Clinical trial results:
A Randomized, Multi-Center, Phase III Trial of Calcineurin Inhibitor-Free Interventions for Prevention of Graft-versus Host-Disease

Summary

EudraCT number	2015-000602-18
Trial protocol	DE
Global end of trial date	05 October 2020

Results information

Result version number	v1 (current)
This version publication date	03 August 2023
First version publication date	03 August 2023

Trial information

Trial identification

Sponsor protocol code	BMT-CTN#1301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02345850
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Heart, Lung, and Blood Institute (NHLBI)
Sponsor organisation address	401 N. Washington St., Suite 700, Rockville, United States,
Public contact	Clinical Trials Information, EMMES Corporation, 001 301-251-1161,
Scientific contact	Clinical Trials Information, EMMES Corporation, 001 301-251-1161,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 October 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 October 2020
Global end of trial reached?	Yes
Global end of trial date	05 October 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the randomized trial is to compare chronic GVHD/relapse-free survival (CRFS) after HSCT across two CNI-free interventions and Tac/Mtx control.

Protection of trial subjects:

The trial compared standard of care interventions using IMPs with marketing authorization/ authorities approval in EEA.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 October 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United States: 344
Worldwide total number of subjects	346
EEA total number of subjects	2

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	2
Adults (18-64 years)	344
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

NA

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	CD34 Selection Arm

Arm description:

Mobilized CD34-selected Peripheral Blood Stem Cell graft Following screening and enrollment, the donor of patients randomized to the CD34-selection arm will receive mobilization therapy with once daily Granulocyte Colony Stimulating Factor (G-CSF). Mobilization will begin on Day -5 prior to the patient's transplant date. Leukapheresis will be performed on a continuous flow cell separator according to institutional standards and will commence on the morning of the fifth day of G-CSF treatment. The anti-coagulant used for the procedure will be acid citrate dextrose (ACD). Decisions concerning the need for further product collection will be based on the known or projected enriched CD34+ cell content of the previously collected products.

Arm type	Experimental
Investigational medicinal product name	Allogeneic stem cells from peripheral blood CD34 selected
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Mobilized CD34-selected Peripheral Blood Stem Cell graft: Mobilized CD34-selected PBSC grafts will be administered on Day 0 to all patients according to individual institutional guidelines after appropriate processing and quantification has been performed by the local laboratory. Stem cells are administered through an indwelling central venous catheter. If infusion occurs over two days, Day 0 is the first day the infusion is initiated.

Arm title	Post-Transplant Cyclophosphamide

Arm description:

Unmanipulated Bone Marrow Graft with Cyclophosphamide

Arm type	Experimental
Investigational medicinal product name	Human allogeneic hematopoietic stem cells from bone marrow
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Unmanipulated BM grafts will be administered on Day 0 to all patients according to individual institutional guidelines after appropriate processing and quantification has been performed by the local laboratory. Stem cells are administered through an indwelling central venous catheter. If infusion occurs over two days, Day 0 is the first day the infusion is initiated.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Mesna will be given in divided doses IV 30 min pre- and at 3, 6, and 8 hours post-cyclophosphamide or administered per institutional standards. Mesna dose will be based on the cyclophosphamide dose being given. The total daily dose of Mesna is equal to 80% of the total daily dose of cyclophosphamide. Cyclophosphamide 50 mg/kg will be given on Day 3 post-transplant (between 60 and 72 hours after marrow infusion) and on Day 4 post-transplant (approximately 24 hours after Day 3 cyclophosphamide). Cyclophosphamide will be given as an IV infusion over 1-2 hours (depending on volume).

Arm title	Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Arm description:

Unmanipulated bone marrow graft with Tacrolimus(Cyclopsorin)/Methotrexate GVHD prophylaxis. Tacrolimus(Cyclosporin) will be maintained at therapeutic doses for a minimum of 90 days. Methotrexate will be dosed at 5-15mg/m^2 for a maximum of 4 doses post-transplant. Cyclosporine may be substituted for tacrolimus in germany or if the patient is intolerant of tacrolimus or per institutional practice.

Arm type	Active comparator
Investigational medicinal product name	Cyclosporin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Capsule, soft, Oral solution
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

Tacrolimus (Cyclosporin) will be given orally or intravenously per institutional standards starting Day -3. The dose of tacrolimus (Cyclosporin) may be rounded to the nearest 0.5 mg for oral formulations. Subsequent dosing will be based on blood levels, with a target of 5-15 ng/ml. If patients are on medications which alter the metabolism of tacrolimus (Cyclosporin) (e.g. azoles), the initial starting dose and subsequent doses should be altered as per institutional practices. Tacrolimus (Cyclosporin) taper can be initiated at a minimum of 90 days post HSCT if there is no evidence of active GVHD. The rate of tapering will be done according institutional practices but patients should be off tacrolimus (Cyclosporin) by Day 180 post HSCT if there is no evidence of active GVHD.

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Methotrexate will be administered at the doses of 15 mg/m^2 IV bolus on Day +1, and 10 mg/m^2 IV bolus on Days +3, +6 and +11 after hematopoietic stem cell infusion. The Day +1 dose of methotrexate should be given at least 24 hours after the hematopoietic stem cell infusion. Dose reduction of MTX due to worsening creatinine clearance after initiation of conditioning regimen, high serum levels or development of oral mucositis is allowed according to institutional practices. Leucovorin rescue is allowed according to institutional practices.

Number of subjects in period 1	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Started	114	114	118
Completed	101	106	112
Not completed	13	8	6
Consent withdrawn by subject	1	-	-

Not transplanted	10	5	4
Lost to follow-up	2	3	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	346	346	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		0	
Newborns (0-27 days)		0	
Infants and toddlers (28 days-23 months)		0	
Children (2-11 years)		0	
Adolescents (12-17 years)		0	
Adults (18-64 years)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	51.1		
full range (min-max)	13.1 to 66	-	
Gender categorical Units: Subjects			
Female	149	149	
Male	197	197	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	21	21	
Not Hispanic or Latino	314	314	
Unknown or Not Reported	11	11	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	9	9	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	9	9	
White	311	311	
More than one race	0	0	
Unknown or Not Reported	17	17	
Lansky/Karnofsky Performance Score			
KPS describes patient-perceived global quality of life and functioning on a scale of 0-100. 100: No evidence of disease; 90: Normal activity. Minor signs or symptoms of disease; 80: Normal activity with effort. Some signs or symptoms of disease; 70: Cares for self. Unable to continue normal activity; 60: Needs occasional assistance, but cares for most personal needs; 50: Needs considerable assistance and medical care; 40: Disabled. Needs special care and assistance; 30: Severely disabled. Hospital admission indicated; 20: Very sick. Active supportive therapy needed; 10: Moribund; 0: Dead			

