Supplementary Appendix

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

Supplement to: Milano F, Gooley T, Wood B, et al. Cord-blood transplantation in patients with minimal residual disease. N Engl J Med 2016;375:944-53. DOI: 10.1056/NEJMoa1602074

Cord blood transplant in patients with minimal residual disease

SUPPLEMENTARY APPENDIX

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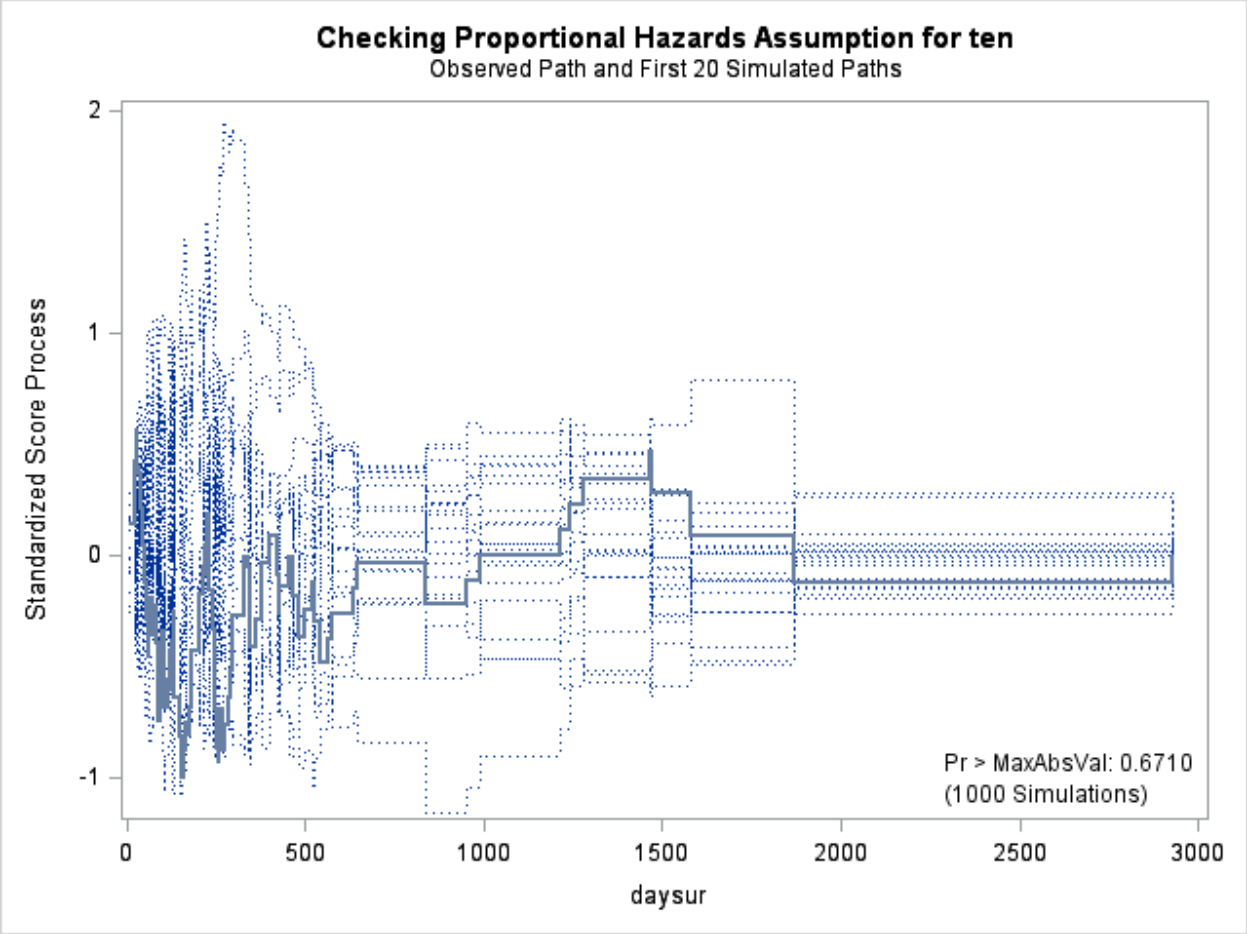
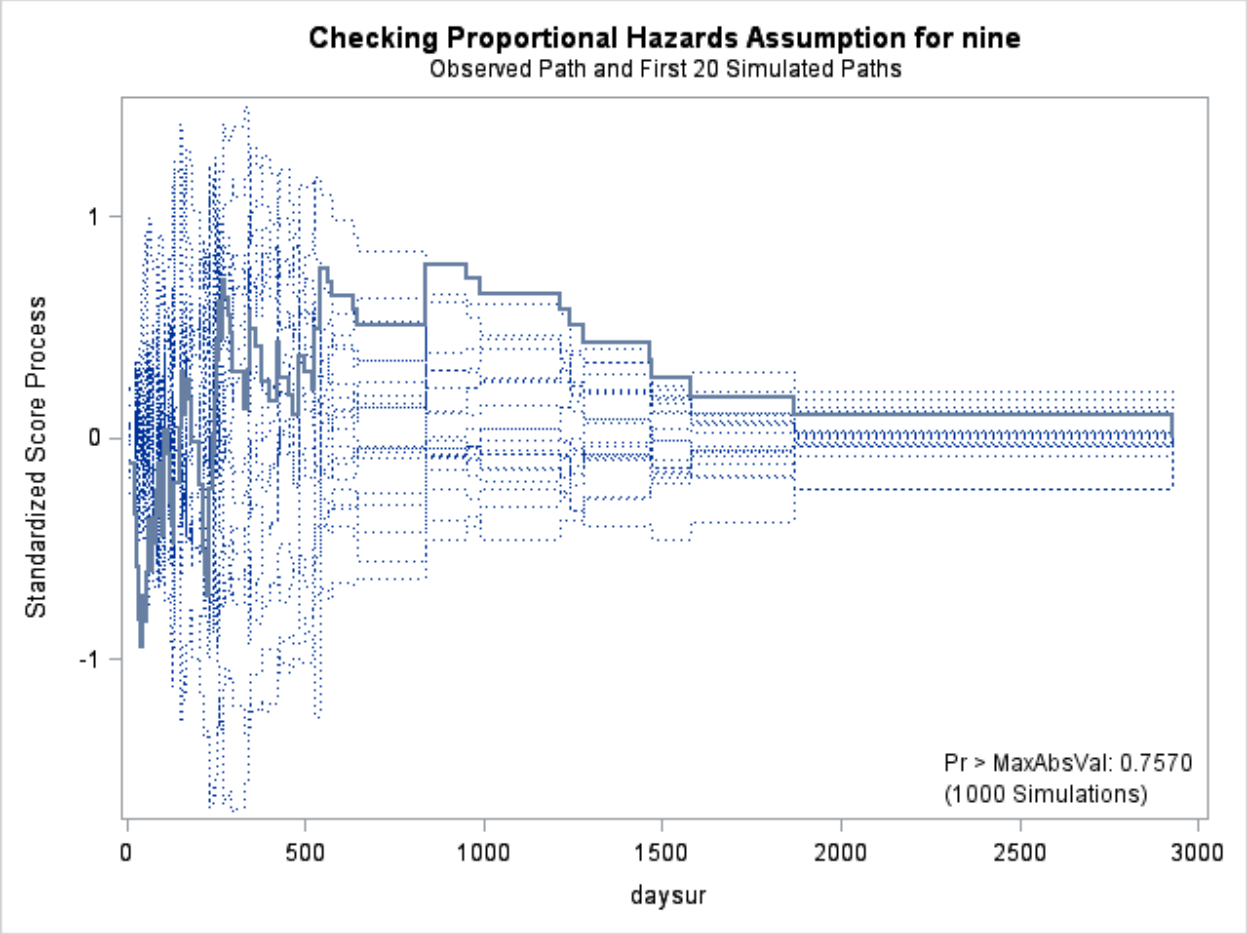
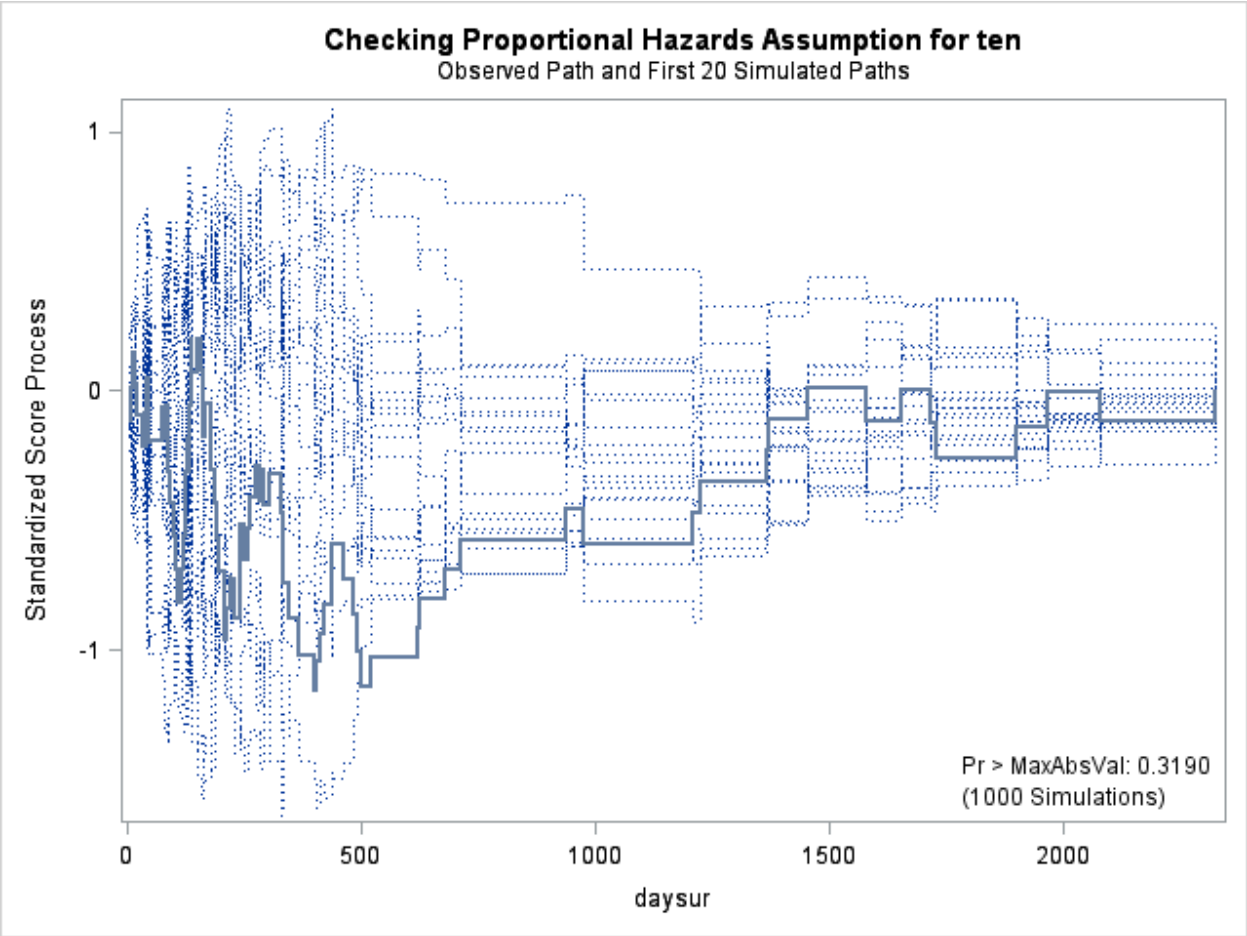
Supplementary Figure 1a. First 20 simulations of cumulative martingale residual plot as a visual check of the assumption of proportional hazards for the outcome of overall mortality comparing CBD and MURD groups among patients with minimal residual disease.



