

CLINICAL TRIALS AND OBSERVATIONS

Omidubichel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study

Mitchell E. Horwitz,¹ Patrick J. Stiff,² Corey Cutler,³ Claudio Brunstein,⁴ Rabi Hanna,⁵ Richard T. Maziarz,⁶ Andrew R. Rezvani,⁷ Nicole A. Karris,⁸ Joseph McGuirk,⁹ David Valcarcel,¹⁰ Gary J. Schiller,¹¹ Caroline A. Lindemans,¹² William Y. K. Hwang,¹³ Liang Piu Koh,¹⁴ Amy Keating,¹⁵ Yasser Khaled,¹⁶ Nelson Hamerschlag,¹⁷ Olga Frankfurt,¹⁸ Tony Peled,¹⁹ Irit Segalovich,¹⁹ Beth Blackwell,²⁰ Stephen Wease,²⁰ Laurence S. Freedman,²¹ Einat Galamidi-Cohen,¹⁹ and Guillermo Sanz²²

¹Duke University Medical Center, Durham, NC; ²Loyola University Medical Center, Chicago, IL; ³Dana-Farber Cancer Institute, Boston MA; ⁴University of Minnesota, Minneapolis, MN; ⁵Taussig Cancer Institute, Department of Hematology & Medical Oncology, Cleveland Clinic, Cleveland, OH; ⁶Oregon Health and Science University, Portland, OR; ⁷Stanford University Cancer Institute, Palo Alto, CA; ⁸City of Hope, Duarte, CA; ⁹University of Kansas Medical Center, Westwood, KS; ¹⁰Department of Hematology, University Hospital Vall d'Hebron, Barcelona, Spain; ¹¹David Geffen School of Medicine at University of California Los Angeles, Los Angeles, CA; ¹²Princes Maxima Children's Hospital and the Department of Pediatrics, University Medical Center, University of Utrecht, Utrecht, The Netherlands; ¹³Singapore General Hospital, Singapore and National Cancer Centre of Singapore, Singapore; ¹⁴National University Cancer Institute, National University Health System Singapore, Singapore; ¹⁵Childrens Hospital Colorado, Aurora, CO; ¹⁶Methodist University Hospital, Memphis, TN; ¹⁷Israelita Albert Einstein Hospital, Sao Paulo, Brazil; ¹⁸Northwestern University, Chicago, IL; ¹⁹Gamida Cell, Jerusalem, Israel; ²⁰Emmes Corporation, Rockville, MD; ²¹Gertner Institute for Epidemiology and Health Policy Research, Sheba Medical Center, Tel Hashomer, Israel; and ²²Hematology Department, Hospital Universitari i Politècnic La Fe, Valencia, Spain

KEY POINTS

- Transplantation with omidubichel provides faster neutrophil and platelet recovery compared with a standard umbilical cord blood graft.
- Transplantation with omidubichel results in fewer early bacterial and viral infections and less time in hospital.

Omidubichel is an ex vivo expanded hematopoietic progenitor cell and nonexpanded myeloid and lymphoid cell product derived from a single umbilical cord blood unit. We report results of a phase 3 trial to evaluate the efficacy of omidubichel compared with standard umbilical cord blood transplantation (UCBT). Between January 2017 and January 2020, 125 patients age 13 to 65 years with hematologic malignancies were randomly assigned to omidubichel vs standard UCBT. Patients received myeloablative conditioning and prophylaxis with a calcineurin inhibitor and mycophenolate mofetil for graft-versus-host disease (GVHD). The primary end point was time to neutrophil engraftment. The treatment arms were well balanced and racially diverse. Median time to neutrophil engraftment was 12 days (95% confidence interval [CI], 10-14 days) for the omidubichel arm and 22 days (95% CI, 19-25 days) for the control arm ($P < .001$). The cumulative incidence of neutrophil engraftment was 96% for patients receiving omidubichel and 89% for patients receiving control transplants. The omidubichel arm had faster platelet recovery (55% vs 35% recovery by 42 days; $P = .028$), had a lower incidence of first grade 2 to 3 bacterial or invasive fungal infection (37% vs 57%; $P = .027$), and spent more time out of hospital during the first 100 days after transplant (median, 61 vs 48 days; $P = .005$) than controls. Differences in GVHD and survival between the 2 arms were not statistically significant. Transplantation with omidubichel results in faster hematopoietic recovery and reduces early transplant-related complications compared with standard UCBT. The results suggest that omidubichel may be considered as a new standard of care for adult patients eligible for UCBT. The trial was registered at www.clinicaltrials.gov as #NCT02730299.

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Introduction

For more than 30 years, umbilical cord blood (UCB) has been an important source of hematopoietic stem cells (HSCs) for use in allogeneic hematopoietic stem cell transplantation (allo-HSCT). It is a particularly critical stem cell source for non-White patients who are underrepresented in the international adult donor registries.¹ Compared with transplants from adult donors, adult umbilical cord blood transplantation (UCBT) has been associated with increased early treatment-related morbidity and mortality

stemming from delayed hematopoietic recovery and immunologic reconstitution. The advent of dual UCB grafts, refinement of pretransplant conditioning regimens, and improved supportive care have addressed many of the limitations of adult UCBT. However, delayed hematopoietic recovery remains a problem, resulting in increased use of resources.^{2,3} Early-phase studies have demonstrated that ex vivo expansion of UCB stem cells before transplantation has the potential to address this critical shortcoming. By expanding both hematopoietic stem and progenitor cells,

