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Omidubicel Versus Standard Myeloablative Umbilical Cord Blood Transplantation: Results of a Phase III Randomized Study

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Abstract:
Omidubicel is an ex vivo expanded hematopoietic progenitor cell, and non-expanded myeloid and lymphoid cell product derived from a single umbilical cord blood unit. We report results of a phase III trial to evaluate the efficacy of omidubicel compared to standard umbilical cord blood transplantation (UCBT). Between January 2017 and January 2020, 125 patients aged 13-65 with hematologic malignancies were randomized to omidubicel versus standard UCBT. Patients received myeloablative conditioning and graft versus host disease (GvHD) prophylaxis with a calcineurin inhibitor and mycophenolate mofetil. The primary endpoint was time to neutrophil engraftment. The treatment arms were well balanced and racially diverse. Median time to neutrophil engraftment was 12 days (95% CI 10-14 days) and 22 days (95% CI 19-25 days) ($p<0.001$) for the omidubicel and control arms, respectively. The cumulative incidence of neutrophil engraftment was 96% and 89% for patients receiving omidubicel and control transplants, respectively. The omidubicel arm had faster platelet recovery (55% vs. 35% recovery by 42 days, $p=0.028$), a lower incidence of first grade 2/3 bacterial or invasive fungal infections (37% vs. 57%, $p=0.027$), and spent more time out of hospital during the first 100 days following transplant (median 61 vs. 48 days, $p=0.005$) than controls. Differences in GvHD and survival between the two arms were not statistically significant. Transplantation with omidubicel results in faster hematopoietic recovery and reduced early transplant-related complications as compared to standard UCBT. The results suggest that omidubicel may be considered as a new standard of care for adult patients eligible for UCBT.

Conflict of interest: COI declared - see note

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Clinical trial registration information (if any): ClinicalTrials.gov NCT02730299

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Running Title: Omidubicel versus Standard Umbilical Cord Blood

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Key Points:

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

Scientific Category: Transplantation and Cellular Therapy

Abstract

Omidubicel is an ex vivo expanded hematopoietic progenitor cell, and non-expanded myeloid and lymphoid cell product derived from a single umbilical cord blood unit. We report results of a phase III trial to evaluate the efficacy of omidubicel compared to standard umbilical cord blood transplantation (UCBT). Between January 2017 and January 2020, 125 patients aged 13-65 with hematologic malignancies were randomized to omidubicel versus standard UCBT. Patients received myeloablative conditioning and graft versus host disease (GvHD) prophylaxis with a calcineurin inhibitor and mycophenolate mofetil. The primary endpoint was time to neutrophil engraftment. The treatment arms were well balanced and racially diverse. Median time to neutrophil engraftment was 12 days (95% CI 10-14 days) and 22 days (95% CI 19-25 days) ($p<0.001$) for the omidubicel and control arms, respectively. The cumulative incidence of neutrophil engraftment was 96% and 89% for patients receiving omidubicel and control transplants, respectively. The omidubicel arm had faster platelet recovery (55% vs. 35% recovery by 42 days, $p=0.028$), a lower incidence of first grade 2/3 bacterial or invasive fungal infections (37% vs. 57%, $p=0.027$), and spent more time out of hospital during the first 100 days following transplant (median 61 vs. 48 days, $p=0.005$) than controls. Differences in GvHD and survival between the two arms were not statistically significant. Transplantation with omidubicel results in faster hematopoietic recovery and reduced early transplant-related complications as compared to standard UCBT. The results suggest that omidubicel 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.

Introduction

For over 30 years, umbilical cord blood has been an important source of hematopoietic stem cells for use in allogeneic hematopoietic stem cell transplantation. It is a particularly critical stem cell source for non-white patients who are underrepresented in the international adult donor registries.[1] Compared to 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 umbilical cord blood grafts, refinement of pre-transplant 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 resource utilization.[2,3] Early phase studies have demonstrated that ex vivo expansion of umbilical cord blood (UCB) stem cells prior to transplantation has the potential to address this critical shortcoming. By expanding both hematopoietic stem and progenitor cells, the time to neutrophil recovery following myeloablative conditioning can be even more rapid than that following a mobilized peripheral blood stem cell graft. [4-7]

Omidubicel (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 non-expanded, CD133- fraction. Nicotinamide, the active agent in the culture system, inhibits differentiation and enhances functionality of cultured hematopoietic stem and progenitor cells. Pre-clinical 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 homing and engraftment potential.[8] The ability of nicotinamide to expand both committed and long-term repopulating hematopoietic stem cells was confirmed in early phase studies of omidubicel.[6,9] In this study, we compared the outcomes of a myeloablative allogeneic stem cell transplantation using omidubicel versus standard umbilical cord blood 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 completed in January 2020. Randomization was performed at the Emmes Company in a 1:1 ratio using minimization factors of age, center, disease risk index (DRI), and intention to use 1 or 2-unit UCB grafts if randomized to the control arm. Randomization occurred as sites enrolled participants using Emmes's centralized data entry system. The primary endpoint was time to neutrophil engraftment. Secondary endpoints were platelet engraftment by 42 days, incidence of grade 2-3 bacterial or invasive fungal infection during the first 100 days and days alive and out of the hospital for the first 100 days following transplantation. Additional planned endpoints included assessment of safety, non-relapse mortality, relapse, overall and disease-free survival, acute and chronic graft versus host disease (GvHD), 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, applicable with local regulations and with the principals of Declaration of Helsinki. Study registration: ClinicalTrials.gov NCT02730299.

Patients

Eligible patients were 12-65 years old with high-risk hematologic malignancies, were candidates for myeloablative allogeneic hematopoietic cell transplantation (HCT), and had no readily available matched sibling or matched unrelated adult donor. Patients with "marked" or "3+" bone marrow fibrosis or chronic lymphocytic leukemia were excluded. Patients were required to have an available umbilical cord blood 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 x 10^9, a TNC dose of $\geq$ 1.5 x 10^7/kg and CD34+ cell count of $\geq$ 8 x 10^6. This unit was designated for use prior to randomization and required to be used in either arm of the study. For patients randomized to the control arm, a double cord blood graft was mandated when the omidubicel-designated unit (designated prior to randomization and required to be used) was HLA-matched at 5-6/6 and contained <2.5 x 10^7 TNC/kg or <1.2 x 10^5 CD34+ cells/kg OR HLA 4/6 matched and contained <3.5 x 10^7 TNC/kg or <1.7 x 10^5 CD34+ cells/kg. Patients were also required to have available back-up cord blood unit(s). The presence of donor-specific antibodies to HLA A, B, C or DRB1 antigens (mean florescence intensity >3000) was not permitted. A detailed list of inclusion and exclusion criteria are provided in the protocol document (Supplemental Material). Planned enrollment was 120 patients. One hundred twenty-five patients were randomized at 33 sites in North and South America, Europe and Singapore. Participating centers and principal investigators are listed in supplementary Table 1. The population of 125 randomized subjects is analyzed as the Intent-to-Treat population (ITT), using the randomized treatment assignment. Of the 125 randomized participants, 117 received an omidubicel or UCB transplant by Day 90 post randomization. This is the transplanted population (TP), which is also analyzed by treatment assignment. The as-treated population includes 108 subjects 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 negative, T-cell–containing flow-through fraction was retained and re-cryopreserved. The CD133+ fraction was cultured in the presence of Flt-3 ligand, stem cell factor, thrombopoietin, IL-6 and nicotinamide for 21 ± 2 days and then cryopreserved. Both fractions were transported together to the transplant center.

