Supplementary Appendix to: Peters C, Dalle J-H, Locatelli F. et al. Total Body Irradiation or Chemotherapy Conditioning in Childhood ALL: A Multinational, Randomised, Non-Inferiority Phase 3 Study.

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

Contents

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3. Study Design

For details of the study design, including randomisation, frontline protocols used by randomising countries, inclusion criteria, and stopping rules, please see the Protocol published on the CCRI website.

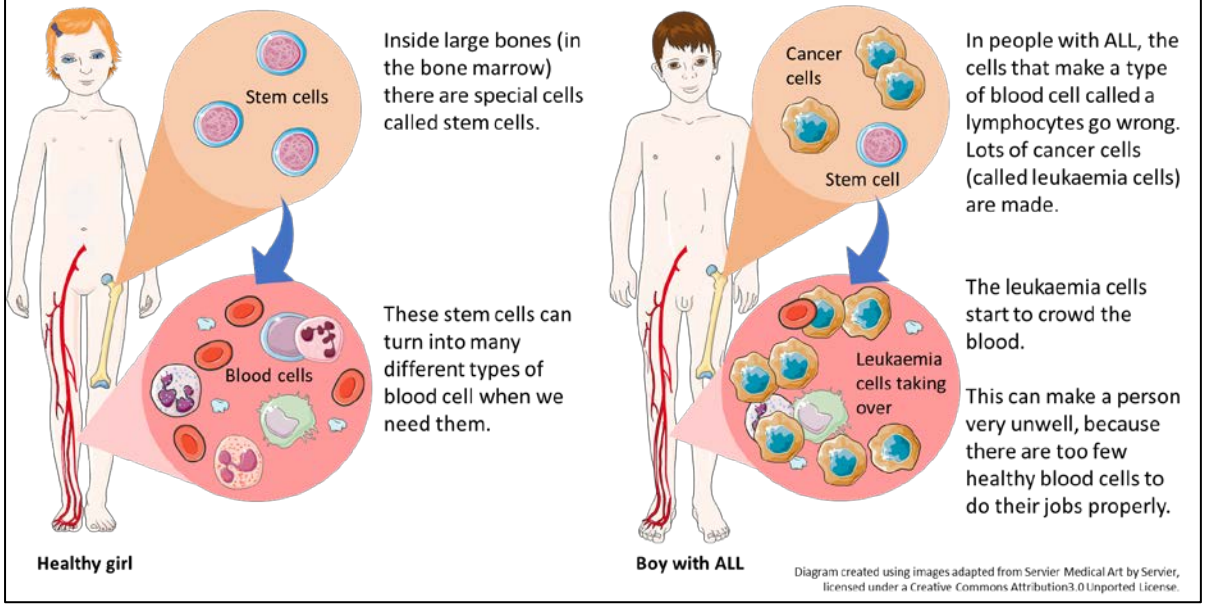
4. Plain Language Summary

Acute lymphoblastic leukaemia and its treatment

Our blood contains lots of different cells. These blood cells do important jobs such as carrying oxygen around the body (red blood cells), fighting infections (lymphocytes and other white blood cells), and forming a blood clot if a blood vessel is injured (platelets).

Very rarely, cells from which lymphocytes are made in the bone marrow can turn cancerous. This causes acute lymphoblastic leukaemia (ALL). Lots of leukaemia cells are produced, while too few healthy blood cells are made (Picture 1). This can make a person ill very quickly. About half of all people diagnosed with ALL are children.

Picture 1: What is acute lymphoblastic leukaemia (ALL)?