Units: Subjects			
90-100	196	196	
70-80	150	150	
Primary Disease Units: Subjects			
Acute Lymphoblastic Leukemia (ALL)	80	80	
Acute Myelogenous Leukemia (AML)	212	212	
Myelodysplastic Syndrome (MDS)	46	46	
Chronic Myelomonocytic Leukemia (CMML)	3	3	
Acute Undifferentiated Leukemia	2	2	
Biphenotypic Leukemia	3	3	
Disease Risk			
Disease risk data was collected by CIBMTR. For AML and ALL: High risk (not in remission): Never treated, PIF, Relapse; Non-high: CR1, CR2 and CR3+. For MDS (including CMML): High risk: High risk: RAEB, RAEB-T, RAEB-1, RAEB-2, CMML; non-high: RA, RARS, RCMD, RCMD/RS, MDS Unclassifiable, isolated 5q- syndrome.			
Units: Subjects			
Non-high	205	205	
High	115	115	
Missing/Unknown	26	26	
Disease Stage for AML and ALL			
1st CR: meet all for >=4 weeks: no blast cells in the peripheral blood, < 5% blasts in the bone marrow, no blasts with Auer rods, normal maturation of all cellular components in the marrow, normal CBC and ANC of > 1000/µL; Platelets ≥ 100000/µL; No other signs or symptoms of disease. >=2nd CR: after CR, relapsed and achieved CR again. Final is CR. PIF: recipient treated but never achieved durable CR. Relapse: ≥ 5% blasts in the marrow; Extramedullary disease; Reappearance of cytogenetic abnormalities and/or molecular markers associated with the diagnosis at a level representing relapse.			
Units: Subjects			
1st complete remission	207	207	
>=2nd complete remission	51	51	
Relapse	4	4	
Primary induction failure (PIF) /Untreated	10	10	
Missing	20	20	
Not Applicable	54	54	
Donor type Units: Subjects			
Related Donor	131	131	
Unrelated Donor	215	215	
Cytogenentic			
For Adult acute myeloid leukemia (AML), Favorable: t(15:17), inv(16), del(16q), t(16:16), [t(8:21) without del(9q) or complex]; Intermediate: normal karyotype, +6, +8, -Y, del(12p), 11q23, t(9:11); Poor: complex karyotype, -5/del(5q), -7/del(7q), abn(3q, 9q, 11q, 21q, 17p), t(6:9), t(9:22). For Acute lymphocytic leukemia (ALL), Poor: Ph+/t(9:22), t(4:11), 11q23, MLL, hypodiploid, t(8:14), complex. For Myelodysplastic Syndrome (MDS): Favorable: normal karyotype, isolated del(5q), del(20q), or -Y; Poor: complex karyotype, 7 chromosome abnormalities; Intermediate: other abnormalities.			
Units: Subjects			
Normal	11	11	
Favorable	37	37	
Intermediate	160	160	
Poor	112	112	
Missing	25	25	
Not tested	1	1	
HLA matching			

Units: Subjects			
8/8	346	346	
HCT-comorbidity index			
The HCT-CI was developed to identify comorbidities relevant to transplant and act as a tool for risk assessment and before allogeneic hematopoietic stem cell transplantation. Patients with no comorbidities are assigned a score of zero. Arrhythmia, cardiac, bowel, diabetes, cerebrovascular, psychological, mild chronic hepatitis, obesity, infection are assigned a score of 1. Rheumatoid arthritis, peptic ulcer, renal moderate/severe, pulmonary moderate, are assigned a score of 2. Solid tumor, heart valve disease, pulmonary sever, hepatic moderate/severe are assigned a score of 3.			
Units: Subjects			
Zero	123	123	
1-2	129	129	
3 or greater	75	75	
Not applicable	19	19	
Pre-transplant CMV status			
Pre-Transplant CMV Status is assessed in transplanted patients.			
Units: Subjects			
Positive	156	156	
Negative	171	171	
Not applicable	19	19	
Donor CMV Status			
Measure Analysis Population Description: Donor CMV Status is assessed in transplanted patients.			
Units: Subjects			
Negative	199	199	
Positive	127	127	
Unknown	1	1	
Not applicable	19	19	
Stem cell source			
Measure Analysis Population Description: Stem cell source is assessed in transplanted patients.			
Units: Subjects			
Peripheral Blodd	121	121	
Bone Marrow	206	206	
Not applicable	19	19	
Time from diagnosis to transplantation			
Units: month			
median	5.0		
full range (min-max)	1.6 to 231.3	-	

End points

End points reporting groups

Reporting group title	CD34 Selection Arm
Reporting group description:	
Mobilized CD34-selected Peripheral Blood Stem Cell graft Following screening and enrollment, the donor of patients randomized to the CD34-selection arm will receive mobilization therapy with once daily Granulocyte Colony Stimulating Factor (G-CSF). Mobilization will begin on Day -5 prior to the patient's transplant date. Leukapheresis will be performed on a continuous flow cell separator according to institutional standards and will commence on the morning of the fifth day of G-CSF treatment. The anti-coagulant used for the procedure will be acid citrate dextrose (ACD). Decisions concerning the need for further product collection will be based on the known or projected enriched CD34+ cell content of the previously collected products.	
Reporting group title	Post-Transplant Cyclophosphamide
Reporting group description:	
Unmanipulated Bone Marrow Graft with Cyclophosphamide	
Reporting group title	Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Reporting group description:	
Unmanipulated bone marrow graft with Tacrolimus(Cyclopsorin)/Methotrexate GVHD prophylaxis. Tacrolimus(Cyclosporin) will be maintained at therapeutic doses for a minimum of 90 days. Methotrexate will be dosed at 5-15mg/m^2 for a maximum of 4 doses post-transplant. Cyclosporine may be substituted for tacrolimus in germany or if the patient is intolerant of tacrolimus or per institutional practice.	