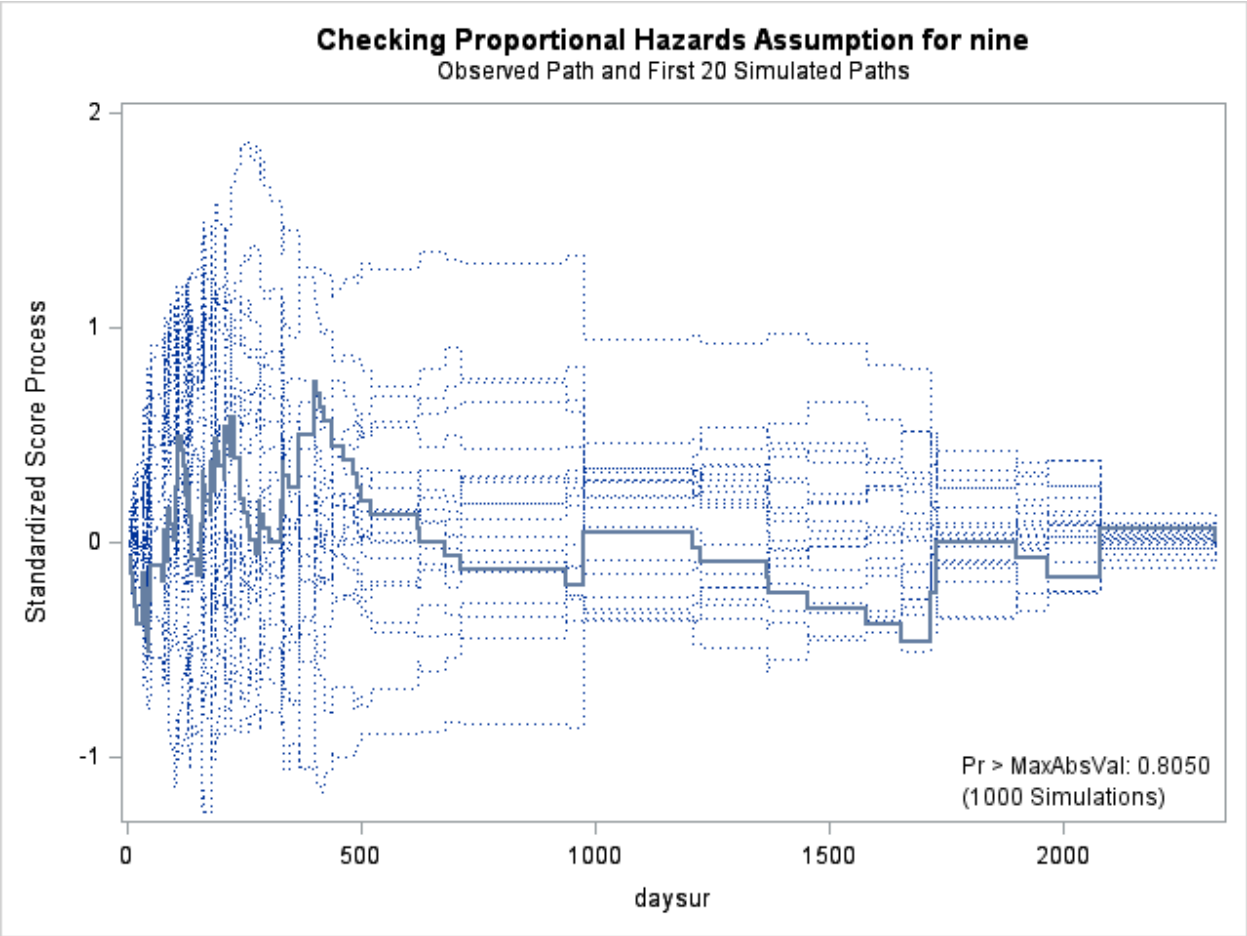
Supplementary Figure 1b. First 20 simulations of cumulative martingale residual plot as a visual check of the assumption of proportional hazards for the outcome of overall mortality comparing CBD and MMURD groups among patients with minimal residual disease.



