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Full Length Article
Quality of Life

Health-Related Quality of Life Following Allogeneic Hematopoietic Cell Transplantation with Omidubicel versus Umbilical Cord Blood

Chenyu Lin[1], Gautam Sajeev[2], Patrick J. Stiff[3], Claudio G. Brunstein[4,14], Corey Cutler[5], Guillermo Sanz[6,15,16], Caroline A. Lindemans[7], Andrew R. Rezvani[8], Rabi Hanna[9], Liang Piu Koh[10], Richard T. Maziarz[11], William Y.K. Hwang[12,17,18], Yan Song[2], Qing Liu[2], Rocio Manghani[13], Smitha Sivaraman[13], James Signorovitch[2], Mitchell E. Horwitz[1], Anthony D. Sung[1,*]

[1] *Division of Hematologic Malignancies and Cellular Therapy, Duke University Medical Center, Durham, North Carolina*
[2] *Analysis Group, Inc, Boston, Massachusetts*
[3] *Division of Hematology and Oncology, Loyola University Medical Center, Chicago, Illinois*
[4] *Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, Minnesota*
[5] *Division of Stem Cell Transplantation and Cellular Therapies, Dana-Farber Cancer Institute, Boston, Massachusetts*
[6] *Hematology Department, Hospital Universitario y Politécnico La Fe, Valencia, Spain*
[7] *Department of Pediatric Immunology, University Medical Center Utrecht, Utrecht, The Netherlands*
[8] *Division of Blood and Marrow Transplantation and Cellular Therapy, Stanford University, Stanford, California*
[9] *Department of Pediatric Hematology Oncology and Bone Marrow Transplantation, Cleveland Clinic Children's Hospital, Cleveland, Ohio*
[10] *Department of Hematology-Oncology, National University Cancer Institute, Singapore*
[11] *Center for Hematologic Malignancies, Knight Cancer Institute, Oregon Health and Science University, Portland, Oregon*
[12] *Department of Haematology, National Cancer Centre Singapore*
[13] *Gamida Cell, Boston, Massachusetts*
[14] *Department of Hematology and Oncology, Cleveland Clinic, Taussig Cancer Institute, Cleveland, Ohio*
[15] *CICERONC, Instituto de Salud Carlos III, Madrid, Spain*
[16] *IIS La Fe, Valencia, Spain*
[17] *Department of Haematology, Singapore General Hospital*
[18] *Cancer and Stem Cell Biology, Duke-NUS Medical School*

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A B S T R A C T

Omidubicel is an advanced cell therapy derived from umbilical cord blood (UCB) for use in allogeneic hematopoietic cell transplantation (HCT). A recent randomized phase 3 clinical trial demonstrated faster engraftment, shorter length of hospital stays, and lower rates of infection with omidubicel compared with standard UCB transplantation in patients with high-risk hematologic malignancies. Despite the proven clinical benefits of omidubicel, its impact on health-related quality of life (HRQL) from the patient's perspective has not been described. This study analyzed patient-reported HRQL measures collected prospectively in the randomized phase 3 trial comparing omidubicel to standard UCB transplantation. A total of 108 patients at 33 international stem cell transplantation centers underwent myeloablative allogeneic HCT with either omidubicel or standard UCB. Patients completed serial HRQL questionnaires at screening and on days 42, 100, 180, and 365 post-transplantation. The HRQL surveys included the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT), a 50-item cancer-specific questionnaire assessing physical, functional, emotional, social/family, and HCT-specific well-being, and the EuroQol 5-Dimension 3-Level, a 5-item generic HRQL survey. A mixed model with repeated measures was used to compare changes in HRQL from baseline in the 2 treatment arms. The average change in HRQL scores over time was compared by estimating the difference in the area under the curve (AUC) in each treatment group. Seventy-five patients (omidubicel arm, n = 37; standard UCB arm, n = 38) who completed the FACT-BMT at baseline and on 1 or more follow-up visits were included in this study. Baseline characteristics were similar in the 2 treatment arms. Over the first year post-transplantation, the AUCs of mean changes in physical, functional, and total FACT-BMT scores indicated significantly better HRQL with omidubicel ($P < .05$), with mean differences across time points ranging from 1.4 to 3.1 points, 1.6 to 3.2 points, and 7.2 to 11.0 points, respectively. The minimal clinically important difference was exceeded at 1 or more time points for each of these measures. The HRQL

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*Correspondence and reprint requests: Anthony D. Sung, MD, Associate Professor of Medicine, Duke University School of Medicine, Duke Cancer Institute, 3961 Med Ctr, Durham, NC 27710
E-mail address: anthony.sung@duke.edu (A.D. Sung).

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improvements with omidubicel were observed as early as 42 days post-transplantation and persisted at 1 year, indicating the potential long-term benefits of omidubicel on HRQL. Across all patients, adverse clinical outcomes, such as grade 3 viral infections and lower rates of neutrophil engraftment, were associated with worse HRQL scores. The observed improvements in HRQL measures may reflect the known clinical benefits of omidubicel. Compared with standard UCB, allogeneic HCT with omidubicel resulted in significant and clinically meaningful improvements in patient-reported HRQL measures.

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INTRODUCTION

Umbilical cord blood (UCB) is an alternative source of hematopoietic stem cells that has expanded the access to allogeneic hematopoietic cell transplantation (HCT) for underrepresented patient populations. Nonetheless, UCB transplantation remains limited by the lower number of hematopoietic stem and progenitor cells, as well as the preponderance of naïve B and T cells, present in cord blood compared with mobilized peripheral blood or bone marrow sources. This has led to higher rates of transplantation-related mortality owing to delayed engraftment and infectious complications [1,2].

Omidubicel is a novel umbilical cord blood-derived advanced cell therapy product comprising an ex vivo nicotinamide-expanded and enhanced $CD133^+$ stem cell fraction and a nonexpanded $CD133^-$ fraction containing mature lymphoid cells [3]. Culturing stem cells with nicotinamide has been shown to inhibit stem cell differentiation and improve bone marrow homing [4]. An international multicenter phase 3 randomized clinical trial conducted comparing allogeneic HCT with omidubicel to standard UCB after myeloablative conditioning in patients with advanced hematologic malignancies found that transplantation with omidubicel resulted in faster neutrophil and platelet engraftment and shorter hospitalization during the first 100 days post-transplantation [5]. Omidubicel also was associated with a lower incidence of infectious complications, including grade 2/3 bacterial infections, grade 3 invasive fungal infections, and grade 3 viral infections. The rates of survival and graft-versus-host disease (GVHD) were similar in the 2 treatment arms. Furthermore, recent reports have suggested rapid immune reconstitution and favorable long-term graft durability with omidubicel [6,7].