Treatment

Three alternative myeloablative conditioning regimens were permitted for study participants: two containing total body irradiation (TBI) and one with 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 15mg/kg three times daily (maximum daily dose 3 grams) starting three days prior to transplantation. Mycophenolate mofetil was continued for a minimum of 60 days and the calcineurin inhibitor for minimum of 100 days following transplantation in the absence of toxicity or relapse.

Supportive Care

Granulocyte-colony stimulating factor (5µg/kg recipient body weight) was given daily starting on day +1 following transplantation until the absolute neutrophil count exceeded 1000 cells/µl. Anti-viral and anti-fungal prophylaxis was administered at the discretion of the

transplant center. Anti-bacterial prophylaxis following transplantation was required by protocol. The agent used was left to 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, 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 following transplantation. The time to engraftment of neutrophils $\geq$500/µl and platelets >20,000/µl was defined as per 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 (Supplementary Table 2).

Statistical Considerations

The main comparisons of the primary and secondary endpoints as well as mortality endpoints were conducted using intention-to-treat (ITT) analysis. Cox proportional hazard models were used in the analysis of disease-free and overall survival, with randomized 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 transplanted population defined as all patients randomized who received an UCBT, grouped by treatment to which they were allocated. GvHD-free, relapse-free survival was evaluated in the as-treated population, grouped by treatment received. The primary endpoint, time to neutrophil engraftment, was compared between treatment groups using a Mann-Whitney-based statistic. A value of 43 days was assigned for transplanted patients who did not engraft by 42 days following

transplantation or patients who did not receive a transplant. P-values for this and other protocol-specified ITT analyses were calculated using the re-randomization distribution.[10] Sample size was chosen to provide at least 90% power for the primary endpoint analysis, based on information on engraftment times derived from the Phase 2 study and the CIBMTR database. Secondary endpoints of proportion of patients with grade 2-3 bacterial or invasive fungal infections up to 100 days post-transplant 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. Cumulative incidence differences were also analyzed for non-relapse mortality and for relapse. For non-ITT analyses, neutrophil engraftment was compared using the Wilcoxon Rank Sum test or Fisher's test and time to platelet engraftment was compared using Gray's test. GvHD for transplanted patients was compared using a z-test on the cumulative incidence difference. Infection densities were compared using the generalized estimating equation approach for a linear model with two periods (0-30 and 31-365 days post-transplant) 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 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 were calculated using bootstrap methods; the multivariable models and GEE models used asymptotic confidence intervals. The multivariable Cox models, the GEE models, CD34+ associations with neutrophil engraftment, Gray's test for platelet engraftment, GvHD-free, relapse-free survival, and moderate/severe chronic GVHD analyses were post hoc analyses. The endpoints were evaluated after all evaluable patients completed six months of follow-up following transplantation; study follow-up is ongoing.

RESULTS

Patient and Stem Cell Transplant Characteristics

Demographics and baseline characteristics were well-balanced across the two arms (Table 1). One hundred twenty-five patients (median age 41; range 13-65) were randomized to receive either omidubicel (n=62) or standard single (33%) or double (67%) umbilical cord blood grafts (n=63). Ten patients randomized to the omidubicel arm did not receive omidubicel per-protocol. Eight patients randomized to the standard UCB arm were not transplanted per protocol (Figure 1). Most patients had AML (48%) or ALL (33%). DRI 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 treated with omidubicel were transplanted at a median 41 days following randomization, compared to 26 days for patients treated with standard cord transplant.

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 prior to expansion, as reported by the cord blood bank prior to cryopreservation, was 0.23 x 10^8 (range 0.11-0.55 x 10^8) and 0.14 x 10^8 (range 0.09-0.4 x 10^8), respectively. Following expansion, the content of the omidubicel unit increased to a median 6.6 x 10^8 (range 2.8-39 x 10^8) CD34+ cells. Median CD34+ cell expansion was 130-fold (range 32-233). The median CD34+ cell dose of omidubicel and control grafts was 9.0 x 10^6/kg (range 2.1-47.6 x 10^6/kg) and 0.3 x 10^6/kg (range 0.1-1 x 10^6/kg), respectively. The CD3+ T-cells in the omidubicel graft were contained solely in the unexpanded, CD133 negative fraction.

The median CD3+ content of the omidubicel grafts prior to cryopreservation was 210 x 10^6 CD3+ cells (range, 71 – 640), and 3 x 10^6 CD3+ cells/kg (range, 1.1 – 12.4). This compared to a median 412.9 x 10^6 CD3+ cells (range, 4.4 – 989.8), and 4.6 x 10^6 CD3+ cells/kg (range, 0 –

14.8) for the control grafts. CD3 content was enumerated post-thaw and prior to infusion from a subset of 25 control patients. Thus, the observed difference in CD3 content is underestimated due to further cell loss after thaw of the omidubicel product.

Hematopoietic Recovery

The median time to neutrophil recovery as per intent to treat analysis was 12 days (95% CI 10-14 days) for those randomized to omidubicel and 22 days (95% CI 19-25 days) for controls ($p<0.001$) (Table 2). The cumulative incidence of neutrophil engraftment by day 42 following transplantation for patients receiving omidubicel (as-treated population, n=52) was 96% at a median of 10 days (95% CI 8-13 days) compared to 89% at median of 20 days (95% CI 18-24 days) for the controls (n=56) ($p<0.001$) (Figure 3A). For patients transplanted with omidubicel, higher total CD34+ cell counts and CD34+ cell doses (per weight) were associated with shorter times to neutrophil engraftment (Figure 4 - correlations: total cells $r=-0.66$, $p<0.001$; cell dose $r=-0.62$, $p<0.001$).

