age group, years	Years							
	0	1	2	3	4	5	6	7
Lymphoma	47	32	28	23	19	12	9	6
CLL	33	21	16	11	10	8	6	4
MM	44	28	21	15	12	10	9	7