With the success of omidubicel and other recent advancements in the field of HCT in improving objective transplant-related outcomes has come an increased focus on understanding how these novel transplantation techniques can impact health-related quality of life (HRQL) and improve the patient's experience with transplantation. Prior studies have consistently demonstrated the profound and multidimensional impact that allogeneic HCT can have on patients' HRQL in the early post-transplantation period, which may continue to long-term impairment [8–11]. In this study, we compared serially collected HRQL measures in recipients of allogeneic HCT with omidubicel versus those with standard UCB in the aforementioned phase 3 randomized trial (ClinicalTrials.gov identifier: NCT02730299) [5]. This investigation complements the primary efficacy analysis from the clinical trial and may provide important insights for key stakeholders and decision makers, including providers, payers, caregivers, and patients themselves.

METHODS

Study Design

The design of the prospective, multicenter, randomized phase 3 clinical trial has been described previously [5]. In brief, 125 patients with an advanced hematologic malignancy were enrolled at 33 sites across North and South America, Europe, and Singapore. These patients were randomized 1:1 to receive either open-label omidubicel (n = 62) or control standard UCB units (n = 63) for allogeneic HCT. Minimization factors for randomization included age, treatment center, Disease Risk Index, and intent to use 1-unit or 2-unit standard UCB grafts in the control arm. Among the randomized patients, 10 patients in the omidubicel arm and 8 in the control arm did not undergo HCT according to protocol, leaving 108 patients in the as-treated population.

Three myeloablative conditioning regimens were permitted for the study: fludarabine 160 mg/m^2 + thiotepa 10 mg/kg + total body irradiation 1350 cGy, fludarabine 75 mg/m^2 + cyclophosphamide 120 mg/kg + total body irradiation 1320 cGy, and busulfan 12.8 mg/kg + fludarabine 150 mg/m^2 + thiotepa 10 mg/kg. GVHD prophylaxis included a calcineurin inhibitor and mycophenolate mofetil starting 3 days prior to transplantation. The primary objective of the clinical trial was to compare the time to neutrophil engraftment after transplantation, which has been reported previously [5]. A planned exploratory objective was to describe and compare HRQL measures between the 2 treatment arms.

This study was approved by the Institutional Review Board at each research site. All patients provided written informed consent for inclusion in the study. The multicenter HRQL data were compiled as part of the clinical trial by Gamida Cell (Jerusalem, Israel) and The Emmes Company (Rockville, MD). Statistical analysis was performed by Analysis Group, Inc (Boston, MA).

Study Population

Eligible study participants were age 12 to 65 years with a high-risk hematologic malignancy. Participants must have been candidates for an allogeneic HCT and must not have had an available matched donor. Exclusion criteria for the trial included chronic lymphocytic leukemia and the presence of 3+ fibrosis in the bone marrow. Between January 2017 and January 2020, 125 patients were randomized, and 108 patients received either omidubicel or standard UCB grafts for HCT (Figure 1) [5]. This HRQL study was performed on the as-treated population and included only those patients who had available HRQL data both at baseline and during at least 1 follow-up visit.

HRQL Questionnaires

Patient-reported HRQL measures were collected prospectively at the time of screening and at 42, 100, 180, and 365 days post-transplantation. Two standardized HRQL instruments were used in this study. The Functional Assessment of Cancer Therapy-General (FACT-G) version 4 is a 27-item cancer-specific HRQL questionnaire that assesses the domains of physical, social/family, emotional, and functional wellness [12]; the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) adds an additional BMT subscale to FACT-G [13]. The inclusion of this multidimensional questionnaire allows for detailed assessment of cancer-specific and transplantation-specific HRQL concerns. The EuroQol 5-Dimension 3-Level (EQ-5D-3L) is a generic, non-disease-specific, 5-item HRQL questionnaire evaluating mobility, self-care, usual activities, pain, and anxiety/depression [14]. This shorter questionnaire can be easily completed during clinic visits and allows for a general assessment of HRQL status. The shorter EQ-5D-3L questionnaire was completed by patients using self-administered instruments provided during clinic visits, whereas the FACT-BMT questionnaires also could be completed electronically at home via a computer. Patients were instructed to fill out the questionnaires themselves rather than designating a surrogate. If a patient's questionnaire was missing >50% of its responses, then the patient data for that entire questionnaire were considered to be missing. Total FACT-G scores range from 0 to 108 points, FACT-BMT ranges from 0 to 148 points, and EQ-5D-3L index score ranges from 0 to 1; higher scores indicate better HRQL.

Among cancer patients who undergo allogeneic HCT, the minimal clinically important difference (MCID) is defined as a change of ≥2 points in the FACT-G domain score, ≥5 points in the FACT-G total score, ≥2 points in the BMT subscale score, and ≥7 points in the FACT-BMT total score [13,15]. For measures of internal consistency, the Cronbach α coefficient ranges from .85 to .92 for FACT-BMT in the transplantation population [13]. The MCID of the EQ-5D-3L index score is defined as .07 point for general use; this has not been investigated specifically in transplantation recipients [16].