The cumulative incidence of platelet engraftment by day 42 following transplantation for patients randomized to omidubicel was 55% versus 35% for controls ($p=0.028$) (Table 3). For the patients transplanted with omidubicel, the cumulative incidence of platelet engraftment by day 100 following transplantation was 83% at a median of 37 days (95% CI 33-42 days) versus 73% at median of 50 days (95% CI 42-58 days) for the controls ($p=0.023$) (Figure 3B).

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

Graft versus Host Disease

Among the patients randomized to omidubicel (n=59) or standard cord blood (n=58), who received a transplant, the incidence of grade II-IV acute GvHD at day 100 was similar, 56% versus 43% (13% difference: 95%CI, –6% - 30%, p=0.18), respectively (Figure 5A). Grade III-IV acute GvHD at day 100 was also similar in the omidubicel and control arms, 14% versus 21% (-7% difference; 95%CI, –21%-7%, p=0.33) (Figure 5B). The cumulative incidence of all chronic GvHD at one year was 35% for the omidubicel arm and 29% for the controls (6% difference; 95% CI, –14%-25%, p=0.57) (Figure 5C). The 1-year cumulative incidence of moderate to severe chronic GvHD was 27% for omidubicel and 21% for the controls (6% difference; 95%CI, –11%-24%, p=0.49)

Non-relapse mortality, Relapse, Disease-free Survival and Overall Survival

The median follow-up of all patients was 10 months following transplantation (range 1-19 months). Using ITT analysis, the cumulative incidence of non-relapse mortality at 210 days following randomization was 11% vs. 24% (p=0.09) for the omidubicel and control arms, respectively (Figure 6A). The cumulative incidence of disease relapse at 15 months following randomization was 25% vs. 17% (p=0.32) for the omidubicel and control arms, respectively (Figure 6B). During the time from randomization to transplant, relapse was reported in 4 subjects 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 post randomization (Figure 1).

The adjusted hazard ratio (HR) for treatment failure (relapse or death, inverse of relapse-free survival) with omidubicel versus standard UCB was 0.79 (95% CI, 0.45 to 1.38; p=0.4). The adjusted HR for mortality with omidubicel versus standard UCB was 0.57 (95% CI, 0.3 to

1.1; p=0.09) (Figure 6CD). The 1-year GvHD-free, relapse-free survival for the omidubicel arm was 36% and for standard UCBT was 45% (p=0.56).

Eleven deaths were reported among the as-treated population of patients transplanted with omidubicel, and 18 deaths among the patients treated with a standard cord blood graft. As reported by the study investigators, 2 patients transplanted with omidubicel died from relapsed disease, compared to 4 patients transplanted with standard cord blood graft. Among the treatment-related causes of death, 4 patients in each group died in the setting of GvHD.

Transplant Course and Toxicity

Patients randomized to the omidubicel graft spent more days alive and out of hospital in the first 100 days following transplantation than those randomized to UCBT; the median time was 61 days (range; 0-89 days) and 48 days (range; 0-84 days), respectively (p=0.005). The median time from transplant to discharge from the hospital was 27 days vs. 35 days for the omidubicel and control arms, respectively (p=0.005). From randomization and up to 100 days following transplantation, the cumulative incidence of first grade 2-3 bacterial or invasive fungal infections was 37% for patients randomized to omidubicel and 57% for the standard UCBT recipients (p=0.03) (Figure 7A). The cumulative incidence of first grade 3 viral infection during the first year following transplant was also lower for those randomized to omidubicel (10% versus 26%, p=0.02) (Figure 7B).

To account for the possibility of multiple infections per single patient and relative differences in periods of risk between the treatment groups, a comparison of infection density during the first year following transplantation was performed. The risk ratio for all infections, irrespective of severity, was significantly lower among recipients of omidubicel compared to 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 omidubicel 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 possibly related to the stem cell product was similar in the two arms (40% versus 41% for omidubicel and standard cord blood grafts, respectively). A breakdown of the treatment- emergent adverse events in both arms of the study is provided in supplementary table 3. Those treatment-emergent events reported as related to the cord blood infusion are outlined in supplementary table 4. Following randomization and prior to starting pre-transplant conditioning, 10 serious adverse events (SAE's) were reported for those assigned to omidubicel and 8 SAE's reported for those assigned to a standard cord blood graft.

Immune reconstitution

Quantitative recovery of lymphoid subsets was monitored at 1, 3, 6, and 12 months following transplantation in a subset of patients on both arms of the study. Despite the lower numbers of CD3+ cells in omidubicel compared to the standard cord blood grafts, the pace of recovery to normal levels of CD3+, CD4+, CD8+, CD19+ and CD56+/CD16+ NK cells was similar in both groups (Supplementary Figure 1A-E).

DISCUSSION

Omidubicel is an ex-vivo expanded, cord blood derived stem cell graft that was designed to address the major limitations of adult umbilical cord blood transplantation. The three main findings from this multi-center randomized trial comparing omidubicel to a standard cord blood graft were: 1) the study confirmed that omidubicel safely addresses the most vexing limitation of umbilical cord blood transplantation, which is the delay in hematopoietic recovery. Omidubicel reduced by 10 days the median time to neutrophil recovery, and by 13 days the

median time to platelet recovery. 2) omidubicel reduced the incidence of infectious complications and time spent in the hospital during the early post-transplant period. 3) the study demonstrated the feasibility and safety of delivering a personalized, manufactured hematopoietic stem cell product to transplant centers around the world.

Multiple techniques designed to expand cord blood stem and progenitor cells have been reported.[5-7,11-13] Omidubicel (previously known as NiCord) is the first to complete phase III testing; the results of which were consistent with the observations from earlier studies examining both safety and efficacy.[6,9] The omidubicel graft provides a CD34+ cell dose that is comparable to an adult mobilized peripheral blood stem cell graft. The 12-day median time to neutrophil recovery is similar to mobilized peripheral blood suggesting both graft sources are enriched for active hematopoietic progenitor cells.[14] Furthermore, long-term follow-up from the earlier studies of omidubicel[6] suggest robust, durable engraftment for over 10 years, confirming the persistence and possibly 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 bone marrow versus PBSC grafts showed that a 5-day reduction in time to neutrophil recovery following PBSC translated into a reduction in bacterial infections.[15] Conversely, a large multicenter study using the CIBMTR database demonstrated delayed hematopoietic recovery following standard adult cord blood transplantation resulted in prolonged hospital utilization.[3] In line with the prior studies, rapid hematopoietic recovery following omidubicel transplantation translated into clinical benefit by reducing infections and time spent in the hospital during the first 100 days following transplantation. Importantly, although omidubicel grafts contain a lower T-cell content, the recovery of T-cells following transplantation is comparable to standard cord blood, and the risk of viral infections was lower than standard cord blood throughout the first year following transplantation. The reduced risk of viral infections for recipients of omidubicel 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.