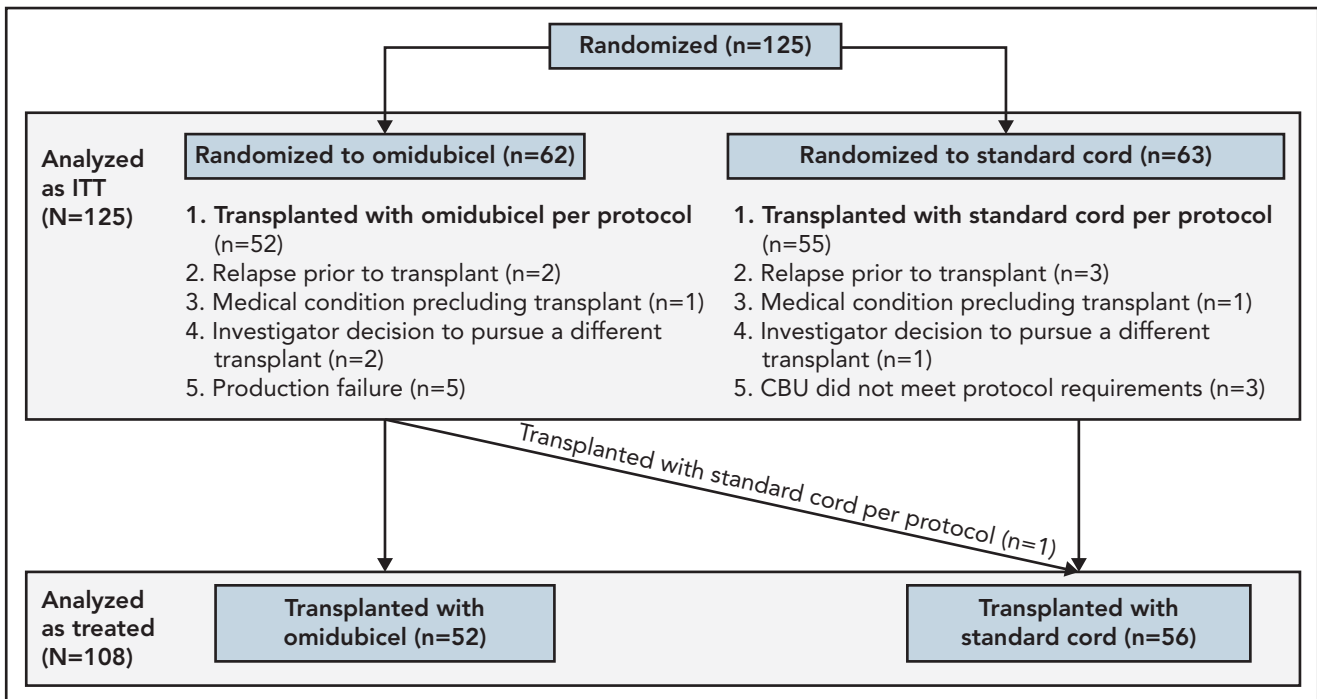


Figure 1. CONSORT diagram. Randomization and treatment of patients. CBU, cord blood unit.

the time to neutrophil recovery after myeloablative conditioning can be even more rapid than the time after a mobilized peripheral blood stem cell (PBSC) graft.⁴⁻⁷

Omidubical (Gamida Cell, Jerusalem, Israel) is a patient-specific cell product derived from a single banked UCB unit. It consists of an ex vivo expanded CD133⁺ fraction and a nonexpanded CD133⁻ fraction. Nicotinamide, the active agent in the culture system, inhibits differentiation and enhances functionality of cultured hematopoietic stem and progenitor cells. Preclinical studies demonstrated that when UCB-derived hematopoietic progenitor cells are cultured in the presence of nicotinamide and stimulatory hematopoietic cytokines, there is an outgrowth of phenotypically primitive CD34⁺CD38⁻ cells and a substantial increase in bone marrow (BM) homing and engraftment potential.⁸ The ability of nicotinamide to expand both committed and long-term repopulating HSCs was confirmed in early-phase studies of omidubical.^{6,9} In this study, we compared the outcomes of a myeloablative allo-HSCT using omidubical with standard UCB grafts.

Methods

Trial design and oversight

The trial was designed by the sponsor (Gamida Cell) in collaboration with a protocol steering committee. Enrollment began in January 2017 and was completed in January 2020. Random assignments were performed at the Emmes Company in a 1:1 ratio using minimization factors of age, center, disease risk index, and intention to use 1- or 2-unit UCB grafts if patients were randomly assigned to the control arm. As sites enrolled participants, they were randomly assigned using the centralized data entry system at Emmes Company. The primary end point was time to neutrophil engraftment. Secondary end points were platelet engraftment by 42 days, incidence of grade 2 to 3 bacterial or

invasive fungal infection during the first 100 days, and days alive and out of the hospital for the first 100 days after transplantation. Additional planned end points included assessment of safety, nonrelapse mortality (NRM), relapse, overall survival (OS) and disease-free survival (DFS), acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD), engraftment, and infectious complications. The trial was approved by the Institutional Review Boards of all participating institutions and the national regulatory authorities. All patients provided written informed consent. The study was performed in accordance with the International Conference on Harmonization, in agreement with local regulations and with the principals of Declaration of Helsinki.

Patients

Eligible patients were age 12 to 65 years with high-risk hematologic malignancies, were candidates for myeloablative allo-HSCT, and had no readily available matched sibling or matched unrelated adult donor. Patients with marked or 3+ BM fibrosis or chronic lymphocytic leukemia were excluded. Patients were required to have an available UCB unit HLA-matched at 4 or more loci (HLA-A, B at the antigen-level, and DRB1 at the allele level) with a total nucleated cell (TNC) count $\geq 1.8 \times 10^9$, a TNC dose of $\geq 1.5 \times 10^7$ cells per kg, and CD34⁺ cell count of $\geq 8 \times 10^6$. This unit was designated for use before random assignments were made and was required to be used in both arms of the study. For patients randomly assigned to the control arm, a double cord blood graft was mandated when the omidubical-designated unit (designated before random assignment and required to be used) was HLA-matched at 5 to 6/6 and contained $< 2.5 \times 10^7$ TNCs per kg or $< 1.2 \times 10^5$ CD34⁺ cells per kg, or were HLA 4/6 matched and contained $< 3.5 \times 10^7$ TNCs per kg or $< 1.7 \times 10^5$ CD34⁺ cells per kg. Patients were also required to have available backup cord blood unit(s). The presence of donor-specific antibodies to HLA-A, -B, -C, or DRB1 antigens (mean fluorescence

Table 1. Patient characteristics

Characteristic	Treatment group	
	Omidubicel	Standard UCB
Total no. of patients randomly assigned	62 (100)	63 (100)
Sex		
Female	30 (48)	23 (36)
Male	32 (52)	40 (64)
Age, y		
Median (range)	40 (13-62)	43 (13-65)
12-17	8 (13)	6 (10)
18-39	23 (37)	23 (36)
40-59	27 (44)	31 (49)
60-65	4 (6)	3 (5)
Median weight, kg (range)	78.6 (43-134)	77.4 (46-133)
Race		
White	35 (57)	37 (59)
Black	11 (18)	9 (14)
Asian	7 (11)	10 (16)
Hispanic or Latino	10 (16)	6 (10)
Other/unknown	9 (14)	7 (11)
Primary diagnosis		
Acute myeloid leukemia	27 (43)	33 (52)
CR1 (morphologic)	18	22
CR2	9	11
Acute lymphoblastic leukemia	20 (32)	21 (34)
High-risk CR1 (morphologic)	13	11
CR2 (morphologic)	6	10
CR3+ (morphologic)	1	0
Myelodysplastic syndrome	6 (10)	3 (5)
High	2	0
Intermediate-1	3	1
Intermediate-2	1	2
Chronic myeloid leukemia	4 (7)	2 (3)
Lymphoma	3 (5)	2 (3)
Hodgkin lymphoma, stable disease	0	1

Table 1. (continued)

Characteristic	Treatment group	
	Omidubicel	Standard UCB
T-cell non-Hodgkin lymphoma	3	1
Other rare disease	2 (3)	2 (3)
Adult T-cell leukemia/lymphoma CR1	1	0
Biphenotypic leukemia	0	1
Dendritic cell leukemia	1	1
Disease risk group		
Low	15 (24)	15 (23)
Moderate	27 (44)	25 (40)
High/very high	20 (32)	23 (37)
HSCT-specific comorbidity index		
0	12 (19)	13 (20)
1-2	19 (31)	18 (29)
3+	31 (50)	32 (51)
Intended UCB transplant		
Single	20 (32)	21 (33)
Double	42 (68)	42 (67)
Antigen-level HLA match score (intended treatment CBU #1)		
4/6	46 (74)	46 (73)
5/6	15 (24)	16 (25)
6/6	1 (2)	1 (2)
Antigen-level HLA match score (intended treatment CBU #2)		
4/6		31 (49)
5/6		10 (16)
6/6		1 (2)
Conditioning regimens		
TBI 1350 cGy, fludarabine 160 mg/m ² , thiotepa 10 mg/kg	7 (11)	9 (15)
TBI 1320 cGy, fludarabine 75 mg/m ² , cyclophosphamide 120 mg/kg	24 (39)	21 (33)

All data are n (%), unless otherwise stated.
CR1, first complete response; TBI, total body irradiation.