Primary: Chronic GVHD-free, Relapse-free Survival (CRFS) Probability

End point title	Chronic GVHD-free, Relapse-free Survival (CRFS) Probability
End point description:	
The primary endpoint of the trial is Chronic GVHD/Relapse-Free Survival (CRFS), treated as a time to event variable. An event for this time to event outcome is defined as moderate to severe chronic GVHD, disease relapse, or death by any cause. Participant will be censored if lost to follow up prior to 2 years. Time is from randomization to the event of moderate to severe chronic GVHD, disease relapse, death, last follow up, or 2 years, whichever comes first. The primary analysis is performed using the intent-to-treat principle (ITT) so that all randomized patients are included in the analysis. All randomized patients are analyzed for this endpoint.	
End point type	Primary
End point timeframe:	
2 years	

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	114	118	
Units: percentage of participants				
number (confidence interval 95%)				
1 year Post Randomization	60.2 (50.3 to 68.7)	60.3 (50.5 to 68.7)	52.6 (43.1 to 61.3)	
2 years Post Randomization	50.6 (40.8 to 59.6)	48.1 (38.5 to 57.1)	41 (32 to 49.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The primary null hypothesis of the study is that there is no difference of the CRFS hazard ratio between CD34 select graft vs. Tac/MTX Control. The data in primary outcome table provides point estimates at specific time points (1 year and 2 years post randomization). The statistics in this session provides comparisons between different arms for the entire period of the study.

Comparison groups	Tacrolimus(Cyclosporin)/Methotrexate Control Arm v CD34 Selection Arm
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2368 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.805
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.562
upper limit	1.154

Notes:

[1] - The primary pairwise comparisons are tested at a Bonferroni adjusted significance level of 0.05/3.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The primary null hypothesis of the study is that there is no difference of the CRFS hazard ratio between Post-Transplant Cyclophosphamide vs. Tac/MTX Control. The data in primary outcome table provides point estimates. The statistics in this session provides comparisons between different arms for the entire period of the study.

Comparison groups	Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4134 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.864
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.609
upper limit	1.228

Notes:

[2] - The primary pairwise comparisons are tested at a Bonferroni adjusted significance level of 0.05/3.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The primary null hypothesis of the study is that there is no difference of the CRFS hazard ratio between CD34 select graft vs. Post-Transplant Cyclophosphamide. The data in primary outcome table provides point estimates. The statistics in this session provides comparisons between different arms for the entire period of the study.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7166 [3]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.933
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.643
upper limit	1.355

Notes:

[3] - The primary pairwise comparisons are tested at a Bonferroni adjusted significance level of 0.05/3.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

The null hypothesis is that there is no difference of the CRFS hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk. The data in primary outcome table provides point estimates. The statistics in this session provides comparisons between different arms for the entire period of the study.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.386 [4]
Method	Regression, Cox

Notes:

[4] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 5

Statistical analysis description:

Subgroup analyses are conducted for CRFS according to disease, disease risk and age. Interaction tests between treatment group and subgroup are conducted within a Cox proportional hazards regression model with treatment, subgroup, and a treatment*subgroup interaction term. The null hypothesis is that there is no Interaction between treatment group and disease risk (Low/Intermediate vs. High) for CRFS.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.461 [5]
Method	Cox proportional hazards regression

Notes:

[5] - A Bonferroni adjusted significance level of 0.05/3=0.0167 is used for each of three interaction tests to account for multiple testing.

Statistical analysis title	Statistical Analysis 6

Statistical analysis description:

Subgroup analyses are conducted for CRFS according to disease, disease risk and age. Interaction tests between treatment group and subgroup are conducted within a Cox proportional hazards regression model with treatment, subgroup, and a treatment*subgroup interaction term. The null hypothesis is that there is no Interaction between treatment group and Age (<=50 vs. >50) for CRFS.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.115 [6]
Method	Cox proportional hazards regression

Notes:

[6] - Cox proportional hazards regression

Statistical analysis title	Statistical Analysis 7

Statistical analysis description:

Subgroup analyses are conducted for CRFS according to disease, disease risk and age. Interaction tests between treatment group and subgroup are conducted within a Cox proportional hazards regression model with treatment, subgroup, and a treatment*subgroup interaction term. The null hypothesis is that there is no Interaction between treatment group and Disease (AML vs. ALL vs. MDS) for CRFS.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.227 [7]
Method	Cox proportional hazards regression

Notes:

[7] - A Bonferroni adjusted significance level of 0.05/3=0.0167 is used for each of three interaction tests to account for multiple testing.

Secondary: Percentage of Participants With Overall Survival (OS)

End point title	Percentage of Participants With Overall Survival (OS)

End point description:

OS is a key secondary endpoint, with explicit control of the type I error rate through a gatekeeper approach. Formal significance testing of OS between a CNI-free strategy and the control will be conducted if the corresponding CRFS comparison is significant. This OS comparison will be done using a Bonferroni adjusted significance level of 0.05/3 to account for three potential CNI-free comparisons to the control. Otherwise, survival analyses will be considered exploratory. Death from any cause is considered as event for this endpoint. Participant is censored if lost to follow up.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	114	114	118	
Units: percentage of subjects				
number (confidence interval 95%)				
1 year post-randomization	75.7 (66.4 to 82.8)	84.6 (76.4 to 90.1)	84.2 (76.1 to 89.7)	
2 year post-randomization	60.1 (50.1 to 68.8)	76.2 (67.1 to 83.1)	76.1 (67.2 to 83.0)	
1 year post-transplantation	74.8 (65.2 to 82.1)	83.4 (74.9 to 89.2)	83.3 (75.0 to 89.0)	
2 year post-transplantation	61.6 (51.4 to 70.3)	76.7 (67.5 to 83.6)	74.2 (65.0 to 81.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of the OS hazard ratio between CD34 select graft vs. Tac/MTX Control.

Comparison groups	CD34 Selection Arm v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0197 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.744
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.086
upper limit	2.8

Notes:

[8] - The OS pairwise comparisons are tested at a Bonferroni adjusted significance level of 0.05/3.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no difference of the OS hazard ratio between Post-Transplant Cyclophosphamide vs. Tac/MTX Control.