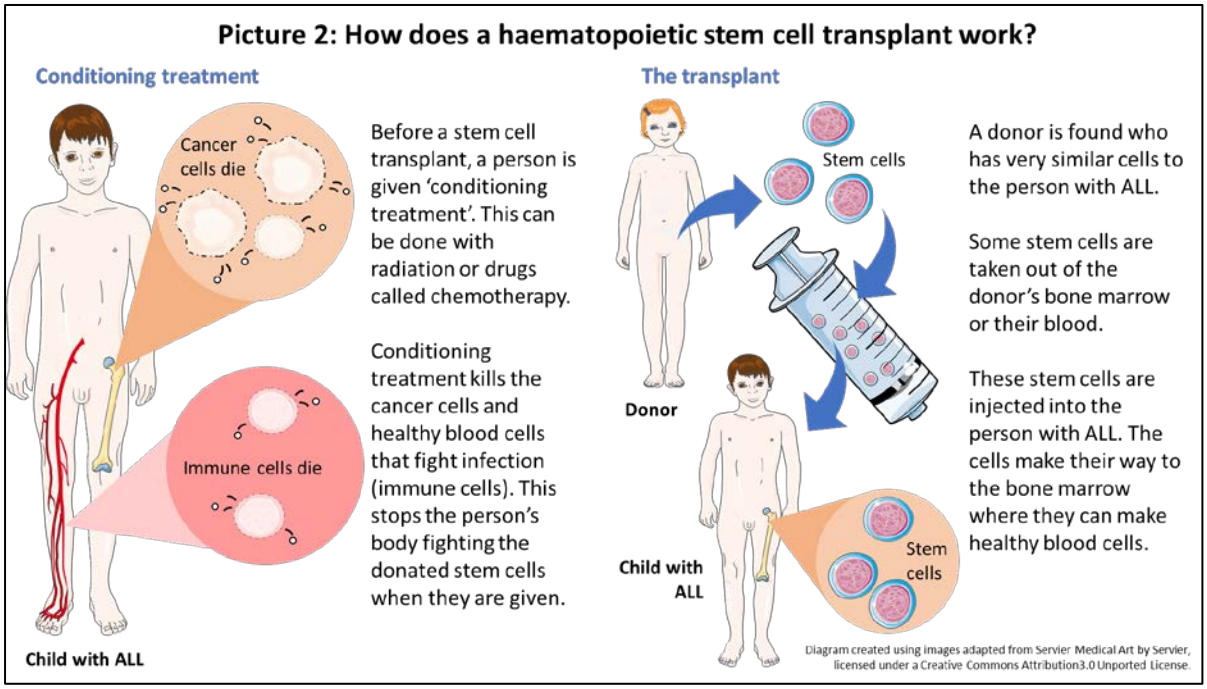
Most patients with ALL are cured with medicines that kill the cancer cells (chemotherapy). However, if these medicines do not destroy all the cancer cells, the leukaemia can come back. This is called relapse. People who have a relapse need additional therapy.

One of the main treatments for relapsed ALL involves healthy stem cells being taken from a donor and transferred into the person with ALL. This is called a haematopoietic stem cell transplant. The transplanted stem cells settle in the recipient's bone marrow, where they produce healthy blood cells.

Before a person can receive a stem cell transplant, they need treatment to kill the leukaemia cells and reduce their immune system. This is called 'conditioning therapy' (see Picture 2). A common conditioning therapy is radiation given to the whole body, known as total body irradiation (TBI). Alternatively, chemotherapy can be used.

When TBI is given to children it can cause life-long problems. These include not growing as much as usual, having learning problems, and the ovaries in girls and testicles in boys not growing fully, which can affect fertility. TBI can also cause new cancers to develop.

Chemotherapy has side effects too. Some chemotherapies can affect fertility. Chemotherapy can also cause new cancers to develop, but less commonly than TBI does.



Introduction to the FORUM study

We conducted the FORUM study to see whether a mixture of chemotherapy drugs could be used instead of TBI for conditioning therapy in children, adolescents, and young people with ALL. We wanted to do this so that, in the future, people surviving ALL might have fewer long-term problems from their leukaemia treatment.

88 hospitals across the world took part in our trial. Participants were under 18 years old when they were diagnosed with ALL and had their stem cell transplant aged between 4 and 21 years. Before their transplant, 212 participants in the trial were assigned to receive TBI plus a chemotherapy drug called etoposide. 201 participants were assigned to receive a mixture of chemotherapy drugs (fludarabine, thiotepa, and either busulfan or treosulfan) but no TBI.