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Table 1. (continued)

Characteristic	Treatment group	
	Omidubicel	Standard UCB
Thiotepa 10 mg/kg, busulfan 12.8 mg/kg, fludarabine 150 mg/m ²	27 (44)	28 (44)
Did not receive a transplant or off-protocol regimen	4 (6)	5 (8)

All data are n (%), unless otherwise stated.

CR1, first complete response; TBI, total body irradiation.

intensity >3000) was not permitted. A detailed list of inclusion and exclusion criteria are provided in the protocol document (supplemental Material, available at the *Blood* Web site). Planned enrollment was 120 patients. In all, 125 patients were randomly assigned at 33 sites in North and South America, Europe, and Singapore. Participating centers and principal investigators are listed in supplemental Table 1. The population of 125 randomly assigned patients was analyzed as the intent-to-treat population (ITT), using the randomized treatment assignment. Of the 125 randomly assigned patients, 117 received an omidubicel or UCB transplant by day 90 after random assignment. This was the population that received transplants, which was also analyzed by treatment assignment. The as-treated population included 108 patients analyzed according to treatment received (Figure 1).

Graft production

The omidubicel-designated unit was transported from the cord blood bank to a Current Good Manufacturing Practice-compliant cell-processing facility (Lonza, Walkersville, MD, or Gamida Cell, Jerusalem, Israel). Omidubicel was manufactured as previously described.⁶ Briefly, the unit underwent immunomagnetic bead selection for CD133⁺ cells. The CD133⁺, T-cell-containing flow-through fraction was retained and recryopreserved. The CD133⁺ fraction was cultured in the presence of Flt-3 ligand, stem cell factor, thrombopoietin, interleukin-6, and nicotinamide for 21 ± 2 days and then cryopreserved. Both fractions were transported together to the transplantation center.

Treatment

Three alternative myeloablative conditioning regimens were permitted for study participants: 2 contained total body irradiation and 1 contained chemotherapy only (Table 1). GVHD prophylaxis was provided by a calcineurin inhibitor (tacrolimus with target trough levels of 5-15 ng/mL or cyclosporine with target trough levels of 200-400 ng/mL) and mycophenolate mofetil 15 mg/kg 3 times per day (maximum daily dose, 3 g) starting 3 days before transplantation. Mycophenolate mofetil was continued for a minimum of 60 days and the calcineurin inhibitor for minimum of 100 days after transplantation in the absence of toxicity or relapse.

Supportive care

Granulocyte-colony stimulating factor (5 µg/kg of recipient body weight) was given once per day starting on day +1 after transplantation until the absolute neutrophil count exceeded 1000 cells per

µL. Antiviral and antifungal prophylaxis were administered at the discretion of the transplantation center. Antibacterial prophylaxis after transplantation was required by protocol. The agent used was at the discretion of the transplant center.

Laboratory and clinical assessments

Donor chimerism was performed by the local transplant center on whole blood, CD15⁺ myeloid, and CD3⁺ T cells using quantitative analysis of informative microsatellite DNA sequences. Quantitative assessment of CD3, CD4, CD8, natural killer (NK) and B-cell recovery was performed on a subset of patients by the transplant center (or designated referral laboratory) at 1, 2, 3, 6, and 12 months after transplantation. The time to engraftment of neutrophils ≥500 cells per µL and platelets >20 000/µL was defined according to Center for International Blood and Marrow Transplant Research (CIBMTR) standards, requiring donor chimerism for neutrophil engraftment. Grading of bacterial and invasive fungal infections was adapted from definitions in the Blood and Marrow Transplant Clinical Trials Network technical manual of procedures (supplemental Table 2).

Statistical considerations

The main comparisons of the primary and secondary end points as well as mortality end points were conducted using ITT analysis. Cox proportional hazards models were used in the analysis of DFS and OS, with randomly assigned treatment and disease risk as covariates in the model. The incidence of engraftment and engraftment kinetics were also calculated in the as-treated population. GVHD was assessed in the population that received a transplant and was defined as all patients randomly assigned to receive a UCBT, grouped by the treatment to which they were allocated. GVHD-free relapse-free survival (RFS) was evaluated in the as-treated population, grouped by treatment received. The primary end point (time to neutrophil engraftment) was compared between treatment groups using a Mann-Whitney-based statistic. A value of 43 days was assigned for patients who had received a transplant who did not engraft by 42 days after transplantation or patients who did not receive a transplant. *P* values for this and other protocol-specified ITT analyses were calculated using the rerandomization distribution.¹⁰ Sample size was chosen to provide at least 90% power for the primary end point analysis, based on information on engraftment times derived from the phase 2 study and the CIBMTR database.

Secondary end points of proportion of patients with grade 2 to 3 bacterial or invasive fungal infections up to 100 days posttransplant and proportion with platelet engraftment by 42 days were compared using cumulative incidence rates. Time out of hospital in the first 100 days was compared using the Mann-Whitney statistic. Differences in cumulative incidence were also analyzed for NRM and for relapse. For non-ITT analyses, neutrophil engraftment was compared using the Wilcoxon rank sum test or Fisher's exact test, and time to platelet engraftment was compared using Gray's test. GVHD for patients who received transplants was compared using a z test on the cumulative incidence difference. Infection densities were compared using the generalized estimating equation (GEE) approach for a linear model with 2 periods (0-30 and 31-365 days posttransplant) and a negative binomial link. The associations of CD34⁺ total cells and CD34⁺ dose with time to engraftment were evaluated using linear regression and correlation analyses of the log-transformed values. Immune

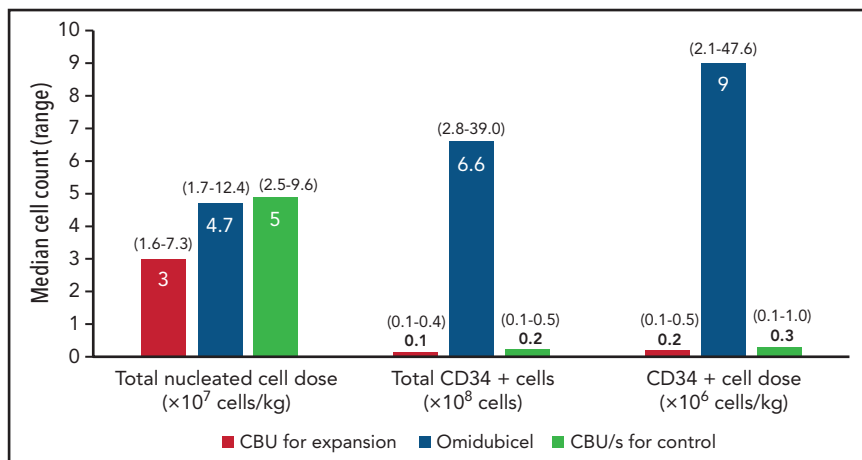


Figure 2. Omidubicel and control cord blood graft characteristics. Median (range) for TNC content, CD34⁺ cell content, and CD34⁺ cell doses before and after ex vivo expansion of the UCB unit. Pre-expansion values represent cell content as reported by the cord blood bank before cryopreservation of the UCB unit. AT, as treated population.