Comparison groups	Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Number of subjects included in analysis	232
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9525 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.016
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.599
upper limit	1.724

Notes:

[9] - The OS pairwise comparisons are tested at a Bonferroni adjusted significance level of 0.05/3.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The null hypothesis is that there is no difference of the OS hazard ratio between CD34 select graft vs. Post-Transplant Cyclophosphamide.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide
Number of subjects included in analysis	228
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0185 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.774
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.093
upper limit	2.877

Notes:

[10] - The OS pairwise comparisons are tested at a Bonferroni adjusted significance level of 0.05/3.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

The null hypothesis is that there is no difference of the OS hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	346
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [11]
Method	Regression, Cox

Notes:

[11] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Percentage of Participants With Relapse-free Survival

End point title	Percentage of Participants With Relapse-free Survival

End point description:

The events for this endpoint RFS are death and relapse of the underlying malignancy. The analyses of this endpoint use the transplanted populations and time is from transplant to the event of disease relapse or death, or last follow up, whichever comes first.
The analyses of this endpoint will use the transplanted population.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)				
1 year post-transplantation	64.1 (54.0 to 72.5)	78.8 (69.9 to 85.4)	70.1 (60.8 to 77.6)	
2 years post-transplantation	57.1 (46.9 to 66.0)	70.3 (60.7 to 78.0)	66.5 (56.9 to 74.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Relapse-Free Survival between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029 [12]
Method	Logrank

Notes:

[12] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no difference of the RFS hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.145 [13]
Method	Regression, Cox

Notes:

[13] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Percentage of Participants With Treatment-related Mortality

End point title	Percentage of Participants With Treatment-related Mortality

End point description:

The events for this endpoint TRM are deaths prior to relapse of the underlying malignancy. The analyses of this endpoint will use the transplanted populations, and time will be from transplant to the first of disease relapse, death, or last follow up. TRM are evaluated using the cumulative incidence function. Deaths without relapse are the events for this endpoint and relapse is a competing risk for this endpoint. The analyses of this endpoint will use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)				
1 year post-transplantation	16.5 (10.1 to 24.3)	12.0 (6.7 to 18.9)	7.0 (3.2 to 12.7)	
2 years post-transplantation	21.5 (14.1 to 30.0)	15.7 (9.6 to 23.2)	7.9 (3.9 to 13.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Transplant-Related Mortality between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02 [14]
Method	Gray's test for cumulative Incidence

Notes:

[14] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no difference of the TRM hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04 [15]
Method	Regression, Cox

Notes:

[15] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Participants With Immunosuppression-free Survival

End point title	Participants With Immunosuppression-free Survival

End point description:

Patients who are alive, relapse-free, and do not need ongoing immune suppression to control GVHD at one year post HSCT are considered successes for this endpoint. Immune suppression is defined as any systemic agents used to control or suppress GVHD.
The analyses of this endpoint will use the transplanted populations. Two participant of CD34 Selected Graft arm and one participants of Post-Transplant Cyclophosphamide arm were lost to follow-up while alive and not relapsed, and they are considered as not evaluable for this endpoint.

End point type	Secondary

End point timeframe:

1 year

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	102	108	114	
Units: participants	59	73	66	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of immunosuppression-free survival at 1-year post-transplant between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2389 [16]
Method	Chi-squared

Notes:

[16] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no agreement between CRFS and immunosuppression-free survival at 1-year post-transplant.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cohen's Kappa

Secondary: Percentage of Participants With Disease Relapse

End point title	Percentage of Participants With Disease Relapse

End point description:

Relapse is defined by either morphological evidence of acute leukemia or MDS consistent with pre-transplant features, or radiologic evidence of lymphoma, documented or not by biopsy. The event is defined as increase in size of prior sites of disease or evidence of new sites of disease, documented or not by biopsy. Relapse is adjudicated by ERC. Disease relapse is analyzed using cumulative incidence function with death as a competing risk. The analyses of this endpoint use the transplanted populations, and the time will be measured from transplant to the earliest of death, relapse/progression, or last follow up.
The analyses of this endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)				
1 year post transplantation	19.4 (12.4 to 27.6)	9.2 (4.7 to 15.6)	22.9 (15.6 to 31.0)	
2 years post transplantation	21.4 (14.0 to 29.8)	13.9 (8.1 to 21.2)	25.6 (17.9 to 33.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Disease Relapse between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.076 [17]
Method	Gray's test for cumulative Incidence

Notes:

[17] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no difference of the Disease Relapse hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.106 [18]
Method	Regression, Cox

Notes:

[18] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Percentage of Participants With Neutrophil Engraftment

End point title	Percentage of Participants With Neutrophil Engraftment

End point description:

Neutrophil recovery is defined as achieving an absolute neutrophil count (ANC) ≥ 500/mm^3 for three consecutive measurements on three different days. The first of the three days will be designated the day of neutrophil recovery. The competing event is death without neutrophil recovery.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

Day 28

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)	97.1 (90.5 to 99.1)	91.7 (84.4 to 95.7)	96.5 (90.3 to 98.8)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Neutrophil Engraftment post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0764 [19]
Method	Gray's test for cumulative Incidence

Notes:

[19] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Percentage of Participants With Platelet Recovery

End point title	Percentage of Participants With Platelet Recovery

End point description:

Platelet recovery is defined as the first day of a sustained platelet count >20,000/mm^3 with no platelet transfusion in the preceding seven days. The first day of sustained platelet count above this threshold will be designated the day of platelet engraftment. The competing event is death without platelet recovery.
The analyses of the endpoint use the transplanted populations. Three transplanted participants (one from the CD34 arm and two from the PTCy arm) are missing platelet data and are not included in the analyses.

End point type	Secondary

End point timeframe:

Day 60

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	103	107	114	
Units: percentage of participants				
number (confidence interval 95%)	94.2 (86.9 to 97.5)	91.6 (84.2 to 95.6)	98.2 (93.4 to 99.9)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Platelet recovery post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	324
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001 [20]
Method	Gray's test for cumulative Incidence

Notes:

[20] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Participants With Primary Graft Failure

End point title	Participants With Primary Graft Failure

End point description:

Primary graft failure is defined as no neutrophil recovery to > 500 cells/µL by Day 28 post HSCT.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

Day 28

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: Participants	3	9	4	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Secondary Graft Failure

End point title	Percentage of Participants With Secondary Graft Failure

End point description:

Secondary graft failure will be assessed according to neutrophil count after initial hematologic recovery.