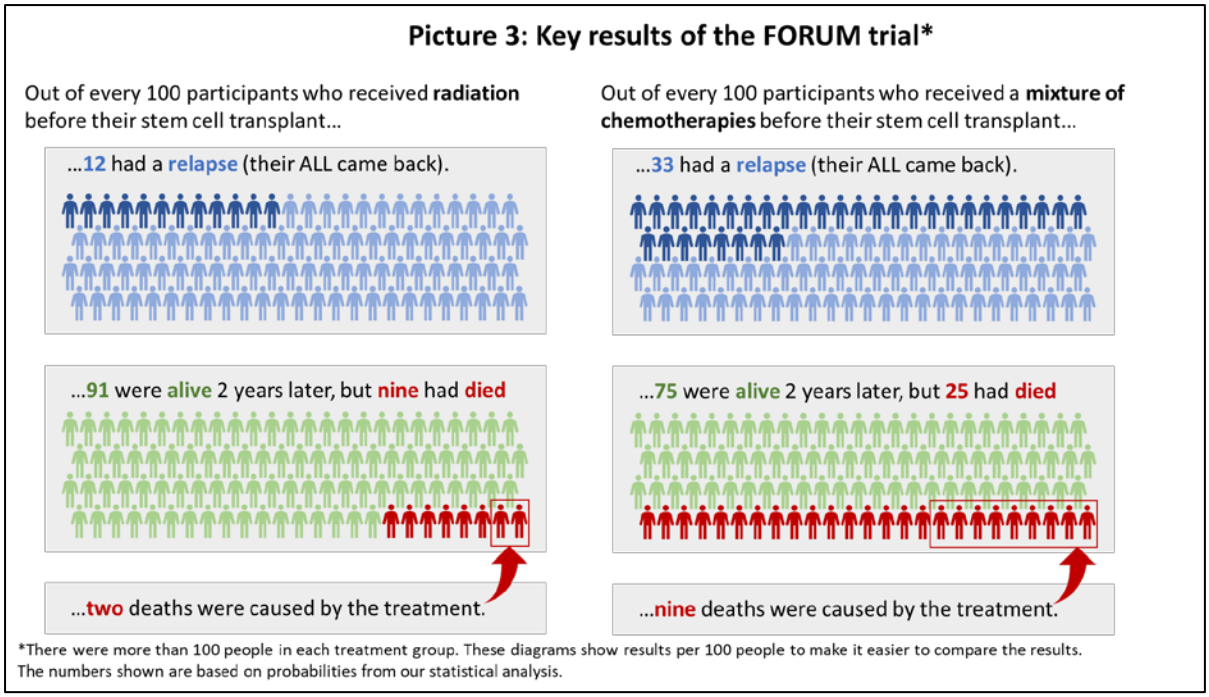
Results of the FORUM study

The following results are based on the chance of particular outcomes predicted by our statistical analysis (maths). We show these results in simple numbers in Picture 3.

In the group allocated TBI, about 12% of participants had a relapse of their ALL within 2 years, i.e. their cancer came back. In the group allocated chemotherapy, about 33% of participants had a relapse of their ALL within 2 years. So, the chance of having a relapse was over twice as high for participants allocated chemotherapy rather than TBI. About 91% of participants allocated TBI were alive 2 years after transplant, but 9% had died. In contrast, in the group allocated chemotherapy, about 75% of participants were alive 2 years after transplant, and 25% had died. About 2% of participants receiving TBI versus 9% receiving chemotherapy died from a side effect of their transplant therapy.

Our statistical analysis tells us that these differences are very unlikely to be due to chance alone. Because chemotherapy was proving to be less effective than TBI, we stopped assigning new participants to chemotherapy. Participants will now be given chemotherapy in our trial only if they cannot have, or choose not to have, TBI.

We recommend that children, adolescents, and young people with ALL who are going to have a haematopoietic stem cell transplant receive conditioning therapy with TBI and etoposide rather than the mixture of chemotherapy drugs that we tested.