reconstitution analyses were evaluated using Wilcoxon rank sum tests. *P* values for the multivariable models and non-ITT analyses were calculated using asymptotic methods. Confidence intervals (CIs) were calculated using bootstrap methods; the multivariable models and GEE models used asymptotic CIs. The multivariable Cox models, the GEE models, CD34⁺ associations with neutrophil engraftment, Gray's test for platelet engraftment, GVHD-free RFS, and moderate-to-severe cGVHD analyses were post hoc analyses. The end points were evaluated after all evaluable patients completed 6 months of follow-up after transplantation; study follow-up is ongoing.

Results

Patient and stem cell transplant characteristics

Demographics and baseline characteristics were well-balanced across the 2 arms (Table 1). In all, 125 patients (median age, 41 years; range, 13-65 years) were randomly assigned to receive omidubicel (*n* = 62) or standard single (33%) or double (67%) UCB grafts (*n* = 63). Ten patients randomly assigned to the omidubicel arm did not receive omidubicel per protocol. Eight patients randomly assigned to the standard UCB arm did not receive a transplant per protocol (Figure 1). Most patients had acute myeloid leukemia (48%) or acute lymphoblastic leukemia (33%). The disease risk index was moderate in 42% and high in 34% of patients. The study population was diverse with 16% Black, 14% Asian, 3% multiracial, and 13% Hispanic or Latino patients. Patients treated with omidubicel received a transplant at a median of 41 days after

random assignment compared with 26 days for patients treated with standard UCBT.

Graft characteristics

Characteristics of the standard single and double cord blood grafts and the omidubicel grafts are shown in Figure 2. The median total CD34⁺ cell content of the control cord blood unit(s) and the omidubicel unit before expansion (as reported by the cord blood bank before cryopreservation) was 0.23×10^8 cells (range, 0.11×10^8 to 0.55×10^8 cells) and 0.14×10^8 cells (range, 0.09×10^8 to 0.4×10^8 cells), respectively. After expansion, the content of the omidubicel unit increased to a median 6.6×10^8 CD34⁺ cells (range, 2.8×10^8 to 39×10^8 cells). Median CD34⁺ cell expansion was 130-fold (range, 32- to 233-fold). The median CD34⁺ cell dose of omidubicel and control grafts was 9.0×10^6 cells per kg (range, 2.1×10^6 to 47.6×10^6 cells per kg) and 0.3×10^6 cells per kg (range, 0.1×10^6 to 1×10^6 cells per kg), respectively. The CD3⁺ T cells in the omidubicel graft were contained solely in the unexpanded CD133⁻ fraction.

The median CD3⁺ content of the omidubicel grafts before cryopreservation was 210×10^6 CD3⁺ cells (range, 71×10^6 to 640×10^6 cells), and 3×10^6 CD3⁺ cells per kg (range, 1.1×10^6 to 12.4×10^6 CD3⁺ cells per kg). This compared with a median 412.9×10^6 CD3⁺ cells (range, 4.4×10^6 to 989.8×10^6 CD3⁺ cells), and 4.6×10^6 CD3⁺ cells per kg (range, 0×10^6 to 14.8×10^6 CD3⁺ cells per kg) for the control grafts. CD3 content was enumerated after thawing and before infusion from a subset

Table 2. Time to neutrophil engraftment

Randomly assigned treatment group	No.	Cumulative incidence		Mann-Whitney <i>P</i>
		Median time to neutrophil engraftment (d)*	95% CI	
Omidubicel	62	12.0	10.0-14.0	<.001
Control	63	22.0	19.0-25.0	

*Patients who did not receive a transplant or who did not engraft on or before day 42 after transplantation were assigned to day 43.

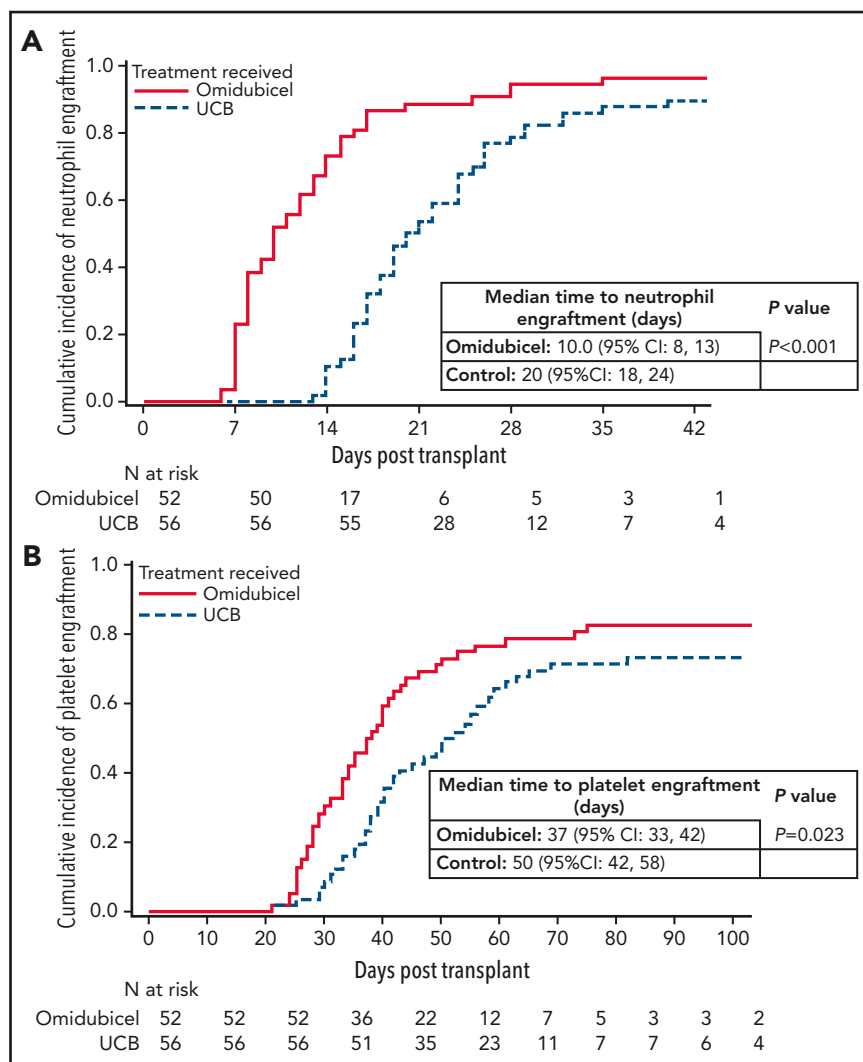


Figure 3. Hematopoietic recovery. Analysis was performed in the as-treated population ($n = 108$). Cumulative incidence of neutrophil engraftment by day 42 (A) and platelet recovery by day 100 (B) among recipients of omidubichel or unmanipulated UCB.

of 25 control patients. Thus, the observed difference in CD3 content is underestimated because of additional cell loss after thawing the omidubichel product.