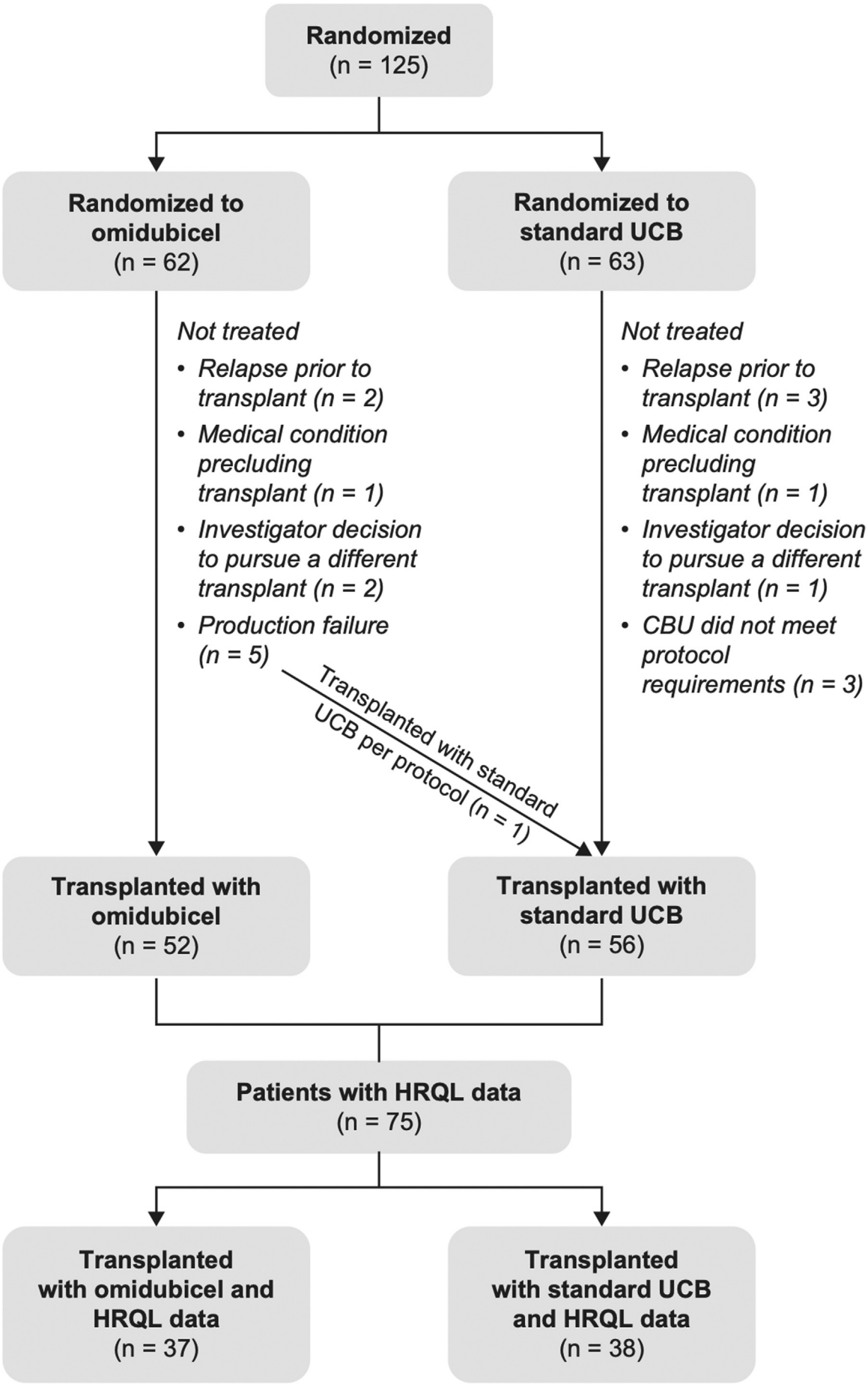

Figure 1. CONSORT diagram depicting randomization and treatment of patients from the phase 3 clinical trial comparing allo-HCT with omidubicel versus standard UCB, as well as subsequent inclusion into the associated HRQL study. Allo-HCT indicates allogeneic HCT; CBU, cord blood unit.

Statistical Analysis

In accordance with the omidubicel phase 3 trial protocol, HRQL data were collected prospectively. However, statistical analyses for comparison of treatment arm differences were not prespecified in the trial analysis plan. Thus, the post hoc analyses described below were conducted to compare treatment arm differences in HRQL. To assess balance, baseline characteristics were compared between the 2 treatment arms and between patients included and excluded from the HRQL study using the *t* test for continuous variables and the chi-square test for categorical variables.

Mixed models for repeat measures (MMRM) were used to compare changes in the HRQL measures over time between groups. The MMRM models included time, treatment group, and the interaction between treatment group and time and were further adjusted for baseline HRQL value, region (United States and not United States), age group, sex, race (white and non-white), HCT-specific comorbidity index, and primary cancer diagnosis. Correlations across repeated HRQL measures from the same individual were accounted for via an unstructured covariance matrix, which allows for possible changes in the variability of HRQL during follow-up. The area under the curve (AUC) for mean HRQL, which represents the average HRQL change over time, was compared between the treatment groups. This approach was selected because of the potential for HRQL scores to both worsen and improve over time, such that no single time point would be representative of the full patient experience [17]. The time from transplantation to first improvement or first worsening greater than the MCID was summarized in each treatment group using Kaplan-Meier analyses and compared between groups using the log-rank test. In these time-to-event analyses, patients with changes less than the MCID were censored at last follow-up.

The association between clinical outcomes and the change in HRQL measures from baseline to day 42 and day 100 post-transplantation was assessed using multivariable linear regression models. Clinical outcomes of interest included neutrophil engraftment, platelet engraftment, infectious complications, grade II-IV acute GVHD, and hospital length of stay during the first 100 days post-transplantation. The time points of 42 days and 100 days post-transplantation were selected for analysis because many of the clinical benefits associated with omidubicel occurred in the early post-transplantation period. The regression models were adjusted for treatment group, baseline HRQL scores, region, age group, sex, race, HCT-specific comorbidity index, and primary cancer diagnosis. Changes in the scores of specific BMT subscale items from baseline to last assessment were evaluated using a similar linear regression model. All analyses were performed using R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). Because these analyses were exploratory, there were no statistical adjustments for multiplicity.

RESULTS

Study Population

Seventy-five of the 108 patients in the as-treated population (69%) completed the FACT-BMT questionnaire both at baseline and on ≥1 follow-up visit(s) and thus were included in this analysis (omidubicel, n = 37; standard UCB, n = 38). Sixty-eight patients (63%) completed the EQ-5D-3L survey at baseline and on ≥1 follow-up visit(s). For both the FACT-BMT and EQ-5D-3L, the rate of survey completion decreased over time. Among the 75 included patients, the FACT-BMT completion rates were 100% at baseline, 81% at day 42, 84% at day 100, 68% at day 180, and 61% at day 365. The EQ-5D-3L completion rates were 89% at baseline, 77% at day 42, 76% at day 100, 61% at day 180, and 40% at day 365.