5. Statistical Methodology According to the Statistical Analysis Plan

The statistical analysis followed a prespecified statistical analysis plan that was a part of the protocol (see protocol pages 57–63).

Randomisation

Patients were randomly assigned in a 1:1 ratio to either TBI plus etoposide or to a chemo-conditioning regimen consisting of fludarabine and thiotepa plus either busulfan or treosulfan. The choice of busulfan or treosulfan was determined by each national coordinator in discussion with study centres. The random allocation sequence was prepared by the study statisticians. Randomisation used a web-based study site and the allocation sequence that was concealed from the researcher enrolling, assessing participants, and coordinating the trial. Randomisation was performed with random blocks of 2, 4, 6, and 8 patients stratified by country, donor type and complete remission (CR1, CR2, or >CR2).

Analysis sets

There is ongoing debate in the methodological literature and no clear agreement on an appropriate analysis set for non-inferiority studies. Although a per-protocol population has been more commonly used than an intention-to-treat (ITT) population for previous non-inferiority studies, we determined that an ITT population was more suitable for primary analysis in the FORUM trial. The rationale for using a per-protocol population is that it may more closely follow the scientific hypothesis, as deviations from the protocol might make the outcomes for the treatment groups more similar. However, recently it has been shown that use of ITT analyses does not systematically lead to smaller estimates. In FORUM, it has been anticipated that patients who do not comply with the randomised arm are a selected sub-sample with respect to their risk profile: patients randomised to TBI but who received chemo-conditioning and patients randomised to chemo-conditioning but who received TBI are unlikely to be comparable. It can be anticipated that patients who are randomised to TBI yet who received chemo-conditioning are selected patients with a lower risk of events, while patients randomised to chemo-conditioning yet who received TBI are selected towards higher risk. In such a setting, a per-protocol analysis would favour chemo-conditioning. To mitigate this risk, in the FORUM study both ITT and modified as-treated populations were used for analyses. The ITT analysis was prospectively defined as primary and the modified as-treated analysis as secondary. Results with both analysis populations are shown in the paper and in this supplementary appendix. Results of the two approaches are superimposable, which strengthens our conclusion.

In the ITT analysis, all eligible randomised patients were analysed according to their randomised arm. Randomisation errors, i.e. patients who were erroneously randomised although not eligible (i.e. one mismatched donor, two patients not in CR, and one patient for whom informed consent was not received) were excluded from the ITT analysis (see manuscript Figure 1). A secondary analysis using the modified as-treated principle was performed (see manuscript Figure 1). The modified as-treated analysis excluded patients who were randomised to the TBI arm but who received chemo-conditioning and, likewise, excluded patients randomised to the chemo-conditioning arm but who received TBI. For the modified as-treated analysis, patients with TBI, treosulfan- and busulfan-based conditioning were separately evaluated.

Endpoints

The primary endpoint was overall survival (OS) calculated from the date of randomisation. Death from any cause was considered an event. Patients lost to follow-up without an event were censored at the date of their last follow-up evaluation.

Secondary efficacy endpoints are as follows:

- Event-free survival (EFS): this was calculated from the date of randomisation to the date of disease progression or relapse, secondary neoplasm, and death from any cause. Patients without an event were censored at the date of their last follow-up evaluation.
- Cumulative incidence of relapse/progression: this was estimated using the competing events of death without relapse/progression and secondary neoplasm. Patients without an event were censored at the date of their last follow-up evaluation.
- Treatment-related mortality (TRM): competing events were relapse/progression and secondary malignancies. Patients lost to follow-up without an event were censored at the date of their last follow-up evaluation.
- Cumulative incidence of disease-related mortality: competing events were deaths not related to the disease. Patients lost to follow-up without an event were censored at the date of their last follow-up evaluation.
- Cumulative incidence of neoplasm: competing events were deaths without neoplasm. Patients lost to follow-up without an event were censored at the date of their last follow-up evaluation.
- The cumulative incidence of chronic graft-versus-host disease (GvHD): this was estimated using the competing events of death without chronic GvHD and relapse. Survivors without chronic GvHD and relapse were censored at the date of their last follow-up evaluation.
- GvHD-free, relapse-free survival: this was calculated from date of randomisation to the first event. Acute GvHD grade III or IV was considered an event at day 0. Furthermore, chronic GvHD, relapse/progression and death from any cause were considered an event. Survivors without events were censored at the date of their last follow-up evaluation.
- Acute GvHD and toxicity at day 100.