Hematopoietic recovery

The median time to neutrophil recovery per ITT analysis was 12 days (95% CI, 10-14 days) for those randomly assigned to omidubichel and 22 days (95% CI, 19-25 days) for controls ($P < .001$) (Table 2). The cumulative incidence of neutrophil engraftment by day 42 after transplantation for patients receiving omidubichel (as-treated population, $n = 52$) was 96% at a median of 10 days (95% CI, 8-13 days) compared with 89% at a median of 20 days (95% CI, 18-24 days) for the controls ($n = 56$) ($P < .001$) (Figure 3A). For patients who received a transplant with omidubichel, higher total CD34⁺ cell counts and CD34⁺ cell doses (per weight) were associated with shorter times to neutrophil engraftment (Figure 4, correlations: total cells, $r = -0.66$; $P < .001$; cell dose, $r = -0.62$; $P < .001$).

The cumulative incidence of platelet engraftment by day 42 after transplantation for patients randomly assigned to omidubichel was 55% vs 35% for controls ($P = .028$) (Table 3). For the patients transplanted with omidubichel, the cumulative incidence of platelet engraftment by day 100 after transplantation was 83% at a median of 37 days (95% CI, 33-42 days) vs 73% at a median of 50 days (95% CI, 42-58 days) for the controls ($P = .023$) (Figure 3B).

Full donor chimerism (defined as >90% in the whole blood fraction) was observed at day +30 and day +100 after transplantation in all but 2 omidubichel recipients; one experienced early relapse and the other experienced primary graft failure. Six standard UCBT recipients experienced graft failure on day +42. The remaining evaluable standard UCBT recipients had full donor chimerism at day +30 and day +100 after transplantation.

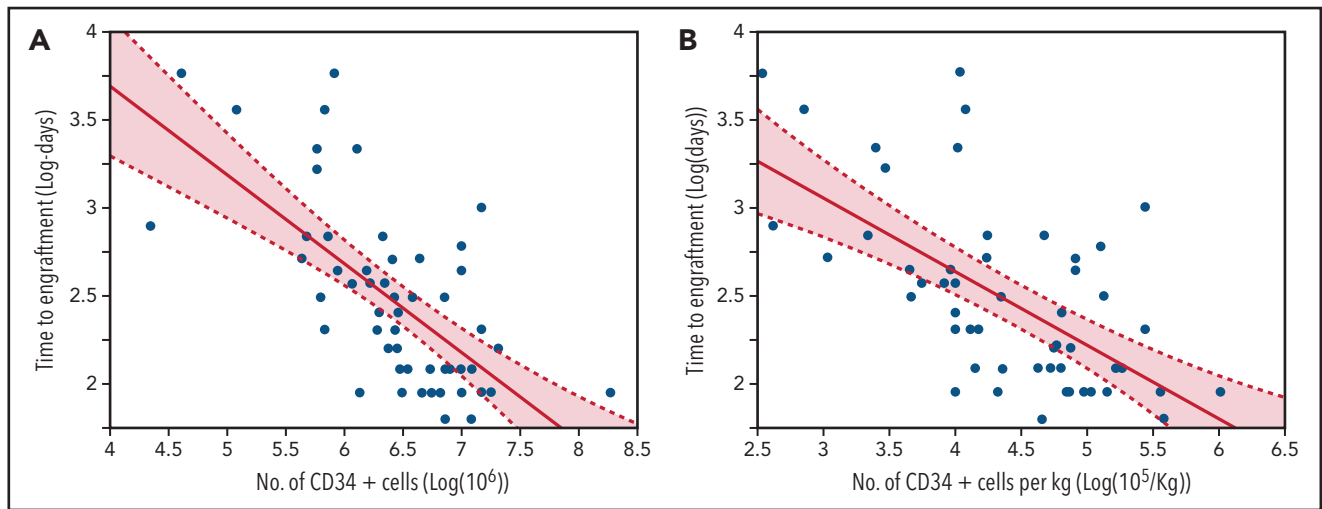


Figure 4. Correlation of CD34⁺ cell content with neutrophil engraftment. Correlation of CD34⁺ total cell count and cell dose with time to neutrophil engraftment. (A) Regression of the time to engraftment on the total number of CD34⁺ cells (both on the natural logarithmic scale). The shaded interval is the pointwise 95% CI around the predicted log time. The regression line is log days to engraftment (5.70-0.50 log [10⁶ total cells]). (B) Regression of the time to engraftment on the number of CD34⁺ cells per patient actual body weight (both on the natural logarithmic scale). The shaded interval is the pointwise 95% CI around the predicted log time. The regression line is log days to engraftment (4.30-0.42 log [10⁵ cells per kg]).

GVHD

Among the patients who received a transplant who were randomly assigned to omidubicel (n = 59) or standard cord blood (n = 58), the incidence of grade 2 to 4 aGVHD at day 100 was similar at 56% vs 43% (13% difference; 95% CI, -6% to 30%; *P* = .18), respectively (Figure 5A). Grade 3 to 4 aGVHD at day 100 was also similar in the omidubicel and control arms at 14% vs 21% (-7% difference; 95% CI, -21% to 7%; *P* = .33) (Figure 5B). The cumulative incidence of all cGVHD at 1 year was 35% for the omidubicel arm and 29% for the controls (6% difference; 95% CI, -14% to 25%; *P* = .57) (Figure 5C). The 1-year cumulative incidence of moderate-to-severe cGVHD was 27% for the omidubicel arm and 21% for the controls (6% difference; 95% CI, -11% to 24%; *P* = .49).

NRM, relapse, DFS, and OS

The median follow-up of all patients was 10 months after transplantation (range, 1-19 months). Using ITT analysis, the cumulative incidence of NRM at 210 days after random assignment was 11% for the omidubicel arm and 24% for the control arm (*P* = .09) (Figure 6A). The cumulative incidence of disease relapse at 15 months after random assignment was 25% for the omidubicel arm and 17% for the control arm (*P* = .32) (Figure 6B). During the time from random assignment to transplantation, relapse was reported in 4 patients allocated to the omidubicel arm and 4 patients allocated to the standard UCBT arm. Among these, relapse prevented 2 patients allocated to the

omidubicel arm and 3 patients allocated to the UCBT arm from receiving a transplant by day 90 after random assignment (Figure 1).

The adjusted hazard ratio for treatment failure (relapse or death, inverse of RFS) with omidubicel vs standard UCB was 0.79 (95% CI, 0.45-1.38; *P* = .4). The adjusted hazard ratio for mortality with omidubicel vs standard UCB was 0.57 (95% CI, 0.3-1.1; *P* = .09) (Figure 6C-D). The 1-year GVHD-free RFS for the omidubicel arm was 36% and 45% for standard UCBT (*P* = .56).