The study establishes for the first time, the feasibility of providing a personalized, ex vivo expanded hematopoietic stem cell graft to recipients throughout the world. This was made possible with logistical support provided by both the sponsor and the regional cord blood registries. For example, the National Marrow Donor Program provided participating centers with advice surrounding selection of units meeting pre-specified characteristics for expansion. Furthermore, they worked with the sponsor to facilitate transport of the unit from the cord blood bank to the cell processing facility. Of note, while the added logistical complexity surrounding production of an ex vivo expanded cord blood graft led to a median 2-week delay in time from randomization to transplantation, this did not result in an increased risk of pre-transplant 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 hematopoietic stem cell graft.

The encouraging results of transplantation with omidubicel have important implications for minority populations in need of allogeneic HCT. Forty-four percent of the patients treated on study were non-Caucasian, a population known to be underrepresented in the world-wide unrelated adult donor and cord blood registries. The underrepresentation of cord blood grafts from black donors has necessitated the use of smaller units compared to white recipients resulting in inferior outcome.[16] Cord blood expansion technologies allow for the use of smaller, better matched units with the aim of improving outcome.

The study has important limitations. While the progression-free and overall survival endpoints trended higher for those receiving omidubicel, the study was not powered to detect a statistically significant difference in these critical endpoints. Adult cord blood transplant trials

have been notoriously difficult to complete, with many previous multicenter trials closing early with incomplete accrual.[17,18] It was for this reason that alternative endpoints of clinical benefit were chosen allowing for a more realistic sample size. Resource utilization surrounding transplantation of umbilical cord blood grafts has historically exceeded that of adult donor stem cell grafts. The reduction in time to engraftment, hospitalization duration and infectious complications is expected to reduce resource utilization over a standard cord blood graft. While not presented in this report, resource utilization data has been captured and will allow for confirmation of this expectation. These, and other pressing questions such as the performance of omidubicel transplantation following reduced intensity conditioning and comparative outcomes to other graft sources and specific disease types will need to be addressed in future studies.

Hematopoietic recovery following omidubicel transplantation was faster, reduced early transplant-related complications and reduced number of days hospitalized as compared to 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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Manuscript writing: MEH wrote the manuscript. All authors reviewed and approved the manuscript.

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Table 1. Patient Characteristics

Characteristic	Omidubicel no. (%)	Standard UCB no. (%)
Total randomized	62 (100)	63 (100)
Gender		
Female	30 (48)	23 (36)
Male	32 (52)	40 (64)
Age (years)		
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)
Weight – median (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)
Other/Unknown	9 (14)	7 (11)
Ethnicity		
Hispanic or Latino	10 (16)	6 (10)
Primary diagnosis		
AML	27 (43)	33 (52)
First complete morphologic remission (CR1)	18	22
Second remission (CR2)	9	11
ALL	20 (32)	21 (34)
High risk first complete morphologic remission (CR1)	13	11
Second complete morphologic remission (CR2)	6	10
Third or subsequent complete morphologic remission (CR3+)	1	0
MDS	6 (10)	3 (5)
High	2	0
Intermediate-1 (INT-1)	3	1
Intermediate-2 (INT-2)	1	2
CML	4 (7)	2 (3)
Lymphoma	3 (5)	2 (3)
Hodgkin lymphoma - Stable disease (SD)	0	1
T-cell Non-Hodgkin lymphoma -	3	1
Other rare disease	2 (3)	2 (3)
Adult T-cell leukemia/lymphoma - First remission (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)
HCT-specific co-morbidity index		
0	12 (19)	13 (20)
1-2	19 (31)	18 (29)
3+	31 (50)	32 (51)
Intended cord blood 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 1350cGy, Fludarabine 160mg/m^2, Thiotepa 10mg/kg	7 (11)	9 (15)
TBI 1320cGy, Fludarabine 75mg/m^2, Cyclophosphamide 120mg/kg	24 (39)	21 (33)
Thiotepa 10mg/kg, Busulfan 12.8mg/kg, Fludarabine 150mg/m^2	27 (44)	28 (44)
Not transplanted or off-protocol regimen	4 (6)	5 (8)

Table 2. Time to Neutrophil Engraftment

		Cumulative Incidence		
Randomized Treatment Group	**N**	**Median Time to Neutrophil Engraftment (Days) ***	**95% CI**	**Mann-Whitney-Based Test P-Value**
Omidubicel	62	12.0	(10.0, 14.0)	p<0.001
Control	63	22.0	(19.0, 25.0)	

*Patients not transplanted or who did not engraft on/before Day 42 following transplantation were assigned to Day 43

Table 3. Platelet Engraftment by Day 42

Randomized Treatment Group	N	Day 42 Cumulative Incidence	Difference in Cumulative Incidence	95% CI	P-Value
Omidubicel	62	0.55	0.20	(0.03, 0.35)	0.028
Control	63	0.35			

Figure Legends

Figure 1. Consort Diagram. Randomization and treatment of patients

Figure 2. Omidubicel and control cord Blood graft characteristics. Median (range) Total nucleated cell content, median (range) CD34+ cell content and median (range) CD34+ cell doses are shown prior to and following ex-vivo expansion of the umbilical cord blood unit. Pre-expansion values represent cell content as reported by the cord blood bank prior to cryopreservation of the umbilical cord blood unit. CBU; Cord Blood Unit.

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

Figure 4. Correlation of CD34+ cell content to 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% confidence interval around the predicted log time. The regression line is log days to engraftment = 5.70 - 0.50 log (10^6 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% confidence interval around the predicted log time. The regression line is log days to engraftment = 4.30 – 0.42 log (10^5 cells/kg).

Figure 5. Cumulative incidence of (A) acute grade II-IV graft versus host disease (GvHD), (B) acute grade III-IV GvHD, (C) chronic GvHD. Analysis was performed in the transplanted population by randomized treatment.

Figure 6. Outcomes of omidubicel and standard umbilical cord blood transplantation, intent-to-treat analysis. (A) cumulative incidence of non-relapse mortality. (B) cumulative incidence of relapse. (C) probability of disease-free survival. (D) probability of overall survival.

Figure 7. Infections following transplantation. (A) Cumulative incidence of first Grades 2-3 bacterial infection or invasive fungal infections- during the first 100 days following transplantation; (ITT population). (B) Cumulative incidence of first Grade 3 viral infection over the first year; (ITT population). All infection events occurring following randomization are accounted for in the analysis. (C) Relative Risk (95% CI) for bacterial, viral and all infections at one year following transplantation in the omidubicel and the standard umbilical cord blood groups; (as-treated population). (D) Grades 1-3 viral infections at one year following transplantation by species (as-treated population).

Figure 1.