Secondary graft failure is defined as initial neutrophil engraftment followed by subsequent decline in absolute neutrophil counts < 500 cells/µL, unresponsive to growth factor therapy, but cannot be explained by disease relapse or medications. Secondary graft failure will be analyzed using cumulative incidence function with death as a competing risk.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)	2.9 (0.8 to 7.5)	0 (0 to 0)	0.9 (0.1 to 4.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Secondary graft failure post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1478
Method	Gray's test for cumulative Incidence

Secondary: Percentage of Participants With Acute GVHD

End point title	Percentage of Participants With Acute GVHD

End point description:

Cumulative incidences of grade II-IV and III-IV acute GVHD were determined. Death prior to acute GVHD is treated as the competing risk. Grading of acute GVHD was derived by consensus grading (Przepiorka 1995) per BMTCTN manual of procedures (MOP). The acute GVHD algorithm calculates the grade based on the organ (skin, GI and liver) stage and etiology/biopsy reported on the weekly GVHD form. Staging for skin: Stage 1. <25% rash; 2. 25-50%; 3. >50%; 4. generalized erythroderma with bullae. Staging for GI: Stage 1. Diarrhea>500ml/d or persistent nausea; 2. >1000ml/d; 3. >1500ml/d; 4. Large volume diarrhea and severe abdominal pain +- ileus. Staging for Liver: Stage 1. bilirubin 2-3mg/dl; 2. bilirubin 3-6 mg/dl; 3. bilirubin 6-15 mg/dl; 4. bilirubin>15mg/dl. Grade 4 is the worst outcome.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

Day 100

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)				
Grade II-IV acute GvHD	16.3 (9.9 to 24.1)	37.6 (28.5 to 46.6)	29.8 (21.7 to 38.4)	
Grade III-IV acute GvHD	2.9 (0.8 to 7.5)	10.1 (5.3 to 16.6)	3.5 (1.1 to 8.1)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of grade II-IV acute GVHD post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0026 [21]
Method	Gray's test for cumulative Incidence

Notes:

[21] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no difference of grade III-IV acute GVHD post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0369 [22]
Method	Gray's test for cumulative Incidence

Notes:

[22] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 3

Statistical analysis description:

The null hypothesis is that there is no difference of the grade II-IV acute GVHD hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 [23]
Method	Regression, Cox

Notes:

[23] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 4

Statistical analysis description:

The null hypothesis is that there is no difference of the grade III-IV acute GVHD hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.046 [24]
Method	Regression, Cox

Notes:

[24] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Participants With Maximum Acute GVHD

End point title	Participants With Maximum Acute GVHD

End point description:

Grading of acute GVHD was derived by consensus grading (Przepiorka 1995) per BMTCTN manual of procedures (MOP). The acute GVHD algorithm calculates the grade based on the organ (skin, GI and liver) stage and etiology/biopsy reported on the weekly GVHD form. Grade I aGVHD is defined as Skin stage of 1-2 and stage 0 for both GI and liver organs. Grade II aGVHD is stage 3 of skin, or stage 1 of GI, or stage 1 of liver. Grade III is stage 2-4 for GI, or stage 2-3 of liver. Grade IV is stage 4 of skin, or stage 4 of liver. Max acute GVHD by Day 100 was computed.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

Day 100

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: participants				
Grade 0, No aGvHD	72	45	55	
Grade I	15	23	25	
Grade II	14	30	30	
Grade III	3	9	4	
Grade IV	0	2	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Chronic GVHD

End point title	Percentage of Participants With Chronic GVHD

End point description:

The cumulative incidence of chronic GVHD will be determined. Death prior to acute GVHD is treated as the competing risk. Data will be collected directly from providers and chart review according to the recommendations of the NIH Consensus Criteria. Eight organs will be scored on a 0-3 scale to reflect degree of chronic GVHD involvement. Liver and pulmonary function test results and use of systemic therapy for treatment of chronic GVHD will also be recorded. This secondary endpoint of chronic GVHD will include mild, moderate and severe chronic GVHD based on NIH Consensus Criteria.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)				
1 year post transplantation	16.4 (9.8 to 24.5)	33.0 (24.0 to 42.3)	31.1 (22.5 to 40.1)	
2 years post transplantation	18.5 (11.5 to 26.8)	37.0 (27.6 to 46.4)	40.0 (30.5 to 49.3)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of chronic GVHD post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0024 [25]
Method	Gray's test for cumulative Incidence

Notes:

[25] - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no difference of the chronic GVHD hazard ratio between treatment groups after adjustment for age, donor type, performance status, primary disease, and disease risk.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.005 [26]
Method	Regression, Cox

Notes:

[26] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Percentage of Participants With Chronic GVHD-free Survival

End point title	Percentage of Participants With Chronic GVHD-free Survival

End point description:

The event for this endpoint includes moderate to severe chronic GVHD according to NIH consensus criteria global score, or death by any cause.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: percentage of participants				
number (confidence interval 95%)				
1 year post-transplantation	71.0 (61.4 to 78.6)	67.4 (57.8 to 75.3)	65.8 (56.3 to 73.7)	
2 years post-transplantation	55.4 (45.3 to 64.3)	54.2 (44.4 to 63.0)	47.1 (37.7 to 56.0)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Chronic GVHD-free Survival post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.229 [27]
Method	Logrank

Notes:

[27] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Participants With Grade ≥ 3 Toxicity

End point title	Participants With Grade ≥ 3 Toxicity

End point description:

All grades ≥ 3 toxicities according to CTCAE, version 4 will be tabulated for each intervention arm. The number of unique patients is counted.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: participants				
Any Grade 3-5 Stem Cell Infusional Toxicities	6	4	17	
Grades 3-5 Oral mucositis	39	51	63	
Grades 3-5 Cystitis noninfective	4	11	2	
Grades 3-5 Acute kidney injury	12	13	15	
Grades 3-5 Chronic kidney disease	4	4	3	
Grade 3-5 Hemorrhage	12	9	4	
Grades 3-5 Hypotension	19	15	11	
Grades 3-5 Hypertension	20	21	30	
Grades 3-5 Cardiac arrhythmia	9	6	8	
Grades 3-5 Levt ventricular systolic dysfunction	5	2	8	
Grades 3-5 Somnolence	7	4	4	
Grades 3-5 Seizure	6	0	2	
Grades 3-5 Thrombotic thrombocytopenic purpura	1	2	4	
Grades 3-5 Capillary leak syndrome	1	0	1	
Grades 3-5 Hypoxia	32	22	14	
Grades 3-5 Dyspnea	23	15	12	
Grades 3-4 ALT	10	26	18	