Eleven deaths were reported among the as-treated population of patients who received a transplant with omidubicel, and 18 deaths among the patients treated with a standard UCB graft. As reported by the study investigators, 2 patients who received a transplant with omidubicel died of relapsed disease compared with 4 patients who received a transplant with a standard UCB graft. Among the treatment-related causes of death, GVHD was the setting for death for 4 patients in each group.

Transplant course and toxicity

Patients randomly assigned to the omidubicel graft spent more days alive and out of hospital in the first 100 days after transplantation than those randomly assigned to UCBT; the median time was 61 days (range, 0-89 days) and 48 days (range, 0-84 days),

Table 3. Platelet engraftment by day 42

Randomly assigned treatment group	No.	Cumulative incidence		95% CI	P
		Day 42	Difference		
Omidubicel	62	0.55	0.20	0.03-0.35	.028
Control	63	0.35			

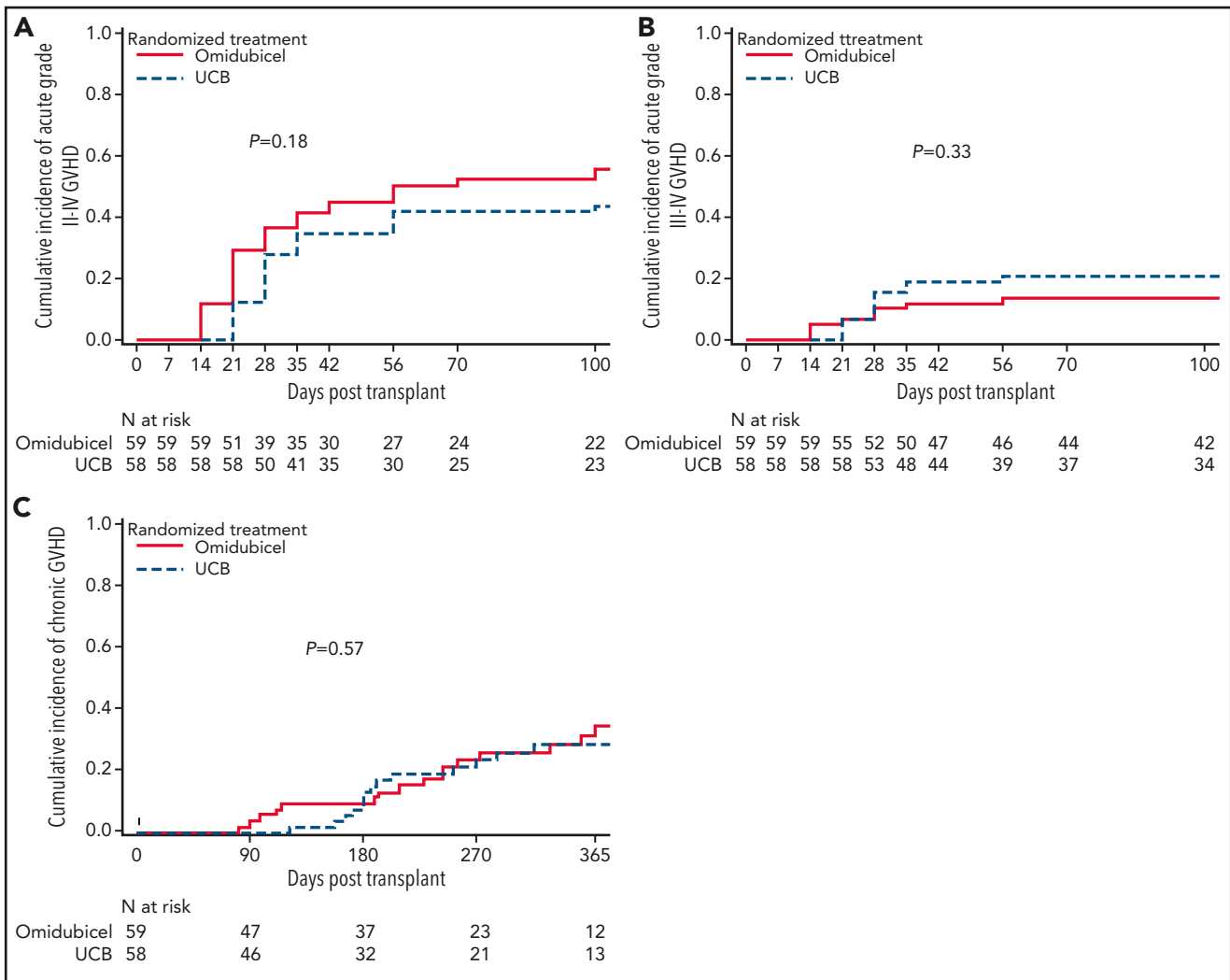


Figure 5. GVHD. Cumulative incidence of grade 2 to 4 aGVHD (A), grade 3 to 4 aGVHD (B), and cGVHD (C). Analysis was performed in the transplanted population by randomly assigned treatment.

respectively ($P = .005$). The median time from transplant to discharge from the hospital was 27 days for the omidubical arm and 35 days for the control arm ($P = .005$). From random assignment and up to 100 days after transplantation, the cumulative incidence of first grade 2 to 3 bacterial or invasive fungal infections was 37% for patients randomly assigned to the omidubical arm and 57% for patients who received the standard UCBT ($P = .03$) (Figure 7A). The cumulative incidence of first grade 3 viral infection during the first year after transplantation was also lower for those randomly assigned to the omidubical arm (10% vs 26%; $P = .02$) (Figure 7B).

To account for the possibility of multiple infections per single patient and relative differences in periods of risk between the treatment groups, we compared infection density during the first year after transplantation. The risk ratio for all infections, irrespective of severity, was significantly lower among recipients of omidubical compared with those who received standard UCBT. The same observation was made when bacterial and viral infections were analyzed individually (Figure 7C). Overall, fewer infections from all reported viral species were observed for omidubical recipients (Figure 7D); however, these differences did not reach

statistical significance. Invasive fungal infections were uncommon in both arms of the study.

The incidence of treatment-emergent serious adverse events (SAEs) possibly related to the stem cell product was similar in the 2 arms (40% for omidubical and 41% for standard cord blood grafts). A breakdown of the treatment-emergent adverse events in both arms of the study is provided in supplemental Table 3. Those treatment-emergent events reported as related to the cord blood infusion are outlined in supplemental Table 4. After random assignment and before starting pretransplant conditioning, 10 serious adverse events (SAEs) were reported for those assigned to the omidubical arm and 8 SAEs were reported for those assigned to a standard UCB graft.