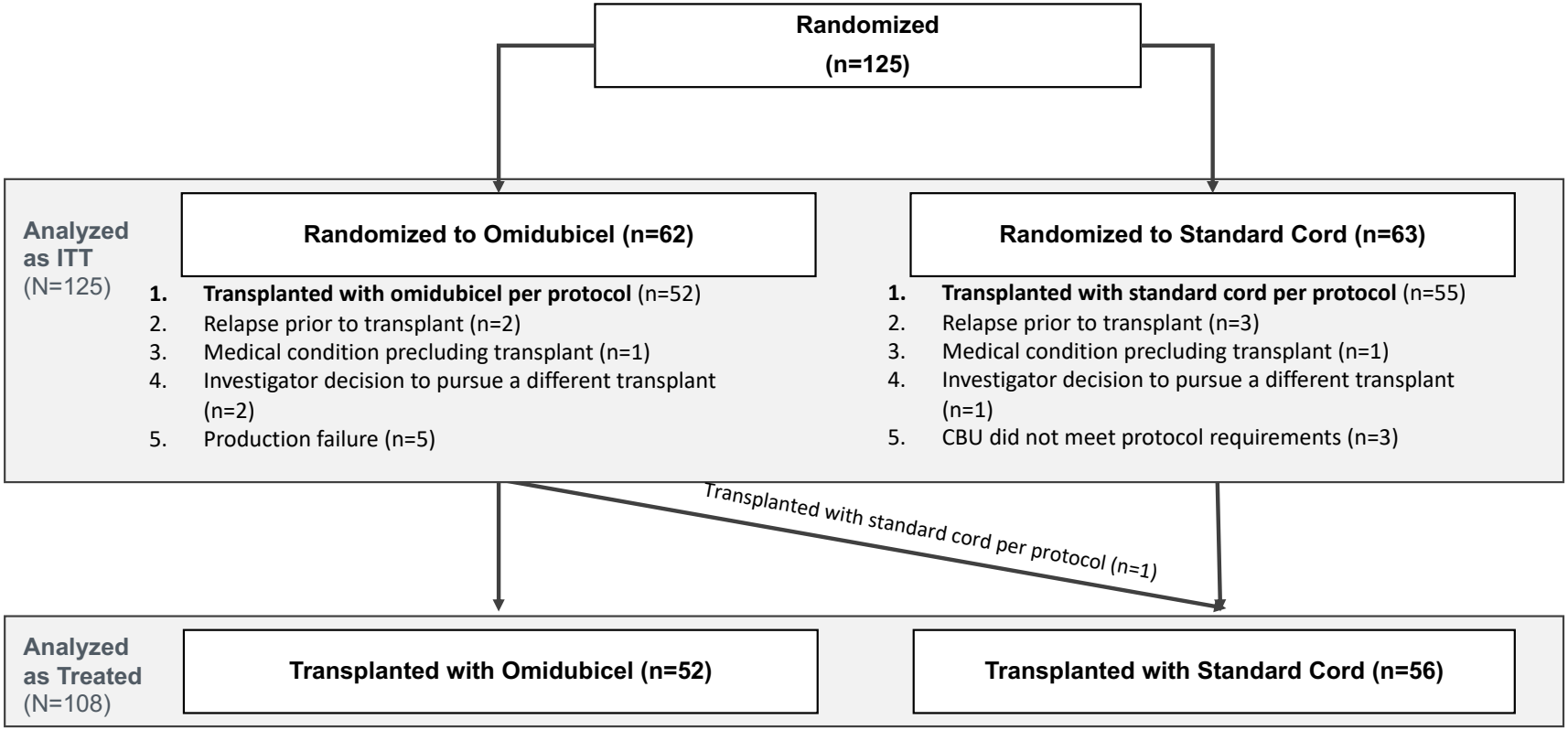


Figure 2 Graft Characteristics (AT)