Grades 3-4 AST	11	27	19	
Grades 3-4 Billirubin	8	14	7	
Grades 3-4 Alkaline Phosphatase	11	12	6	
Received dialysis	5	2	6	
Abnormal liver function	12	14	24	
SOS/VOD	0	2	1	
IPS	2	2	3	
Toxicities Within Day 100	68	82	81	
Toxicities Day 100 to 1 year	26	33	41	
Toxicities 1 year to 2 years	23	18	24	
Overall NCI CTCAE Grade 3-5 Toxicities	80	88	100	

Statistical analyses

No statistical analyses for this end point

Secondary: Participants Infected Post Transplant

End point title	Participants Infected Post Transplant

End point description:

All grade 2 and grade 3 infections, as defined by the BMT CTN Technical MOP, occurring post transplantation will be reported. The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each intervention arm.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: participants				
Patients with Grades 2-3 infections	72	66	50	
Patients with Grade 3 infections	31	23	16	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

The null hypothesis is that there is no difference of Grades II-III infection post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006 [28]
Method	Gray's test for cumulative Incidence

Notes:

[28] - Superiority - Statistical significance was determined using a pre-specified threshold of 0.05.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

The null hypothesis is that there is no difference of Grades III infection post-transplantation between the treatment groups.

Comparison groups	CD34 Selection Arm v Post-Transplant Cyclophosphamide v Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Number of subjects included in analysis	327
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0145 [29]
Method	Gray's test for cumulative Incidence

Notes:

[29] - Statistical significance was determined using a pre-specified threshold of 0.05.

Secondary: Incidence of Infections

End point title	Incidence of Infections

End point description:

All grade 2 and grade 3 infections, as defined by the BMT CTN Technical MOP, occurring post transplantation will be reported. The incidence of definite and probable viral, fungal and bacterial infections will be tabulated for each intervention arm.
The analyses of the endpoint use the transplanted populations.

End point type	Secondary

End point timeframe:

2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: Events	157	161	123	

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HQL) - Medical Outcomes Study Short Form 36 (SF36)

End point title	Health-Related Quality of Life (HQL) - Medical Outcomes Study

	Short Form 36 (SF36)

End point description:

HQL will be measured post-transplant using patient-reported survey SF36. The SF36 is a 36 item general assessment of health quality of life with eight components: Physical Functioning, Role Physical, Pain Index, General Health Perceptions, Vitality, Social Functioning, Role Emotional, Mental Health Index. Each domain is positively scored, indicating that higher scores are associated with positive outcome. The total score ranges from 0 to 100. This scale is being used in this protocol as a generic measure of quality of life. To facilitate comparison of results with published norms, the Physical Component Summary and Mental Component Summary are used as the outcome measures in summarizing the SF36 data. These summary scores are derived by multiplying the z-score for each scale by its respective physical or mental factor score coefficient and summing the products. Resulting scores are then transformed into Tscores (mean=50; standard deviation=10). The SF36 takes 6 minutes to complete.

End point type	Secondary

End point timeframe:

Baseline, Day 100, Day 180, 1 year, 2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: Score on a Scale				
arithmetic mean (standard error)				
STANDARDIZED MENTAL COMPONENT SCALE at Baseline	48 (± 1.0)	46 (± 1.2)	48 (± 1.1)	
STANDARDIZED MENTAL COMPONENT SCALE at Day 100	48 (± 1.0)	48 (± 1.1)	48 (± 1.0)	
STANDARDIZED MENTAL COMPONENT SCALE at Day 180	50 (± 1.1)	50 (± 1.1)	49 (± 0.9)	
STANDARDIZED MENTAL COMPONENT SCALE at 1 year	50 (± 1.2)	52 (± 1.1)	49 (± 1.2)	
STANDARDIZED MENTAL COMPONENT SCALE at 2 years	50 (± 1.5)	50 (± 1.5)	51 (± 1.1)	
STANDARDIZED PHYSICAL COMPONENT SCALE at Baseline	42 (± 1.0)	44 (± 1.0)	41 (± 1.2)	
STANDARDIZED PHYSICAL COMPONENT SCALE at Day 100	40 (± 1.1)	41 (± 1.1)	40 (± 1.0)	
STANDARDIZED PHYSICAL COMPONENT SCALE at Day 180	43 (± 1.1)	44 (± 1.2)	44 (± 0.9)	
STANDARDIZED PHYSICAL COMPONENT SCALE at 1 year	46 (± 1.2)	47 (± 1.2)	44 (± 1.1)	
STANDARDIZED PHYSICAL COMPONENT SCALE at 2 years	46 (± 1.4)	47 (± 1.2)	47 (± 1.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HQL) - Functional Assessment of Cancer Therapy - Bone Marrow Transplant (FACT-BMT)

End point title	Health-Related Quality of Life (HQL) - Functional Assessment of Cancer Therapy - Bone Marrow Transplant (FACT-BMT)

End point description:

The FACT-BMT is a 37 item scale comprised of a general core questionnaire, the FACT-G with a possible range of 0-108 points, that evaluates the health-related quality of life (HQL) of patients receiving treatment for cancer, and a specific module, BMT Concerns, that addresses disease and treatment-related questions specific to bone marrow transplant. The FACT-G consists of four subscales developed and normed in cancer patients: Physical Well-being, Social/Family Well-being, Emotional Wellbeing, and Functional Well-being. Each subscale is positively scored, with higher scores indicating better functioning. The FACT-BMT Trial Outcome Index, comprised of the physical well-being scale, the functional well-being scale and the BMT specific items, will be used as the outcome measure in summarizing the FACT-BMT data. The FACT-BMT takes 6 minutes to complete. The final score for FACT-BMT ranges from 0 to 196. Higher scores for the scales and subscales indicate better quality of life.