Power

The study was designed as non-inferiority study with a non-inferiority margin of 8%. With a sample size of 1000 patients randomised in 5 years, a minimum follow-up of 2 years and a one-sided alpha of 5%, a power of 80% was calculated. The 8% margin was a result of several simulation models to anticipate the probability to equalise (outweigh) the possible late benefits of fewer secondary malignancies against a higher relapse incidence in the chemo-conditioning arms. However, it turned out that twice as much patients died due to relapse in the chemo-conditioning arm; thus, this margin is no longer relevant.

The primary analysis of the primary endpoint was planned using a one-sided confidence interval for the difference of the Kaplan-Meier estimate of the 4-year OS.[1] Efficacy in the chemo-conditioning arm would have been considered equal to that of the TBI arm if the lower limit of this confidence interval was less than 8% in both ITT and as-treated analyses. A total recruitment of 1000 patients over 5 years was anticipated. The final analysis was planned 2 years after the last randomisation. According to the previous experience from the ALL-SZT 2003 and ALL-SCT International studies,[2,3] a 4-year OS in the control arm (i.e., with TBI) of 70% was anticipated. Monte-Carlo simulations show that, with a non-inferiority margin of about 8%, the power will be above 80% (given a one-sided alpha of 5%). (Note that due to early trial termination, follow-up was too short at the time of the current data analysis to conduct this primary analysis of 4-year OS.)

Interim monitoring was performed annually as pre-specified in the protocol (see below stopping rules). The impact of the stopping rule on the power of the study was explored in a simulation study. Our simulation study confirmed that, with the stopping rules, the power was somewhat lower as compared with a study without such stopping rules. However, power remained above 80% in all investigated scenarios. For the design of the study, the sample size and non-inferiority margin were chosen that led to a statistical power above 80%, taking into account the impact of stopping rules.

Stopping rules

The study was monitored by an annual report to the Independent Data Monitoring Committee (IDMC). It was planned that the study would be stopped if overall survival in the chemo-conditioning arm was significantly worse than overall survival in the TBI arm at a 5% level using log-rank test. For the randomised question, early stopping rules were implemented to retain the null hypotheses – it was planned that the study would be stopped if the chemo-conditioning arm was significantly worse than the TBI arm at a 5% level using a log-rank test. Monitoring reports were planned after 200 patients were recruited and then annually thereafter until recruitment was completed. This stopping rule was to be implemented for safety reasons only (i.e., when the chemo-conditioning arm was worse) and, accordingly, the approach reduced both the type I error rate and power. Note that stopping in favour of the chemo-conditioning arm was not implemented and accordingly no type-I error adjustment was necessary. Monte-Carlo simulations show that the impact of this stopping rule on power is small. This stopping rule was breached in December 2018; randomisation was suspended while confirmatory analyses were conducted and randomisation was stopped in March 2019 (after 413 eligible patients had been randomised).

A similar approach to that described above was planned to compare OS in the two chemo-conditioning strata. A stopping rule based on a log-rank test using a 10% significance level was implemented. Simulation studies were performed to investigate the impact of this approach on type-I error rates and power. This stopping rule was not breached.

Furthermore, TRM was reviewed bi-annually. If the 6-month TRM rate in one arm or strata exceeded 15%, the information would be forward to the IDMC. This stopping rule was not breached.