Comparing patients who were included (n = 75) versus those in the as-treated population who were excluded (n = 33), included patients had a higher incidence of platelet engraftment by day 42 after transplantation (90.7% versus 54.6%; $P < .001$), fewer days in the hospital during the first 100 days (43.6 versus 66.3 days; $P < .001$), and better 1-year overall survival (82.7% versus 42.4%; $P < .001$). There were no statistically significant differences in the rates of neutrophil engraftment, grade II-IV acute GVHD, chronic GVHD, or disease relapse.

Table 1
Baseline Characteristics of Patients Included in the HRQL Study

Characteristic	Omidubicel Arm (N = 37)	Standard UCB Arm (N = 38)	*P* Value
Demographics			
Age, yr, mean ± SD	37.3 ± 15.5	35.1 ± 14.8	.54
Age range, n (%)			
12-17 yr	5 (13.5)	5 (13.2)	
18-39 yr	15 (40.5)	16 (42.1)	
40-65 yr	17 (45.9)	17 (44.7)	
Male sex, n (%)	20 (54.1)	24 (63.2)	.57
Weight, kg, mean ± SD	82.4 ± 20.5	79.7 ± 21.3	.57
White race, n (%)	24 (64.9)	20 (52.6)	.72
US resident, n (%)	27 (73.0)	28 (73.7)	>.99
Clinical measures			
Primary diagnosis, n (%)			
Acute myelogenous leukemia	17 (45.9)	17 (44.7)	.97
Acute lymphoblastic leukemia	12 (32.4)	14 (36.8)	
Chronic myelogenous leukemia	3 (8.1)	2 (5.3)	
Myelodysplastic syndrome	3 (8.1)	2 (5.3)	
Lymphoma	1 (2.7)	2 (5.3)	
Other	1 (2.7)	1 (2.6)	
Disease Risk Index, n (%)			
Low risk	11 (29.7)	6 (15.8)	.31
Intermediate risk	12 (32.4)	17 (44.7)	
High risk	14 (37.8)	15 (39.5)	
HCT-specific comorbidity index, n (%)			
0	8 (21.6)	6 (15.8)	.81
1-2	11 (29.7)	12 (31.6)	
3+	18 (48.6)	20 (52.6)	

Table 2
Frequencies of Clinical Outcomes (Prespecified Endpoints in the Phase 3 Study) in the 2 Treatment Arms at 100 Days and 365 Days Post-Transplantation

Outcome	Omidubicel Arm (N = 37)	Standard UCB Arm (N = 38)	*P* Value
Time to engraftment, d, median (95% CI)	10.0 (8.0-13.0)	19.5 (18.0-25.0)	<.001*
During 1-yr follow-up post-transplantation			
Neutrophil engraftment, n (%)	37 (100)	35 (92.1)	.240
Platelet engraftment, n (%)	36 (97.3)	32 (84.2)	.108
Grade 2/3 bacterial or invasive fungal infection (grade 3), n (%)	20 (54.1)	25 (65.8)	.423
Grade 3 viral infection, n (%)	2 (5.4)	12 (31.6)	<.01*
Grade II-IV acute GVHD, n (%)	24 (64.9)	15 (39.5)	<.05*
Grade III-IV acute GVHD, n (%)	4 (10.8)	5 (13.2)	>.99
Chronic GVHD, n (%)	17 (46.0)	10 (26.3)	.126
First 100 days post-transplantation			
Neutrophil engraftment, n (%)	37 (100)	35 (92.1)	.240
Platelet engraftment, n (%)	36 (97.3)	31 (81.6)	.056
Grade 2/3 bacterial infections or grade 3 invasive fungal infections, n (%)	18 (48.7)	21 (55.3)	.732
Grade 3 viral infection, n (%)	1 (2.70)	6 (15.8)	.108
Grade II-IV acute GVHD, n (%)	23 (62.2)	15 (39.5)	.083
Grade III-IV acute GVHD, n (%)	4 (10.8)	5 (13.2)	>.99
Length of inpatient stay during the first 100 d post-transplantation, d, mean ± SD	38.0 ± 21.3	49.0 ± 24.0	<.05*

* Statistically significant difference.

Baseline Characteristics

Among the 75 patients included in this study, baseline characteristics were comparable between patients who received omidubicel and those who received standard UCB (Table 1). The mean age of the patients was 36 years, and approximately 59% were male. More than 40% of the participants were nonwhite, highlighting a key underrepresented demographic. The most common indications for allogeneic HCT were acute myeloid leukemia (45%) and acute lymphoblastic leukemia (35%). Most patients (77%) had either intermediate-risk or high-risk disease, and 51% had an HCT comorbidity index of ≥3. Comparing the availability of HRQL data over time, patients who received omidubicel tended to have comparable or less missing data than standard UCB (19% versus 18% on day 42, 14% versus 18% on day 100, 27% versus 37% on day 180, and 38% versus 40% on day 365).

Regarding clinical outcomes of interest, in this sample, the median time to neutrophil engraftment was 10.0 days for the omidubicel group versus 19.5 days for the standard UCB group ($P < .001$). In addition, the omidubicel group had a lower rate of grade 3 viral infections (5.4% versus 31.6%; $P < .01$) and a higher rate of grade II-IV acute GVHD (64.9% versus 39.5%, $P < .05$) compared with the standard UCB group in the first year post-transplantation (Table 2). The omidubicel group also had fewer days in the hospital during the first 100 days (38 days versus 49 days; $P < .05$). There were no between-group differences in the rates of chronic GVHD, grade III-IV acute GVHD, or the combined endpoint of grade 2/3 bacterial infections and grade 3 fungal infections.

HRQL Changes over Time and between Groups

Baseline HRQL measures, including FACT-G total and domain scores, BMT subscale scores, FACT-BMT total scores, and EQ-5D-3L index scores, were similar in the 2 treatment arms (Table 3). An initial decline in mean scores from baseline to day 42 post-transplantation was observed in both treatment arms for all HRQL measures. The mean declines during this period were numerically smaller in the omidubicel arm compared with the standard UCB arm.