End point type	Secondary

End point timeframe:

Baseline, Day 100, Day 180, 1 year, 2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: Score on a scale				
arithmetic mean (standard error)				
FACT-G Total at Baseline	81 (± 1.6)	79 (± 1.4)	80 (± 1.9)	
FACT-G Total at Day 100	79 (± 1.7)	80 (± 1.5)	79 (± 1.6)	
FACT-G Total at Day 180	80 (± 1.9)	83 (± 1.7)	82 (± 1.6)	
FACT-G Total at 1 Year	84 (± 2.1)	86 (± 2.0)	84 (± 1.7)	
FACT-G Total at 2 Years	87 (± 2.5)	86 (± 2.1)	84 (± 2.1)	
FACT-BMT Trial Outcome Index at Baseline	67 (± 1.6)	67 (± 1.3)	65 (± 1.8)	
FACT-BMT Trial Outcome Index at Day 100	63 (± 1.9)	66 (± 1.5)	63 (± 1.6)	
FACT-BMT Trial Outcome Index at Day 180	67 (± 1.8)	69 (± 1.8)	67 (± 1.5)	
FACT-BMT Trial Outcome Index at 1 Year	73 (± 1.9)	72 (± 2.0)	69 (± 1.7)	
FACT-BMT Trial Outcome Index at 2 Years	73 (± 2.3)	73 (± 2.1)	71 (± 2.0)	
FACT-BMT Total at Baseline	109 (± 2.1)	108 (± 1.8)	108 (± 2.4)	
FACT-BMT Total at Day 100	106 (± 2.4)	108 (± 2.0)	105 (± 2.2)	
FACT-BMT Total at Day 180	108 (± 2.5)	112 (± 2.3)	110 (± 2.1)	
FACT-BMT Total at 1 Year	114 (± 2.8)	116 (± 2.6)	113 (± 2.2)	
FACT-BMT Total at 2 Years	117 (± 3.4)	115 (± 2.8)	113 (± 2.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HQL) - MDASI

End point title	Health-Related Quality of Life (HQL) - MDASI

End point description:

HQL will be measured post-transplant using patient-reported survey MD Anderson Symptom Inventory (MDASI). The MDASI is a 19 item instrument that captures 13 symptoms (0="not present" to 10="as bad as you can imagine") and 6 items measuring interference with life from 0 ("did not interfere") to 10 ("interfered completely"). MDASI Tool questions are negatively scored - higher levels indicate more severe symptoms and levels of interference. Codelist for each question is from 0 to 10. Scoring is taking the mean of items, so the range is 0-10. Lower scores for the scales indicate better quality of life. It provides two summary scales: symptoms and interference. The MDASI takes less than 5 minutes to complete.

End point type	Secondary

End point timeframe:

Baseline, Day 100, Day 180, 1 year, 2 years

End point values	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	104	109	114	
Units: Score on a scale				
arithmetic mean (standard error)				
Symptoms Score at Baseline	2 (± 0.2)	2 (± 0.2)	2 (± 0.2)	
Symptoms Score at Day 100	2 (± 0.2)	2 (± 0.1)	2 (± .02)	
Symptoms Score at Day 180	2 (± 0.2)	2 (± 0.2)	2 (± 0.2)	
Symptoms Score at 1 Year	2 (± 0.2)	1 (± 0.2)	2 (± 0.2)	
Symptoms Score at 2 Years	1 (± 0.2)	2 (± 0.2)	2 (± 0.2)	
Interference Score at Baseline	2 (± 0.2)	2 (± 0.2)	3 (± 0.2)	
Interference Score at Day 100	2 (± 0.2)	2 (± 0.2)	2 (± 0.2)	
Interference Score at Day 180	2 (± 0.3)	2 (± 0.3)	2 (± 0.2)	
Interference Score at 1 Year	2 (± 0.3)	2 (± .03)	2 (± 0.3)	
Interference Score at 2 Years	1 (± 0.3)	2 (± 0.3)	2 (± 0.3)	

Statistical analyses

No statistical analyses for this end point

Secondary: Health-Related Quality of Life (HQL) - PedsQL

End point title	Health-Related Quality of Life (HQL) - PedsQL[30]

End point description:

HQL will be measured post-transplant using patient-reported survey PedsQL. The PedsQL™ Stem Cell Transplant Module is a 46-item instrument that measures health-related quality of life in children and adolescents undergoing hematopoietic stem cell transplant and is developmentally appropriate for self-report in ages 8 through 18 years. The score ranges from 0 to 100 with higher scores associated with positive outcome.

End point type	Secondary

End point timeframe:

Baseline, Day 100, Day 180, 1 year, 2 years

Notes:

[30] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Only 2 trial subjects were pediatrics, both randomized to Tacrolimus/Methotrexate Control arm.

End point values	Tacrolimus(Cyclosporin)/Methotrexate Control Arm			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: Score on a scale				
arithmetic mean (standard error)				
Pediatric Quality of Life Score at Baseline	80.18 (± 14.94)			
Pediatric Quality of Life Score at Day 100	69.82 (± 2.75)			
Pediatric Quality of Life Score at Day 180	72.56 (± 3.05)			
Pediatric Quality of Life Score at 1 Year	78.05 (± 4.27)			
Pediatric Quality of Life Score at 2 Years	53.66 (± 21.34)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting and monitoring were conducted throughout the study, up to 2 years.

Adverse event reporting additional description:

Adverse event (AE) reporting was conducted according to the BMT CTN's manual of operating procedures (MOP). Unexpected, grade 3-5 AE were reported through an expedited AE reporting system. Expected AEs were reported using National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 at regular intervals and re

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	CD34 Selection Arm

Reporting group description:

Mobilized CD34-selected Peripheral Blood Stem Cell graft Following screening and enrollment, the donor of patients randomized to the CD34-selection arm will receive mobilization therapy with once daily Granulocyte Colony Stimulating Factor (G-CSF). Mobilization will begin on Day -5 prior to the patient's transplant date. Leukapheresis will be performed on a continuous flow cell separator according to institutional standards and will commence on the morning of the fifth day of G-CSF treatment. The anti-coagulant used for the procedure will be acid citrate dextrose (ACD). Decisions concerning the need for further product collection will be based on the known or projected enriched CD34+ cell content of the previously collected products.

Reporting group title	Post-Transplant Cyclophosphamide

Reporting group description:

Unmanipulated Bone Marrow Graft with Cyclophosphamide

Reporting group title	Tacrolimus(Cyclosporin)/Methotrexate Control Arm

Reporting group description:

Unmanipulated bone marrow graft with Tacrolimus(Cyclopsorin)/Methotrexate GVHD prophylaxis. Tacrolimus(Cyclosporin) will be maintained at therapeutic doses for a minimum of 90 days. Methotrexate will be dosed at 5-15mg/m^2 for a maximum of 4 doses post-transplant. Cyclosporine may be substituted for tacrolimus in germany or if the patient is intolerant of tacrolimus or per institutional practice.