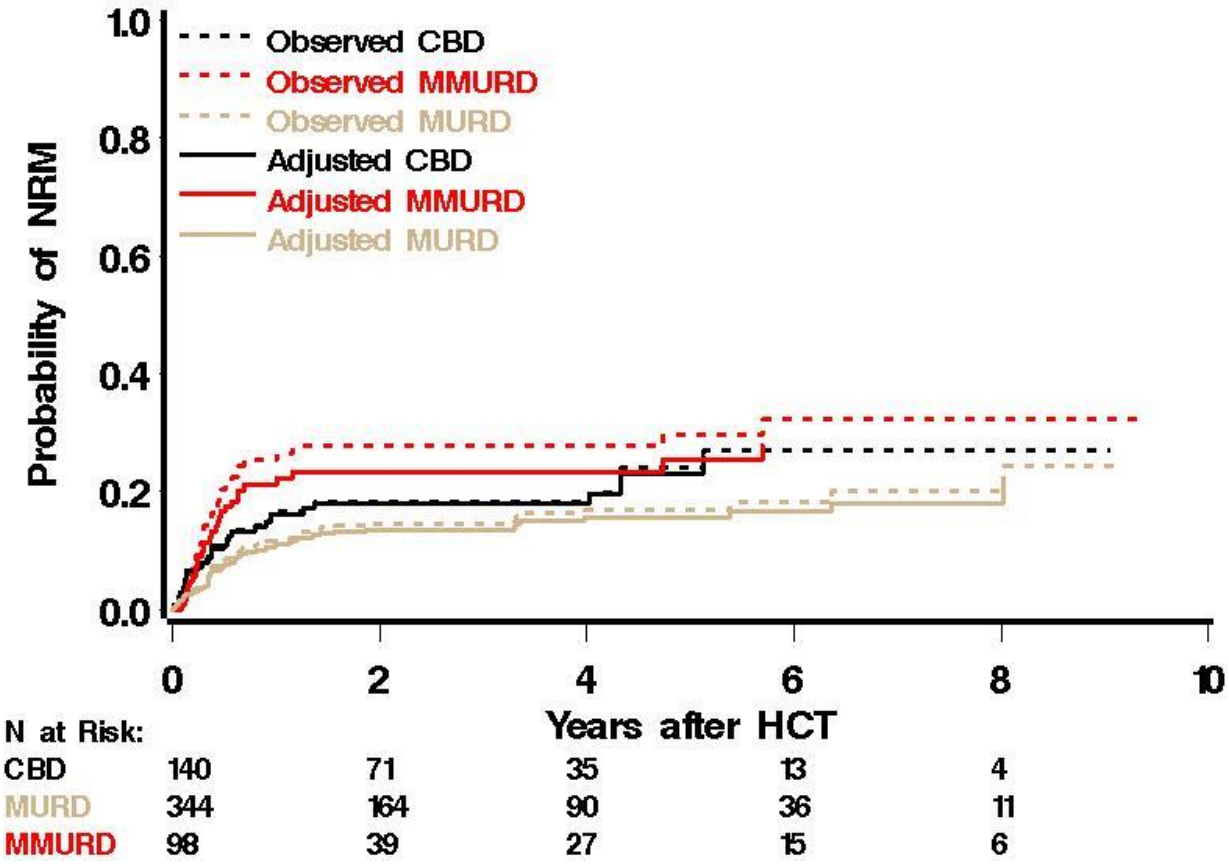
Supplementary Figure 1c. First 20 simulations of cumulative martingale residual plot as a visual check of the assumption of proportional hazards for the outcome of relapse comparing CBD and MURD groups among patients without minimal residual disease.