FACT-G domain scores

Regarding individual FACT-G domain scores, differences in the AUC of the mean change in physical well-being domain scores over time indicate better HRQL with omidubicel compared with standard UCB ($P = .02$), with mean differences across time points ranging from 1.5 to 3.1 points (Figure 2A). Differences exceeding the MCID of 2 points were observed at days 180 and 365. Patients in the omidubicel arm also had better social/family and emotional HRQL, with mean differences across time points ranging from 0 to 1.3 points for social/family well-being and from .5 to 1.4 points for emotional well-being (Figure 2B,C); however, these differences did not meet statistical significance or exceed the MCID. In the functional well-being domain, the AUC of mean change over time favored

Table 3
Mean HRQL Questionnaire Scores for the Omidubicel and Standard UCB Arms at Screening

HRQL Measures	Omidubicel Arm (N = 37), mean ± SD	Standard UCB Arm (N = 38), mean ± SD	*P* Value
FACT-G total score	80.2 ± 14.3	83.9 ± 11.9	.22
Physical well-being score	22.3 ± 5.1	23.6 ± 4.5	.26
Social/family well-being score	22.2 ± 5.2	24.1 ± 3.6	.07
Emotional well-being score	18.1 ± 4.4	18.4 ± 3.6	.72
Functional well-being score	17.6 ± 6.2	17.9 ± 5.7	.84
BMT subscale score	28.2 ± 5.7	27.9 ± 6.6	.82
FACT-BMT total score	108.4 ± 19.1	111.8 ± 17.3	.42
EQ-5D-3L index score	.86 ± .16	.87 ± .13	.70

There were no statistically significant differences between the 2 groups.

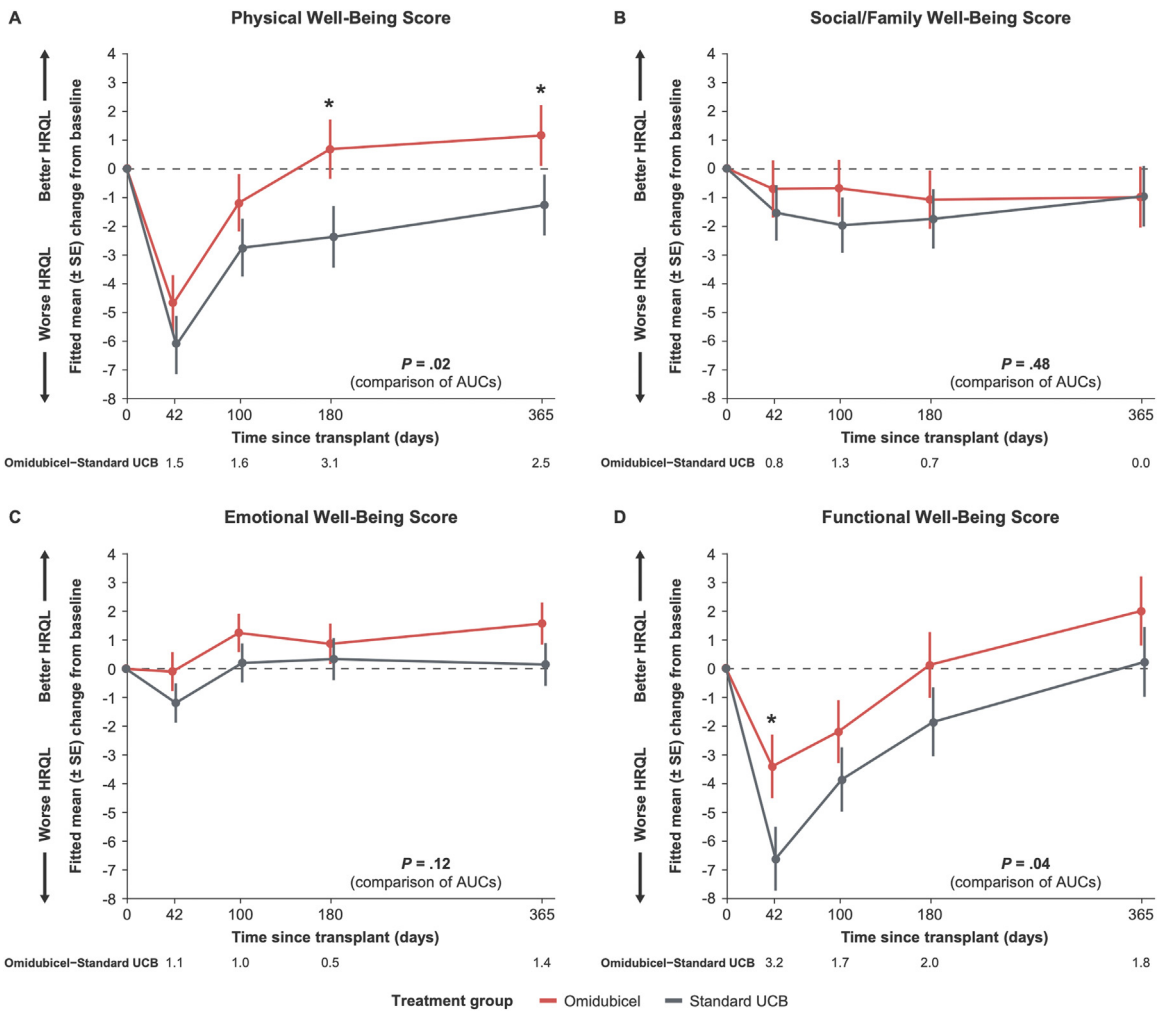

Figure 2. Mean changes from baseline HRQL scores at predefined follow-up visits for omidubicel and standard UCB reported for each of the 4 FACT-G domains: physical well-being score (A), social/family well-being score (B), emotional well-being score (C), and functional well-being score (D). The difference in FACT-G domain scores between the omidubicel and standard UCB arms at each respective time point are indicated below the *x*-axis. *This difference exceeded the MCID (2 points).

the omidubicel arm (P = .04), with mean differences between the 2 arms ranging from 1.7 to 3.2 points (Figure 2D). The MCID for the functional well-being domain was exceeded only at day 42. In all FACT-G domains except social/family well-being, mean scores in the omidubicel arm were able to recover back to at least baseline scores by day 180.