Serious adverse events	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 114 (7.89%)	7 / 114 (6.14%)	7 / 118 (5.93%)
number of deaths (all causes)	42	27	30
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
NEW MALIGNANCY-RECTAL ADENOCARCINOM			

subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
SUPERIOR VENA CAVA SYNDROME			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
FETAL DEATH			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
NON CARDIAC CHEST PAIN			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SUDDEN CARDIAC ARREST			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
DEATH			
subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
EDEMA			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
DISSEMINATED ADENOVIRUS INFECTION			

subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY FAILURE			
subjects affected / exposed	2 / 114 (1.75%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PLEURAL EFFUSION			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	2 / 114 (1.75%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
GRADE 3 UNEXPECTED WEIGHT LOSS			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Sudden cardiac death			
subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
WORSENING EYESIGHT DUE TO CATARACT			

subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
COLONIC PERFORATION			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETROPERITONEAL BLEED			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
CHOLECYSTITIS			
subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
SEPSIS			
subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HOSPITAL ADMISSION FOR INFECTION			
subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	CD34 Selection Arm	Post-Transplant Cyclophosphamide	Tacrolimus(Cyclosporin)/Methotrexate Control Arm
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 114 (2.63%)	1 / 114 (0.88%)	2 / 118 (1.69%)
Investigations			
PLATELET COUNT DECREASE			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
ELEVATED FERRITIN			
subjects affected / exposed	0 / 114 (0.00%)	1 / 114 (0.88%)	0 / 118 (0.00%)
occurrences (all)	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
FOLLICULAR LYMPHOMA			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
RESPIRATORY FAILURE			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	0 / 114 (0.00%)	0 / 114 (0.00%)	1 / 118 (0.85%)
occurrences (all)	0	0	1
Product issues			
ELEVATED ENDOTOXIN LEVEL			
subjects affected / exposed	1 / 114 (0.88%)	0 / 114 (0.00%)	0 / 118 (0.00%)
occurrences (all)	1	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 May 2015	The major changes to the protocol include the addition of a requirement for informed consent from donors of patients randomized to the CD34 selection arm (the protocol document only includes the informed consent for related donors, while the NMDP will have purview over consenting the unrelated donors); a modification to the way that chemotherapy doses are calculated; exclusion of modifications to the conditioning regimens in Arms A and B and of modifications to MTX regimens; addition of information regarding data submission and adverse event reporting; addition of information about ethics and regulatory requirements and procedures; addition of risks for rATG and risk language for lymphoproliferative syndrome as well as Mesna.
21 July 2016	Major changes to the Protocol include: 1. Inclusion criteria for patients with CMML were added as follows: "Patients with CMML must have a WBC count ≤ 10,000 cells/µL and < 5% blasts in the marrow." 2. FLT3 and other tyrosine kinase inhibitors for post-transplant maintenance and for prevention of disease relapse are now allowed. 3. The fourth dose of Mesna may now be infused 8-9 hours after the completion of cyclophosphamide. 4. Toxoplasmosis NAAT for patients on the CD34+ arm considered at risk for infection/reactivation has been replaced with placing such patients on prophylactic agents. 5. The window from randomization to initiation of conditioning has been removed. 6. After randomization of MDS patients, the bone marrow assessment must be repeated if it did not occur within 6 weeks prior to the initiation of the transplant conditioning regimen. Patient Informed Consent: 1. Weekly monitoring of toxoplasmosis until Day 100 then at each clinical assessment until Day 180 was removed from §Health Evaluations After the Transplant, as for NAAT for toxoplasmosis were removed from the protocol. 2. The volume of optional blood samples to be collected after transplant was corrected from 80mL to 86mL as required by Table 1 of Appendix C, Laboratory Procedures. Donor Informed Consent: 1. Language was updated to limit confusion with regards to charges for the cell manipulation procedure. The selection procedure will be paid for, for this study. 2. Clarification was provided to explain that the investigational device that is part of the cell selection system that will be used to remove T cells from your stem cell donation, called stem cell manipulation, prior to transplantation. 3. The costs section was updated to reflect that the patient will need to pay for the cell selection procedure and that the donor will not be charged for the selection procedure.

22 August 2017	Major changes to the Protocol include: Clarification of the definition of "leukemia in complete morphologic CR with or without hematologic recovery". Added Inclusion Criteria statement: "Patients with > 5% blasts due to a regenerating marrow must contact the protocol chairs for review.". Clarification for sites to declare planned post-transplant maintenance therapy prior to randomization. Addition of new Exclusion Criterion: "If it is known prior to enrollment that the hematopoietic stem cell product will need to be cryopreserved, the patient should not be enrolled.". Addition of extra day of rest in the conditioning regimens of any treatment arm when delivery of the patient's graft is delayed. Addition of cryopreservation language. Addition of new secondary endpoint "graft failure." Primary graft failure defined as "no neutrophil recovery to > 500 cells/µL by Day 28 post HSCT." Secondary graft failure defined as "initial neutrophil engraftment followed by subsequent decline in absolute neutrophil counts < 500 cells/µL for > 3 days, unresponsive to growth factor therapy, but cannot be explained by disease relapse or medications." Clarification of systemic steroid usage to "if clinically indicated". Loosened the requirement of the pre-transplant bone marrow aspirate for MDS patients prior to randomization. The protocol still requires that it must be repeated if not within 6 weeks prior to the initiation of the transplant conditioning regimen. Addition of Adverse Device Effect Reporting requirement. Patient Informed Consent: A new "Risks and Toxicities Related to GVHD Prophylaxis" from Investigator's Brochure v8.0 was added to the patient informed consent. A new complication from the Investigator's Brochure v8.0 "PTLD can be fatal" was added to the "Lymphoproliferative Syndrome-other Complication section. Donor Informed Consent: New information from the Investigator's Brochure v8.0 was added to the protocol and donor informed consent on effectiveness of the device.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

SPONSOR=NHLBI; COLLABORATORS=BMT-CTN, NCI;INVESTIGATORS=Study Director:Mary Horowitz, MD, CIBMTR

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34855460

http://www.ncbi.nlm.nih.gov/pubmed/33811823