Immune reconstitution

Quantitative recovery of lymphoid subsets was monitored at 1, 3, 6, and 12 months after transplantation in subsets of patients on both arms of the study. Despite the lower numbers of CD3⁺ cells in patients on the omidubical arm compared with those who received standard UCB grafts, the pace of recovery to normal

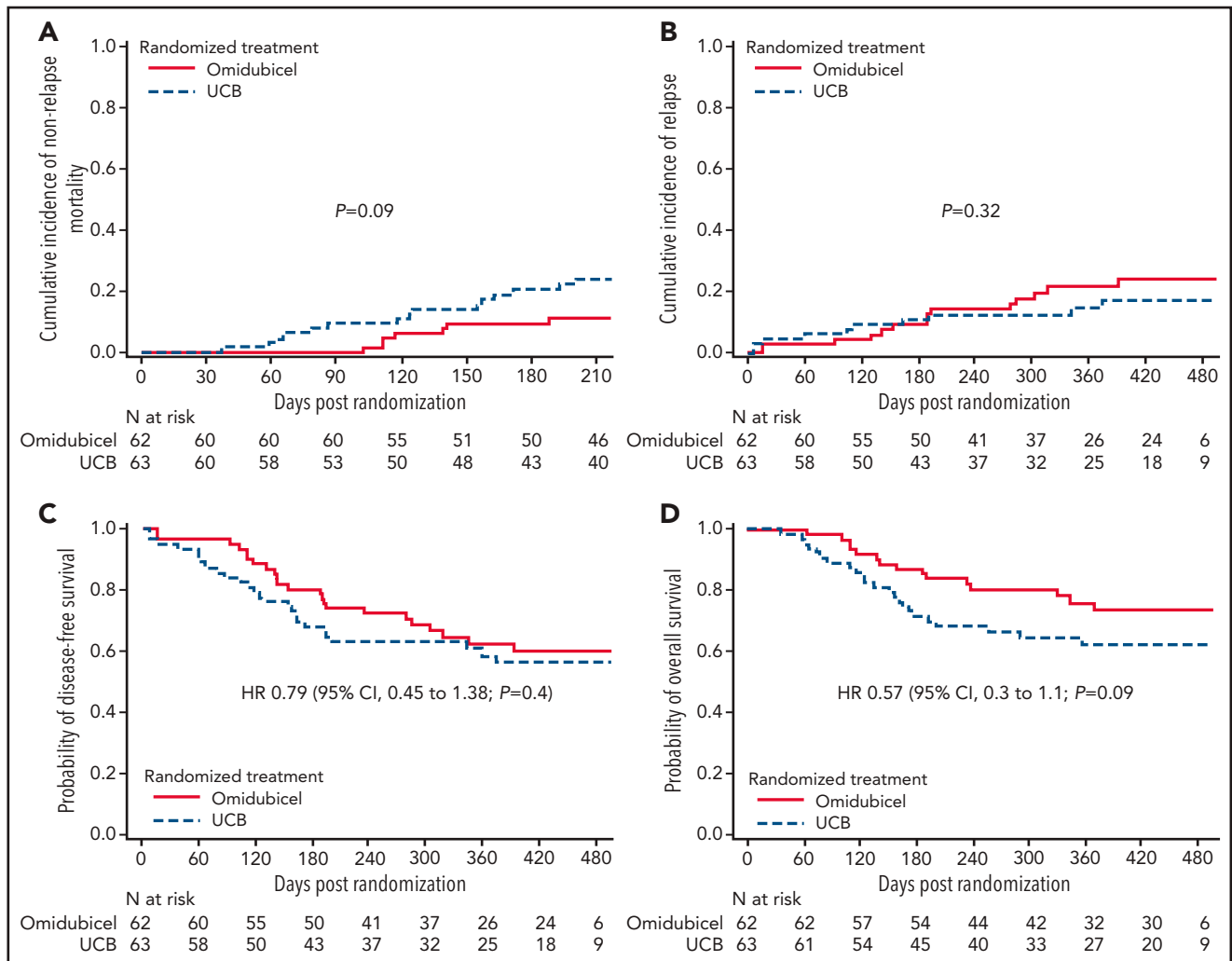


Figure 6. Outcomes of omidubichel and standard UCB, ITT analysis. (A-B) Cumulative incidence of NRM (A) and relapse (B). (C-D) Probability of DFS (C) and OS (D). HR, hazard ratio.

levels of CD3⁺, CD4⁺, CD8⁺, CD19⁺, and CD56⁺/CD16⁺ NK cells was similar in both groups (supplemental Figure 1A-E).

Discussion

Omidubichel is an ex vivo expanded, UCB-derived stem cell graft that was designed to address the major limitations of adult UCBT. There were 3 main findings from this multicenter randomized trial comparing omidubichel to a standard UCB graft. (1) The study confirmed that omidubichel safely addresses the most vexing limitation of UCBT, which is the delay in hematopoietic recovery. Omidubichel reduced the median time to neutrophil recovery by 10 days and the median time to platelet recovery by 13 days. (2) Omidubichel reduced the incidence of infectious complications and time spent in the hospital during the early posttransplantation period. (3) The study demonstrated the feasibility and safety of delivering a personalized, manufactured HSC product to transplantation centers around the world.

Multiple techniques designed to expand UCB stem and progenitor cells have been reported.^{5-7,11-13} Omidubichel (previously

known as NiCord) is the first drug to complete phase 3 testing, the results of which were consistent with observations from earlier studies that examined both safety and efficacy.^{6,9} The omidubichel graft provides a CD34⁺ cell dose that is comparable to an adult mobilized PBSC graft. The 12-day median time to neutrophil recovery is similar to that for mobilized PB, suggesting that both graft sources are enriched for active hematopoietic progenitor cells.¹⁴ Furthermore, long-term follow-up from the earlier studies of omidubichel⁶ suggest robust, durable engraftment for more than 10 years, confirming the persistence and possible expansion of long-term repopulating cells during the ex vivo culture period. The clinical impact of reducing the time to hematopoietic recovery has been well characterized in the literature. A prospective multicenter study of BM vs PBSC grafts showed that a 5-day reduction in time to neutrophil recovery after PBSC graft translated into a reduction in bacterial infections.¹⁵ Conversely, a large multicenter study using the CIBMTR database demonstrated delayed hematopoietic recovery after standard adult UCBT resulted in prolonged hospital use.³ In line with the previous studies, rapid hematopoietic recovery after omidubichel transplantation translated into clinical benefit by reducing infections and time spent in the hospital during the first 100 days after transplantation.