Regarding the time to meaningful change—defined as change greater than or equal to the MCID—the time from transplantation to first meaningful improvement of physical well-being scores was shorter in the omidubicel group compared with the standard UCB group (Supplementary Figure S1A). Correspondingly, the time from transplantation to the first meaningful worsening of physical well-being scores was longer in the omidubicel group (Supplementary Figure S1B). Significant differences in the time to meaningful improvement or worsening were not detected for the other HRQL domains.

FACT-G Total, BMT Subscale, FACT-BMT Total, and EQ-5D-3L scores

AUC differences in the mean change of FACT-G total scores indicated significantly better HRQL with omidubicel, with mean differences ranging from 6.0 to 6.9 points (P = .01). The MCID of 5 points was exceeded at all follow-up time points, beginning at day 42 and continuing up until day 365 post-transplantation (Figure 3A). Similarly, HRQL based on the mean change of BMT subscale scores over time was better in the omidubicel group (P = .04 for difference in AUCs), with mean differences ranging from 1.0 to 4.1 points across the time points (Figure 3B). The improvements exceeded the MCID of 2 points at days 42, 100, and 180 and reconverged by day 365. Notably, under the BMT subscale question asking patients whether the transplantation-related side effects were "worse than [they] had imagined," the standard UCB arm had an increase in the proportion answering in the affirmative (ie, "somewhat," "quite a bit," and "very much") from 32% at baseline to 48% at the last assessment. In contrast, the omidubicel arm had a reduction in the proportion of affirmative answers, from 34% at baseline to 22% at last assessment (Supplementary Figure S2). The change in affirmative response from baseline to last assessment, measured as an item score derived from a Likert scale, was significantly different between the 2 arms (P = .046).

Finally, AUC differences of the mean change of FACT-BMT total scores indicated better HRQL with omidubicel (P = .01), with mean differences ranging from 7.2 to 11.0 points (Figure 3C). The MCID of 7 points for the FACT-BMT total score was exceeded at all follow-up time points from day 42 to day 365. The mean change in the EQ-5D-3L index also was numerically superior with omidubicel, with a difference that trended toward significance (P = .06 for

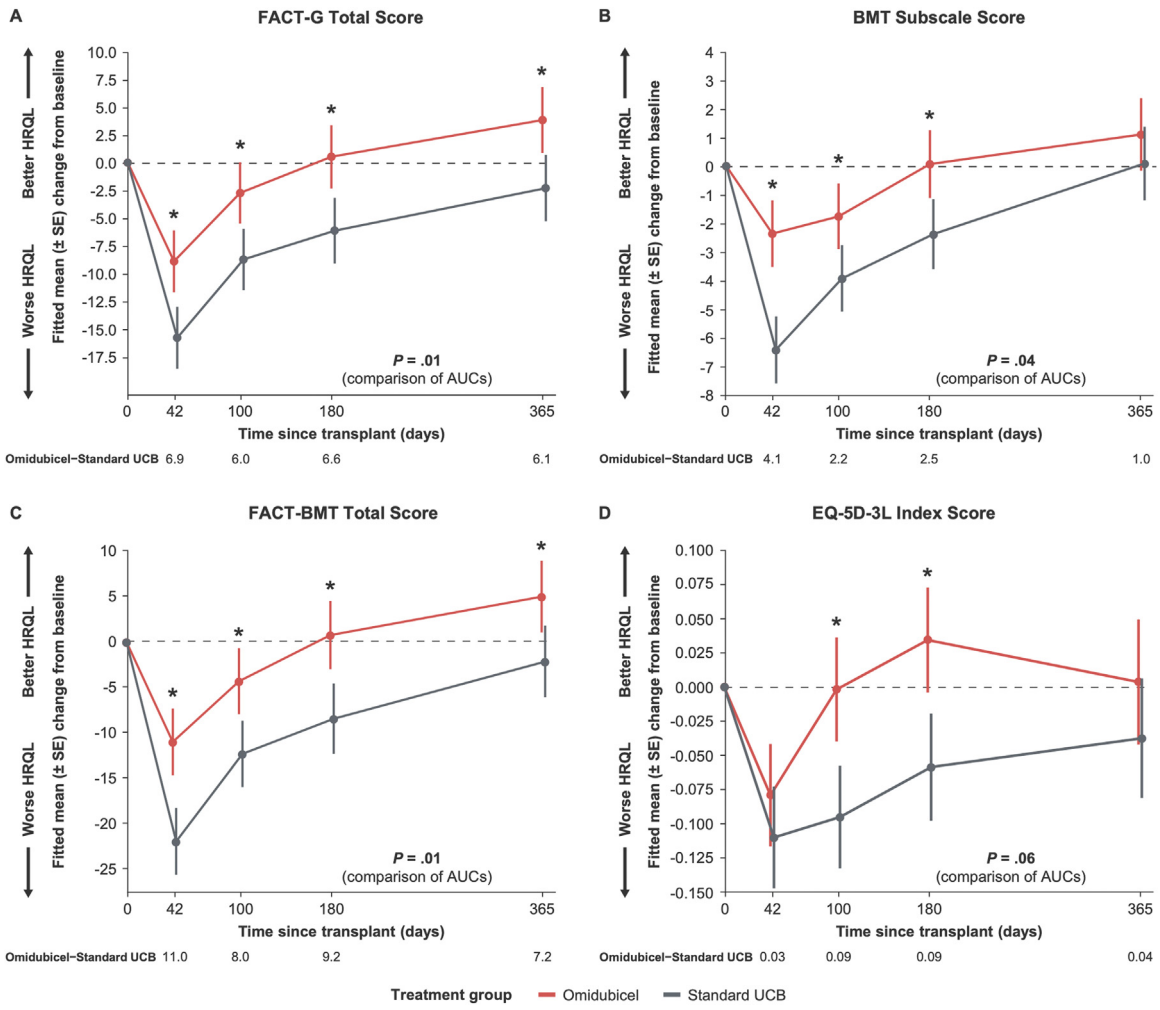

Figure 3. Mean changes from baseline HRQL measures for the FACT-G total score (A), BMT subscale score (B), FACT-BMT total score (C), and EQ-5D-3L index score (D). The difference in HRQL scores between the omidubicel and standard UCB arms at each respective time point are indicated below the *x*-axis. *This difference exceeded the MCID (5 points for FACT-G total score, 2 points for the BMT subscale, 7 points for the FACT-BMT total score, and .07 point for the EQ-5D-3L index).

difference in AUCs). The MCID for EQ-5D-3L was exceeded on days 100 and 180 (Figure 3D).