Supplementary Figure 1d. First 20 simulations of cumulative martingale residual plot as a visual check of the assumption of proportional hazards for the outcome of relapse comparing CBD and MMURD groups among patients without minimal residual disease.



Supplementary Figure 2. Unadjusted (dotted lines) and adjusted (solid lines) estimates of overall non-relapse mortality. Adjusted estimates are to be interpreted as the expected outcome if the URD groups were the same, on average, as the CBD group with respect to disease severity, patient age, year of HCT, and presence of minimal residual disease.



Testing assumption of proportional hazards

We used cumulative martingale residual plots as a visual check for proportional hazards, and the Kolmogorov-type supremum test (from 1,000 simulations) to generate a p-value for testing the hypothesis of proportional hazards. Shown below in Supplementary Figures 1a -1d are martingale residual plots showing the first 20 simulated results for patients with minimal residual disease (MURD vs. CBD (Figure 1a), MMURD vs. CBD (Figure 1b)) and for patients without minimal residual disease (MURD vs. CBD (Figure 1c), MMURD vs. CBD (Figure 1d)) for the outcome overall mortality. Supplementary Table 1 below summarizes the p-values for overall mortality and relapse for the respective comparisons.

Supplementary Table 1. Summary of Kolmogorov-type supremum test of proportional hazards for the main effects MURD vs. CBD and MMURD vs. CBD by minimal-residual-disease status (based on 1,000 simulations).

	Overall Mortality	Relapse
MURD vs. CBD, minimal residual disease	p=.67	p=.29
MURD vs. CBD, no minimal residual disease	p=.32	p=.74
MMURD vs. CBD, minimal residual disease	p=.76	p=.17
MMURD vs. CBD, no minimal residual disease	p=.81	p=.22

Supplementary Table 2. Unadjusted Cox regression models for various outcomes.

Outcome	Unadjusted HR (95% CI)	p-value
Mortality		
CBT	1	---
MURD	1.04 (0.73-1.47)	.85
MMURD	1.84 (1.23-2.74)	.003
Relapse		
CBT	1	---
MURD	1.60 (0.98-2.61)	.06
MMURD	1.90 (1.05-3.43)	.03
NRM		
CBT	1	---
MURD	0.78 (0.50-1.22)	.29
MMURD	1.53 (0.91-2.56)	.11
Grade III-IV aGVHD[#]		
CBT	1	---
MURD	0.75 (0.46-1.22)	.24
MMURD	1.45 (0.83-2.54)	.19
Chronic GVHD[#]		
CBT	1	---
MURD/BM	0.75 (0.51-1.11)	.15
MURD/PBSC	0.98 (0.73-1.32)	.90
MMURD/BM	0.81 (0.44-1.49)	.49
MMURD/PBSC	1.20 (0.80-1.79)	.39

[#]Diagnosis and clinical grading of acute and chronic GVHD were performed according to established criteria [15-16].

Supplementary Table 3. : Adjusted* Cox regression models for various outcomes.

Non-Relapse Mortality		
CBD	1	---
MURD	0.72 (0.44-1.19)	.20
MMURD	1.44 (0.81-2.58)	.22
Grade III-IV aGVHD[#]		
CBT	1	---
MURD	0.74 (0.44-1.25)	.26
MMURD	1.51 (0.81-2.83)	.19
Chronic GVHD[#]		
CBT	1	---
MURD/BM	0.66 (0.44-0.99)	.05
MURD/PBSC	0.97 (0.70-1.36)	.88
MMURD/BM	0.60 (0.30-1.21)	.15
MMURD/PBSC	1.07 (0.68-1.68)	.76

*adjusted for age (as a cubic polynomial), severity of disease, year of HCT (as a continuous linear variable), use of high-dose TBI, and presence of minimal residual disease (in cases where the interaction with donor group was not deemed important). [#]Diagnosis and clinical grading of acute and chronic GVHD were performed according to established criteria [15-16].