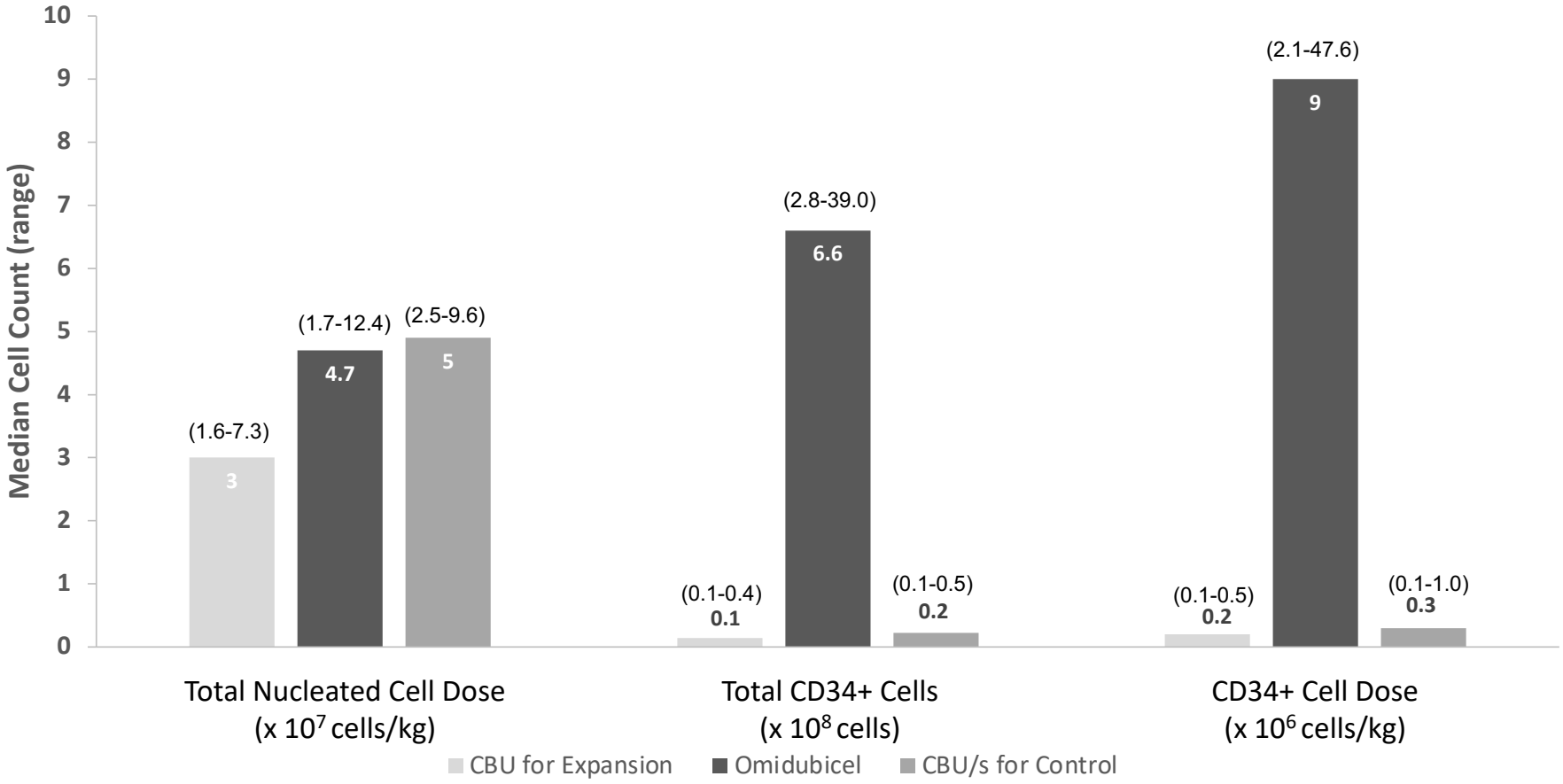
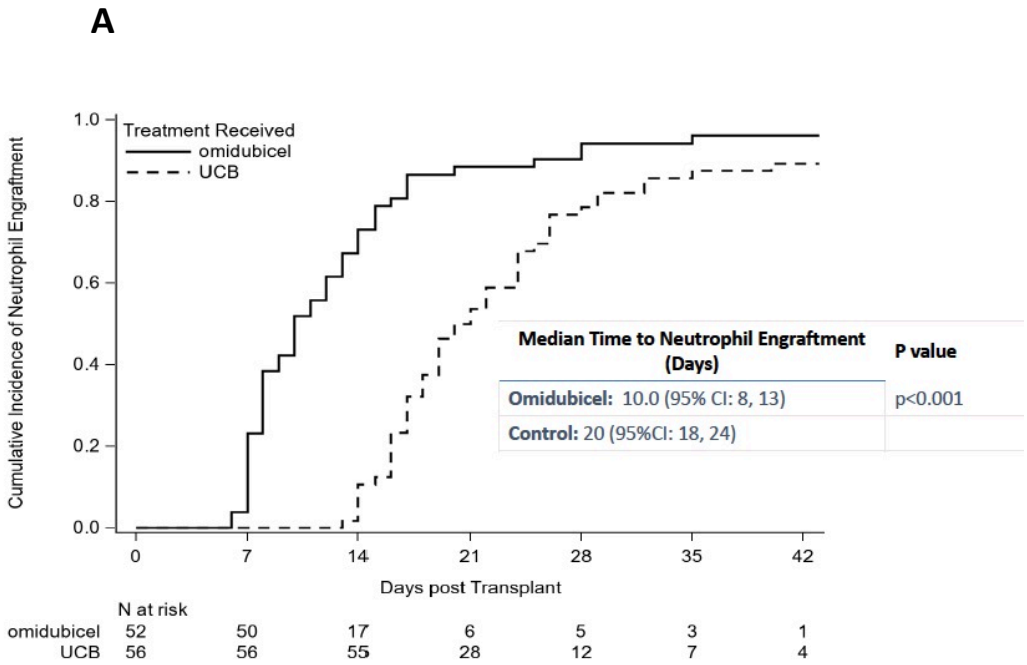


Figure 3 Neutrophil and Platelet Engraftment (AT)



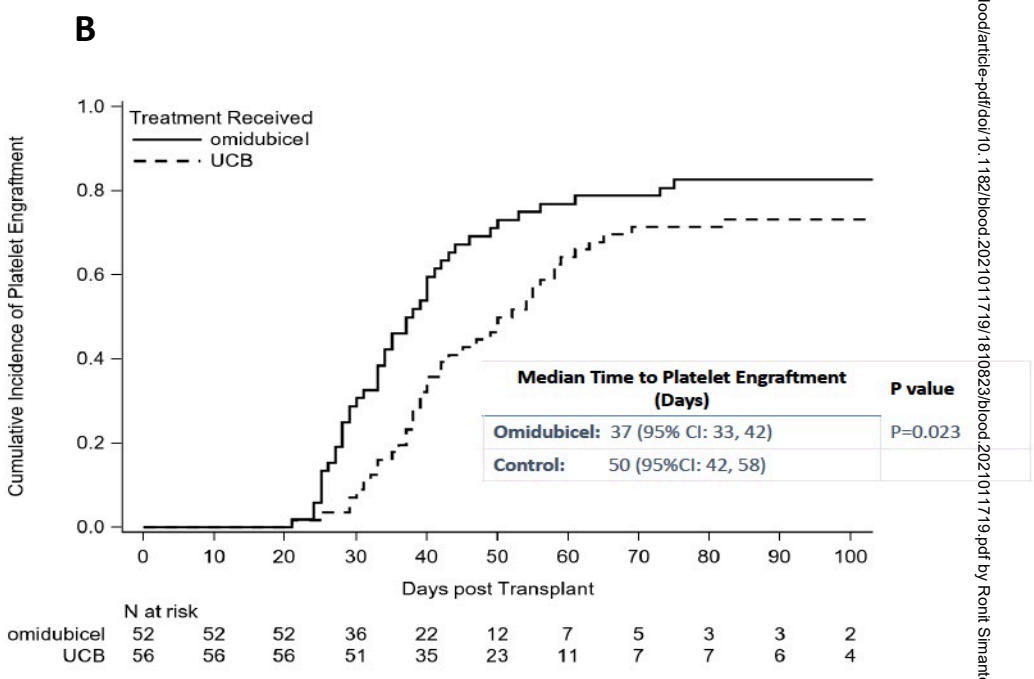


Figure 4. Correlation of CD34+ cell content to neutrophil engraftment.