HRQL associations with clinical outcomes

HRQL scores were analyzed for all patients regardless of treatment arm in the context of significant clinical outcomes at days 42 and 100. Achieving neutrophil engraftment by day 42 was associated with significantly better FACT-G emotional well-being at day 42 compared to baseline. Specifically, the mean change between baseline and day 42 was 8.1 points greater (95% confidence interval [CI], 2.5 to 13.6) for those who achieved engraftment compared with those who did not. Earlier neutrophil engraftment also was associated with better FACT-G domain scores at day 42, but these differences did not reach statistical significance. Grade II-IV acute GVHD was associated with worse functional well-being (-3.7 points; 95% CI, -6.1 to -1.3), lower BMT subscale scores (-2.7 points; 95% CI, -5.1 to -.3), and lower FACT-BMT total scores (-12.0 points; 95% CI, -20.2 to -3.8) at day 100.

With respect to infectious complications, in the entire study population, having a grade 3 viral infection in the first 42 days was associated with significantly worse emotional well-being (-6.0 points; 95% CI, -9.1 to -2.8) and numerically worse physical well-being, although the latter difference was not significant. Grade 2/3 bacterial or grade 3 invasive fungal infections were not associated with changes in HRQL measures at day 42 but were associated with worse physical well-being scores at day 100 (-3.2 points; 95% CI, -5.7 to -.7). Finally, the total number of days hospitalized in the first 100 days, a prespecified secondary endpoint in the phase 3 trial, was associated with slightly worse physical well-being (-.1 point; 95% CI, -.2 to -.03), social/family well-being (-.1 point; 95% CI, -.2 to -.03), FACT-G total (-.2 point; 95% CI, -.4 to -.1), and FACT-BMT total (-.3 point; 95% CI, -.5 to -.1) scores at day 100.

DISCUSSION

Omidubicel is an advanced cell therapy product that has demonstrated faster hematopoietic recovery and a lower incidence of infectious complications compared with standard UCB in allogeneic HCT recipients. Despite the observed objective benefits with omidubicel, information regarding how this novel therapy impacts quality of life from the patient perspective has been lacking. Our present study examined this question via an analysis of prospectively collected HRQL measures

during the first year after allogeneic HCT in the phase 3 clinical trial comparing omidubicel and standard UCB.

Prior HRQL studies in allogeneic HCT have shown reductions in quality of life measures across multiple domains, often reaching a nadir within the first 100 days after transplantation and returning to pretransplantation levels by the 1-year mark [8,9,18]. In our study, the FACT-BMT domain and total scores all followed a similar downward trajectory in the early post-transplantation period that corresponded to the expected early transplantation-related toxicities. However, the omidubicel arm tended to have a less precipitous initial decline in HRQL scores, and clinically meaningful differences were observed as early as 42 days after transplantation. Notably, at 6 months post-transplantation, physical well-being scores recovered back to baseline in patients who received omidubicel, in contrast to the standard UCB group. In addition, the separations in physical well-being, FACT-G, and FACT-BMT scores between these 2 groups persisted at last follow-up on day 365, which may imply the presence of a more extended benefit and is consistent with prior studies suggesting long-term advantages with omidubicel [7,19].

In our study population with available HRQL data, there was a slight imbalance in clinical outcomes between the 2 treatment groups, reflecting the decreased rate of grade 3 viral infections, reduced duration of hospitalization, and numerically higher incidence of grade II-IV acute GVHD observed in the omidubicel arm of the full trial population. With the association between acute GVHD and poorer HRQL outcomes, this imbalance in acute GVHD that was skewed in favor of standard UCB would not have explained the HRQL benefit seen with omidubicel and instead may have led to an underestimation of its true effect size. However, it is plausible that the improvement in HRQL scores with omidubicel may be explained in part by the fewer number of days hospitalized and the lower rates of grade 3 viral infections. Adverse infectious events in the post-transplantation period, including viral, bacterial, and fungal infections, are common and have been demonstrated to be associated with negative impacts on HRQL [20,21].

One of the main limitations of this study is the exclusion of patients (31%) from the analysis because of incomplete baseline or follow-up HRQL data. Patients who were excluded had slightly worse HRQL scores in most domains, as well as poorer clinical outcomes, including lower rates of platelet engraftment, longer hospitalizations, and worse survival. This is an expected association, as patients with worse clinical status may be less likely to fill out HRQL surveys and are assumed to have poorer HRQL scores in most domains. Interestingly, the rate of missing HRQL data was more pronounced in the standard UCB group, suggesting that a selective loss of follow-up is more likely to create bias against omidubicel. Although the HRQL burden might have been underestimated in both treatment arms, the specific HRQL benefits estimated for omidubicel compared with standard UCB likely are conservative relative to the true effect. In addition, the subjective nature of patient-centric assessments may make certain HRQL measures more prone to potential open-label bias owing to patients' greater optimism for an experimental intervention [22,23]. However, the true impact of open-label bias in this setting is uncertain, with a recent systemic review of 110 randomized controlled trials in prostate cancer failing to find evidence of significant bias related to the absence of blinding [24]. Finally, although the HRQL data were collected prospectively in the phase 3 trial, statistical analyses of HRQL measures were not prespecified, and the results reported here are based on post hoc analyses of the trial data.