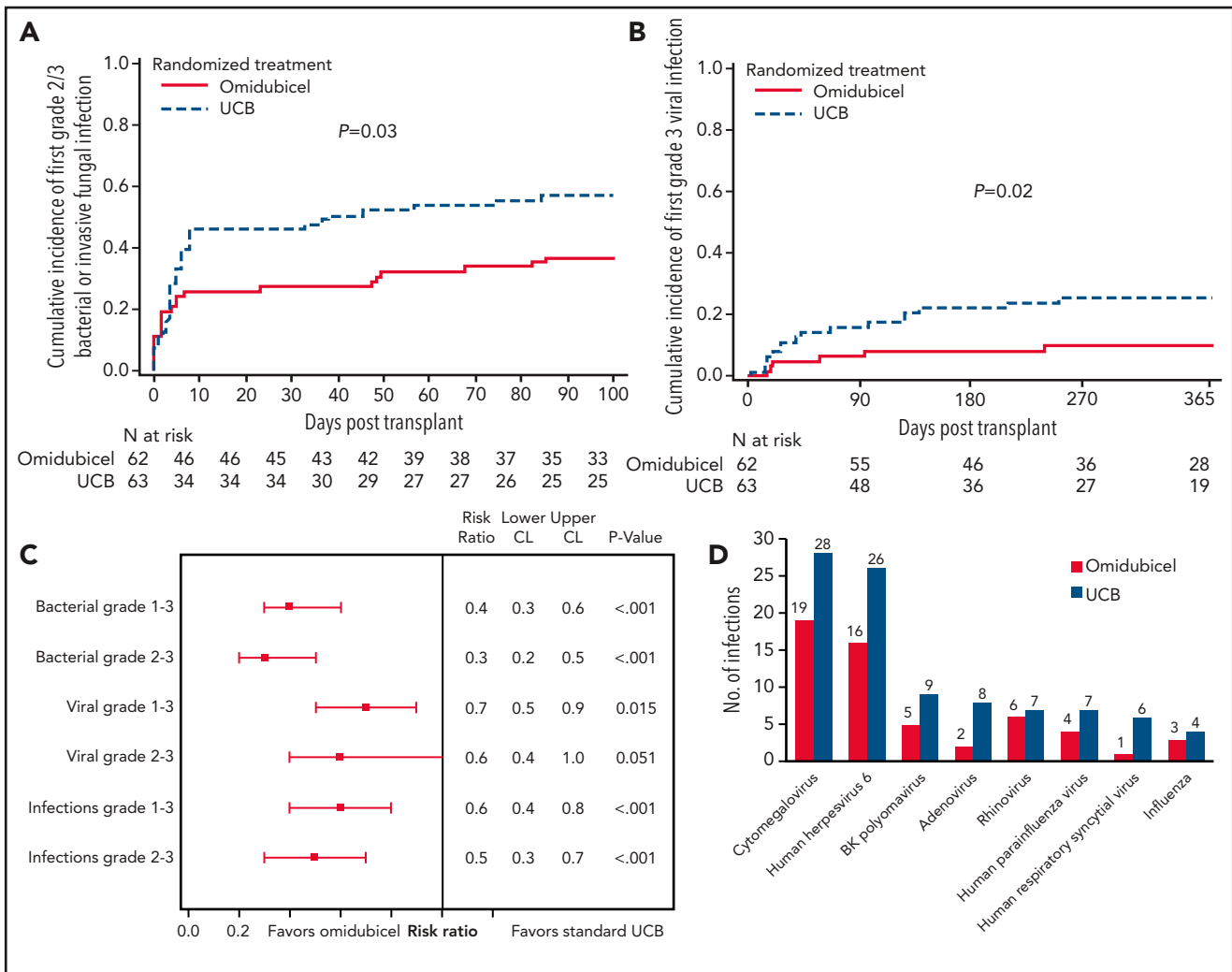


Figure 7. Infections after transplantation. (A) Cumulative incidence of first grade 2 to 3 bacterial infection or invasive fungal infections during the first 100 days after transplantation for the ITT population. (B) Cumulative incidence of first grade 3 viral infection during the first year for the ITT population. All infection events that occurred after random assignment are accounted for in the analysis. (C) Relative risk (95% CI) for bacterial, viral, and all infections at 1 year after transplantation in the omidubichel and the standard UCB groups for the as-treated population. (D) Grade 1 to 3 viral infections at 1 year after transplantation by species for the as-treated population. CL, confidence level.

Importantly, although omidubichel grafts had a lower T-cell content, the recovery of T cells after transplantation is comparable to that with standard UCB, and the risk of viral infections was lower than that with standard UCB throughout the first year after transplantation. The reduced risk of viral infections for recipients of omidubichel was an unexpected finding and could perhaps be attributable to more robust NK cell reconstitution. Further studies of the T-cell receptor diversity are planned and may provide additional insight into this observation.

This study establishes for the first time, the feasibility of providing a personalized, ex vivo expanded HSC graft to recipients throughout the world. This was made possible with logistical support provided by both the sponsor and the regional UCB registries. For example, the National Marrow Donor Program provided participating centers with advice on selecting units that meet prespecified characteristics for expansion. Furthermore, they worked with the sponsor to facilitate transportation of the unit from the cord blood bank to the cell processing

facility. Of note, although the added logistical complexity of producing an ex vivo expanded UCB graft led to a median 2-week delay in time from random assignment to transplantation, this did not result in an increased risk of pretransplant relapse. The study suggests that what is now possible with a commercial, personalized T-cell product in the form of chimeric antigen receptor T-cell therapy can be accomplished at the same scale with a personalized HSC graft.

The encouraging results of transplantation with omidubichel have important implications for minority populations in need of allo-HSCT. Forty-four percent of the patients treated on study were non-White, a population known to be underrepresented in the world-wide unrelated adult donor and UCB registries. The underrepresentation of UCB grafts from Black donors has necessitated the use of smaller units compared with those used for White recipients, which results in inferior outcome.¹⁶ UCB expansion technologies allow for the use of smaller, better matched units with the aim of improving outcome.

The study has important limitations. Although the progression-free survival (PFS) and OS end points trended higher for those receiving omidubicel, the study was not powered to detect a statistically significant difference in these critical end points. Adult UCBT trials have been notoriously difficult to complete, with many previous multicenter trials closing early because of incomplete accrual.^{17,18} For this reason, alternative end points of clinical benefit were chosen to allow for a more realistic sample size. Use of resources for transplantation of UCB grafts has historically exceeded that for adult donor stem cell grafts. The reduction in time to engraftment, hospitalization duration, and infectious complications is expected to reduce the need to use resources over those for a standard UCB graft. Although data on use of resources are not presented in this report, those data have been captured and will allow for confirmation of this expectation. These, and other pressing questions such as the performance of omidubicel transplantation after reduced intensity conditioning and comparative outcomes to other graft sources and specific disease types will need to be addressed in future studies.

Hematopoietic recovery after transplantation with omidubicel was faster, reduced early transplant-related complications, and reduced the number of days patients were hospitalized compared with standard UCBT. The results of this trial demonstrate that omidubicel represents a major therapeutic advance and should be considered as a new standard of care for adult patients eligible for UCBT.

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Authorship

Contribution: E.G.-C., M.E.H., L.S.F., and G.S. conceived the study design and protocol; L.S.F., B.B., and S.W. performed statistical analyses; M.E.H. performed the research and wrote the manuscript; and M.E.H., P.J.S., C.C., C.B., R.H., R.T.M., A.R.R., N.A.K., J.M., D.V., G.J.S., C.A.L., W.Y.K.H., L.P.K., A.K., Y.K., N.H., O.F., T.P., I.S., B.B., S.W., L.S.F., E.G.-C., and G.S. collected, assembled, analyzed, and interpreted the data, reviewed and approved the manuscript, and are accountable for all aspects of the work.

Conflict-of-interest disclosure: M.E.H. served as consultant to AbbVie, CareDx, and Magenta, received honoraria from Kadmon, and received

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ORCID profiles: J.M.G., 0000-0002-0539-4796; D.V., 0000-0002-8747-078X; W.Y.K.H., 0000-0003-0143-6263; N.H., 0000-0002-5140-5310.

Correspondence: Mitchell E. Horwitz, Duke University Medical Center, 2400 Pratt St DUMC 3961, Durham, NC 27710; e-mail: mitchell.horwitz@duke.edu.

Footnotes

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