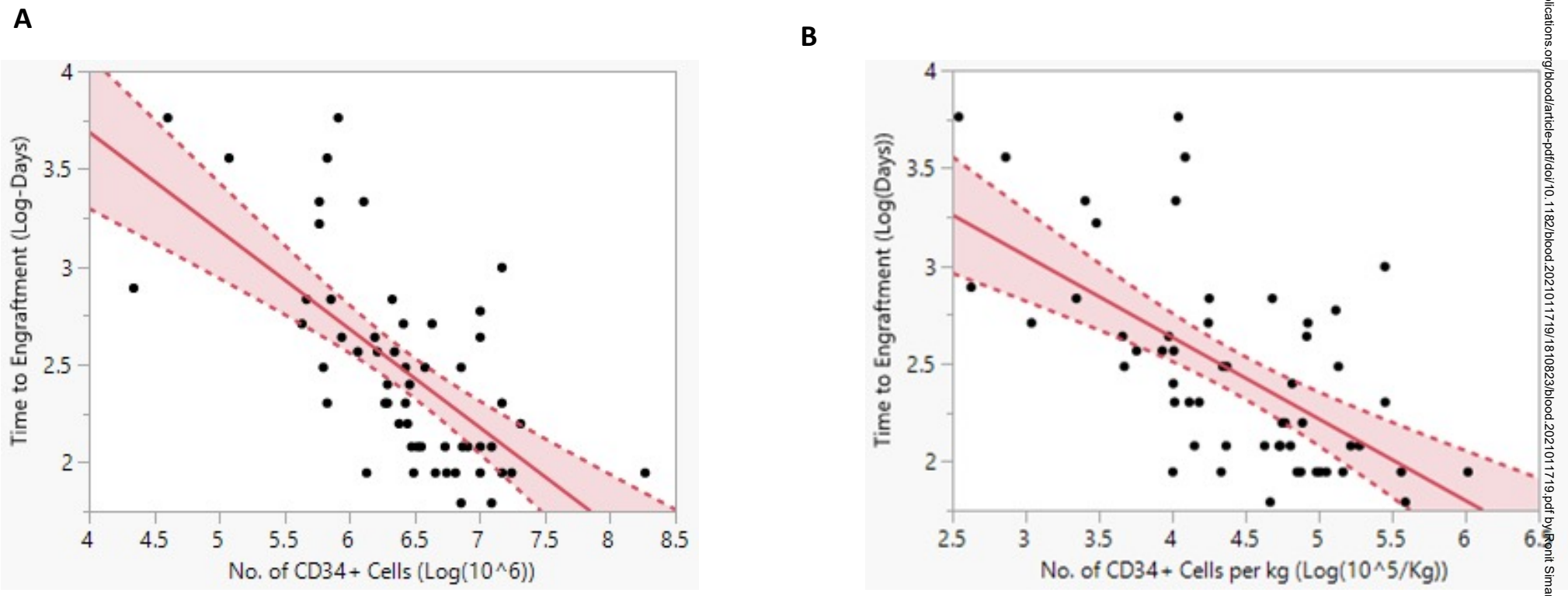
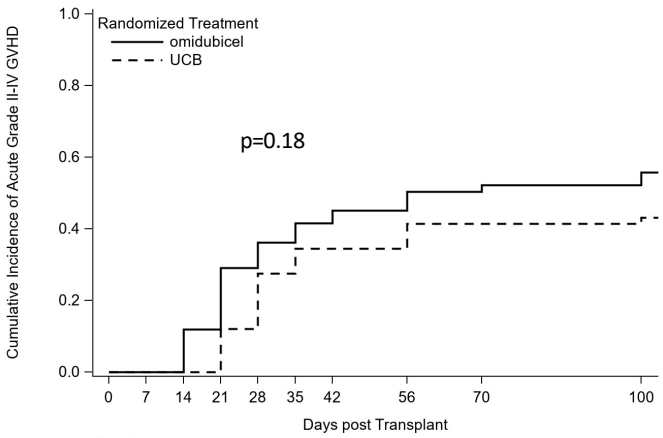
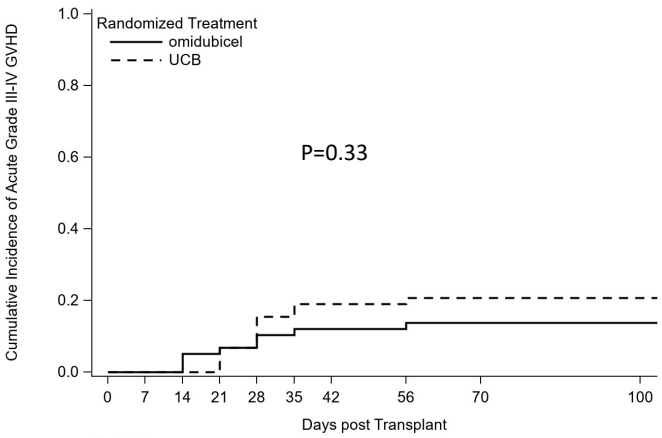


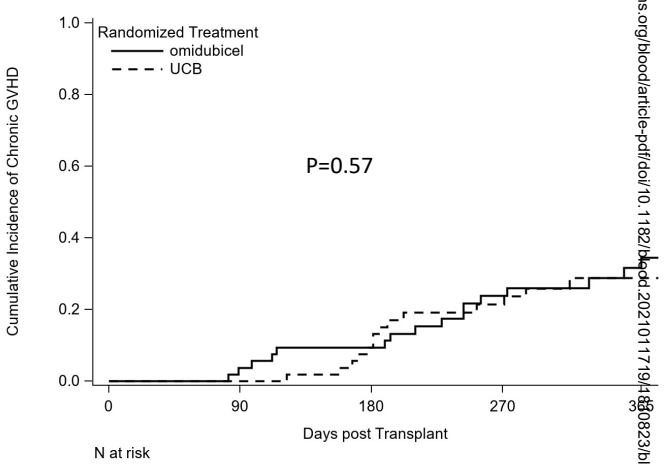
Figure 5. Graft versus Host Disease



N at risk										
omidubicel	59	59	59	51	39	35	30	27	24	22
UCB	58	58	58	58	50	41	35	30	25	23



N at risk										
omidubicel	59	59	59	55	52	50	47	46	44	42
UCB	58	58	58	58	53	48	44	39	37	34



N at risk				
omidubicel	59	47	37	23
UCB	58	46	32	21

Figure 6. Non-relapse mortality, Relapse, Disease-free survival, Overall Survival