Available literature on patient-reported quality of life measures with novel transplantation and cell therapy products is limited. In recent years, increasing importance has been placed on the inclusion of patient-reported outcomes in the assessment of novel therapeutics [25–27]. Our study shows that omidubicel was associated with meaningfully greater preservation or improvement of several important patient-reported HRQL measures compared with standard UCB. Along with statistically significant faster time to engraftment, lower risk of infection, and shorter hospitalizations, omidubicel appears to positively influence functional and physical well-being domains, as well as the overall HRQL measures. Across all patients, regardless of treatment group, adverse clinical events, such as longer time to engraftment and grade 3 viral infections, were associated with negative impacts on various HRQL domains. Overall, these findings suggest that HRQL following allogeneic HCT is sensitive to clinical outcomes, and that the clinical benefits of omidubicel may be associated with important and concordant benefits on patient-centric HRQL measures that reflect the overall effects of treatment. The results of this study may be informative in guiding discussions with patients when considering the use of omidubicel.

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Data sharing statement*:* Individual participant data will not be shared. Queries about the data can be addressed to the corresponding author or medicalinformation@gamidacell.com.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.jtct.2022.09.018.

REFERENCES

1. Eapen M, Rocha V, Sanz G, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol*. 2010;11:653–660.
2. Ballen K, Woo Ahn K, Chen M, et al. Infection rates among acute leukemia patients receiving alternative donor hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2016;22:1636–1645.
3. Islam P, Horwitz ME. Small-molecule nicotinamide for ex vivo expansion of umbilical cord blood. *Exp Hematol*. 2019;80:11–15.
4. Peled T, Shoham H, Aschengrau D, et al. Nicotinamide, a SIRT1 inhibitor, inhibits differentiation and facilitates expansion of hematopoietic progenitor cells with enhanced bone marrow homing and engraftment. *Exp Hematol*. 2012;40:342–355. e1.
5. Horwitz ME, Stiff PJ, Cutler C, et al. Omidubicel vs standard myeloablative umbilical cord blood transplantation: results of a phase 3 randomized study. *Blood*. 2021;138:1429–1440.
6. Szabolcs P, Levy S, Yackoubov D, Pato A, Galamidi-Cohen E, Horwitz ME. Hematopoietic stem cell transplantation (HSCT) with omidubicel is associated with robust immune reconstitution and lower rates of severe infection compared to standard umbilical cord blood transplantation. *Blood*. 2021;138:333.
7. Lin C, Morrison L, Alyea 3rd EP, et al. Allogeneic stem cell transplantation with omidubicel: long-term follow-up from a single center. *Blood*. 2021;138(suppl 1):1827.
8. Pidala J, Anasetti C, Jim H. Quality of life after allogeneic hematopoietic cell transplantation. *Blood*. 2009;114:7–19.
9. Bevans M. Health-related quality of life following allogeneic hematopoietic stem cell transplantation. *Hematology Am Soc Hematol Educ Program*. 2010;2010:248–254.
10. Kopp M, Holzner B, Meraner V, et al. Quality of life in adult hematopoietic cell transplant patients at least 5 yr after treatment: a comparison with healthy controls. *Eur J Haematol*. 2005;74:304–308.
11. Hjermstad M, Holte H, Evensen SA, Fayers PM, Kaasa S. Do patients who are treated with stem cell transplantation have a health-related quality of life comparable to the general population after 1 year? *Bone Marrow Transplant*. 1999;24:911–918.
12. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570–579.
13. McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant*. 1997;19:357–368.
14. EuroQol Research Foundation. EQ-5D-3L user guide: basic information on how to use the EQ-5D-3L instrument. Version 6.0. December 2018. Available at: https://euroqol.org/publications/user-guides. Accessed March 15, 2022.
15. Yost KJ, Eton DT. Combining distribution- and anchor-based approaches to determine minimally important differences: the FACIT experience. *Eval Health Prof*. 2005;28:172–191.
16. Pickard AS, Neary MP, Cella D. Estimation of minimally important differences in EQ-5D utility and VAS scores in cancer. *Health Qual Life Outcomes*. 2007;5:70.
17. Bell ML, King MT, Fairclough DL. Bias in area under the curve for longitudinal clinical trials with missing patient reported outcome data: summary measures versus summary statistics. *SAGE Open*. 2014;4. https://doi.org/10.1177/2158244014534858.
18. Palmer J, Kosiorek HE, Wolschke C, et al. Assessment of quality of life following allogeneic stem cell transplant for myelofibrosis. *Biol Blood Marrow Transplant*. 2019;25:2267–2273.
19. Horwitz ME, Chao NJ, Rizzieri DA, et al. Umbilical cord blood expansion with nicotinamide provides long-term multilineage engraftment. *J Clin Invest*. 2014;124:3121–3128.
20. Sanders JE, Hoffmeister PA, Storer BE, Appelbaum FR, Storb RF, Syrjala KL. The quality of life of adult survivors of childhood hematopoietic cell transplant. *Bone Marrow Transplant*. 2010;45:746–754.
21. Norkin M, Shaw BE, Brazauskas R, et al. Characteristics of late fatal infections after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019;25:362–368.
22. Chakravarti PB, Basch EM, Hirshfield KM, et al. Exploring open-label bias in patient-reported outcome (PRO) emotional domain scores in cancer trials. *J Clin Oncol*. 2018;36:e18702.
23. Atkinson TM, Wagner JS, Basch E. Trustworthiness of patient-reported outcomes in unblinded cancer clinical trials. *JAMA Oncol*. 2017;3:738–739.
24. Mouillet G, Efficace F, Thiery-Vuillemin A, et al. Investigating the impact of open label design on patient-reported outcome results in prostate cancer randomized controlled trials. *Cancer Med*. 2020;9:7363–7374.
25. U.S. Food and Drug Administration. FDA announces first of its kind pilot program to communicate patient reported outcomes from cancer clinical trials. June 23, 2020. Available at: https://www.fda.gov/news-events/press-announcements/fda-announces-first-its-kind-pilot-program-communicate-patient-reported-outcomes-cancer-clinical. Accessed March 15, 2022.
26. Matts ST, Webber CM, Bocell FD, Caldwell B, Chen AL, Tarver ME. Inclusion of patient-reported outcome instruments in US FDA medical device marketing authorizations. *J Patient Rep Outcomes*. 2022;6:38.
27. Mercieca-Bebber R, King MT, Calvert MJ, Stockler MR, Friedlander M. The importance of patient-reported outcomes in clinical trials and strategies for future optimization. *Patient Relat Outcome Meas*. 2018;9:353–367.