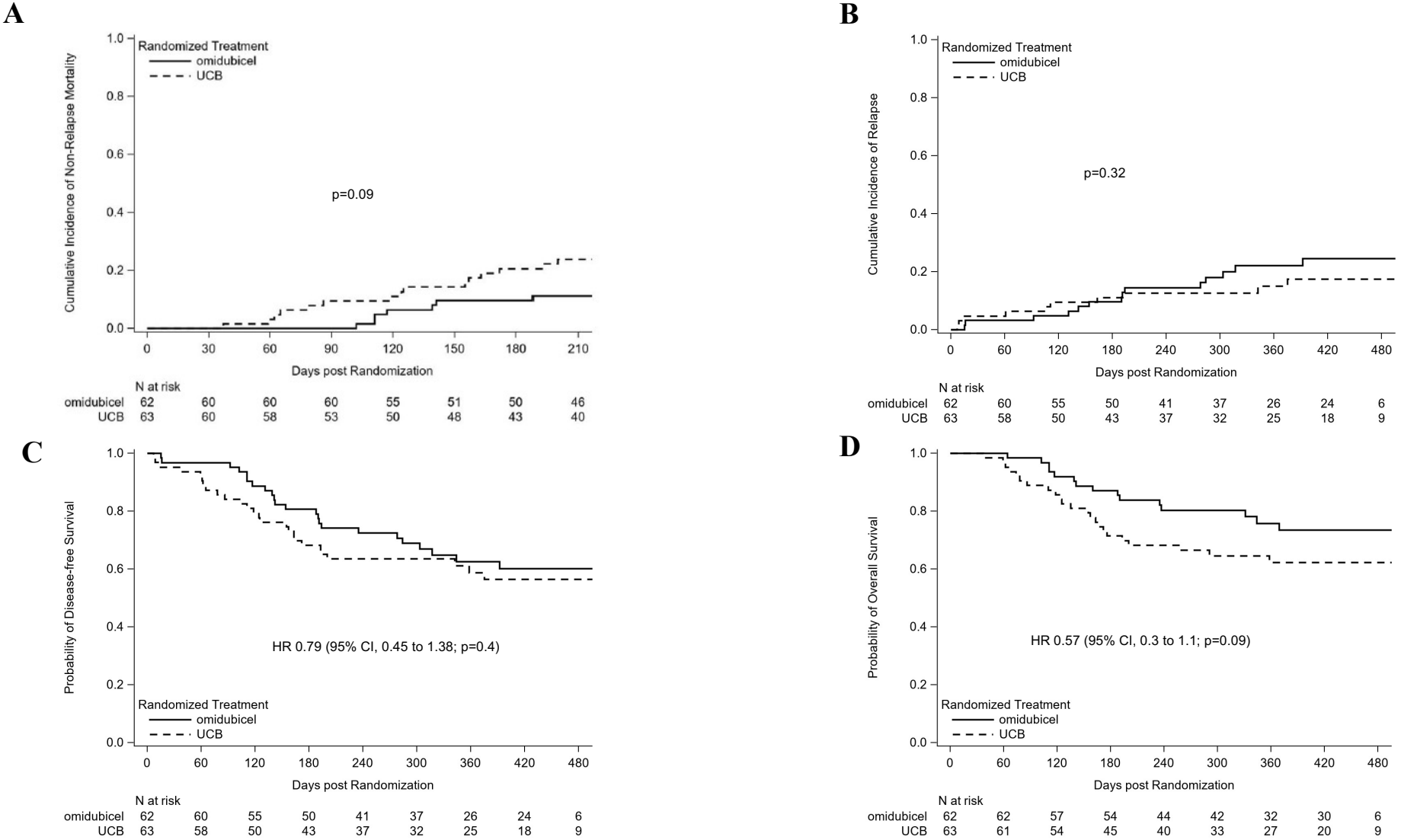
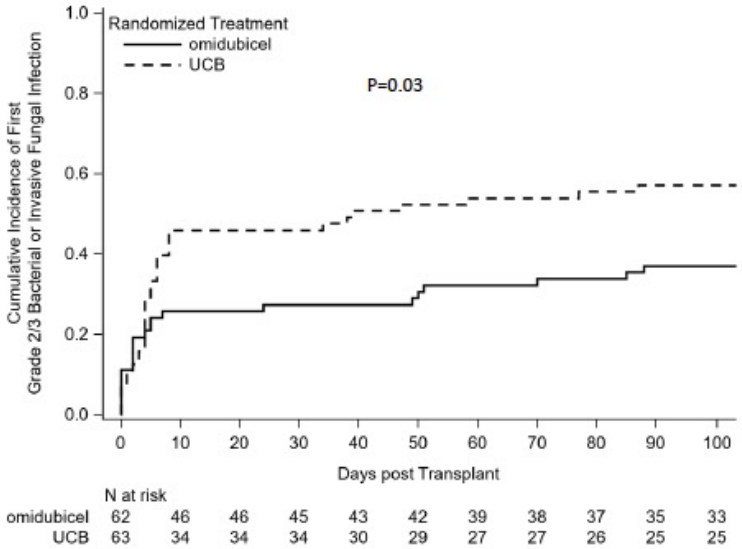


Figure 7. Infections

A



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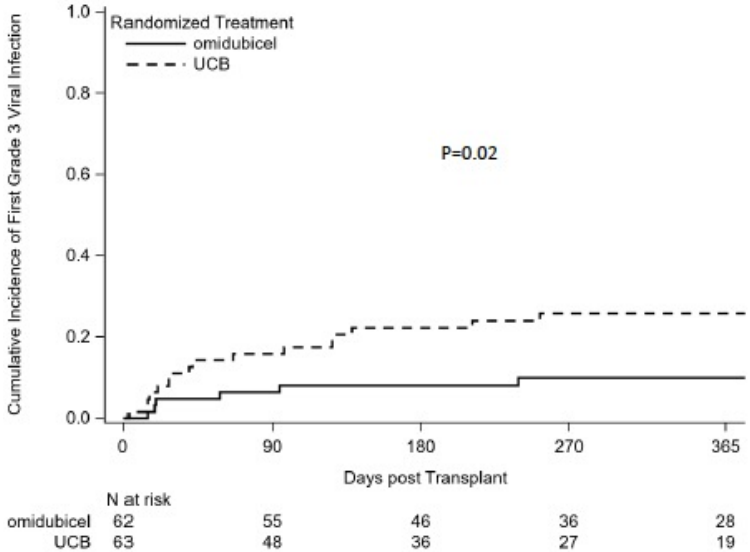
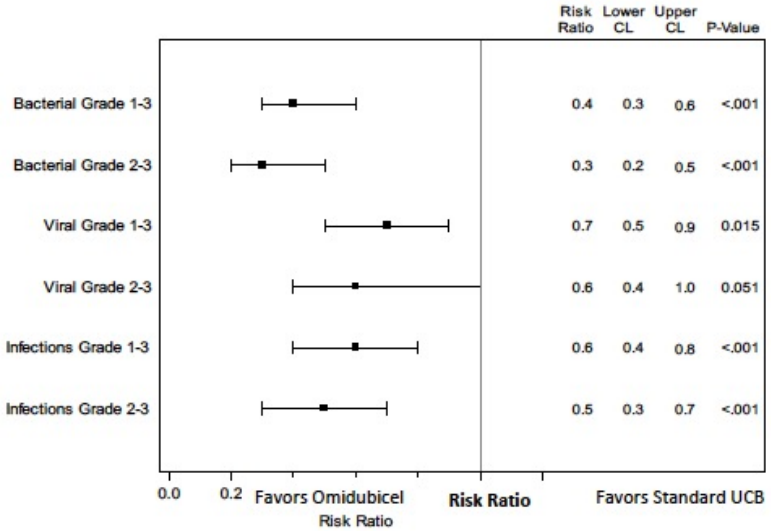


C



D