Statistical analysis

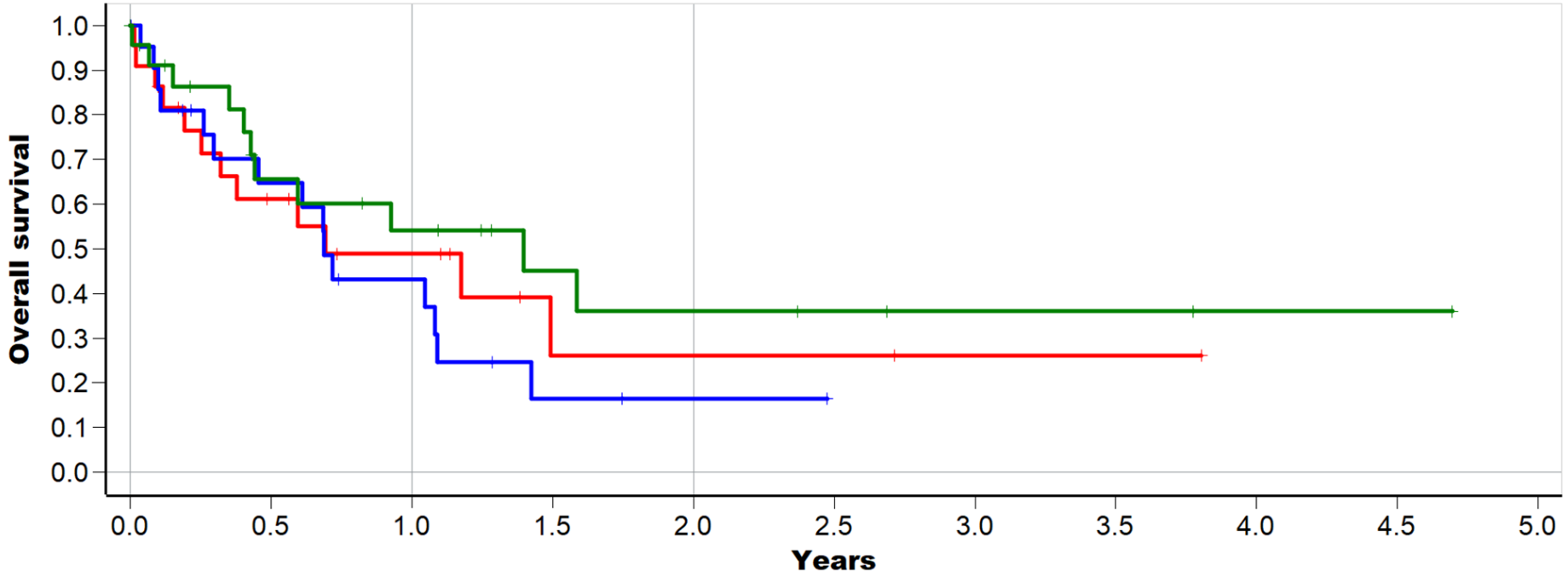
OS, EFS, and GvHD-free, relapse-free survival were estimated with Kaplan-Meier methodology[2]and compared using the log-rank test.[3] Two-year estimates and 95% confidence intervals using log transformation are given in the manuscript.[1] The significance level was 0.05 for all analyses. For the ITT analysis, patients were compared by randomised arm. For the modified as-treated analysis evaluating TBI conditioning and the two chemo-conditioning strata separately, pairwise comparisons were performed provided that the global p value was significant.

Univariate evaluation of risk factors used the same approach. Risk factors evaluated were sex, age, immunophenotype, minimal residual disease (MRD) pre-HSCT, donor type, remission status, and type and time of first relapse in patients in CR2. For multivariable analyses, Cox regression[4] was used to explore the impact of these risk factors and conditioning type on OS and EFS. In the presence of monotone likelihoods (i.e., absence of events in one subgroup), Firth correction was used.[5] To explore whether one of these risk factors was an effect modifier, subgroup analyses were performed. Cox regression was used to formally test these interactions. The proportions of patients in each study arm with grade III or IV acute GvHD and grade 3 or 4 adverse events at day 100 were compared using a chi-squared test.

The cumulative incidences of relapse, TRM, and chronic GvHD were estimated accounting for competing events and compared using a Gray's test.[6] The multivariable evaluation of relapse incidence used the characteristics specified above for other multivariable analyses. The model of Fine and Gray was used.[7]

Median follow-up was estimated using the inverse Kaplan-Meier method.[8]

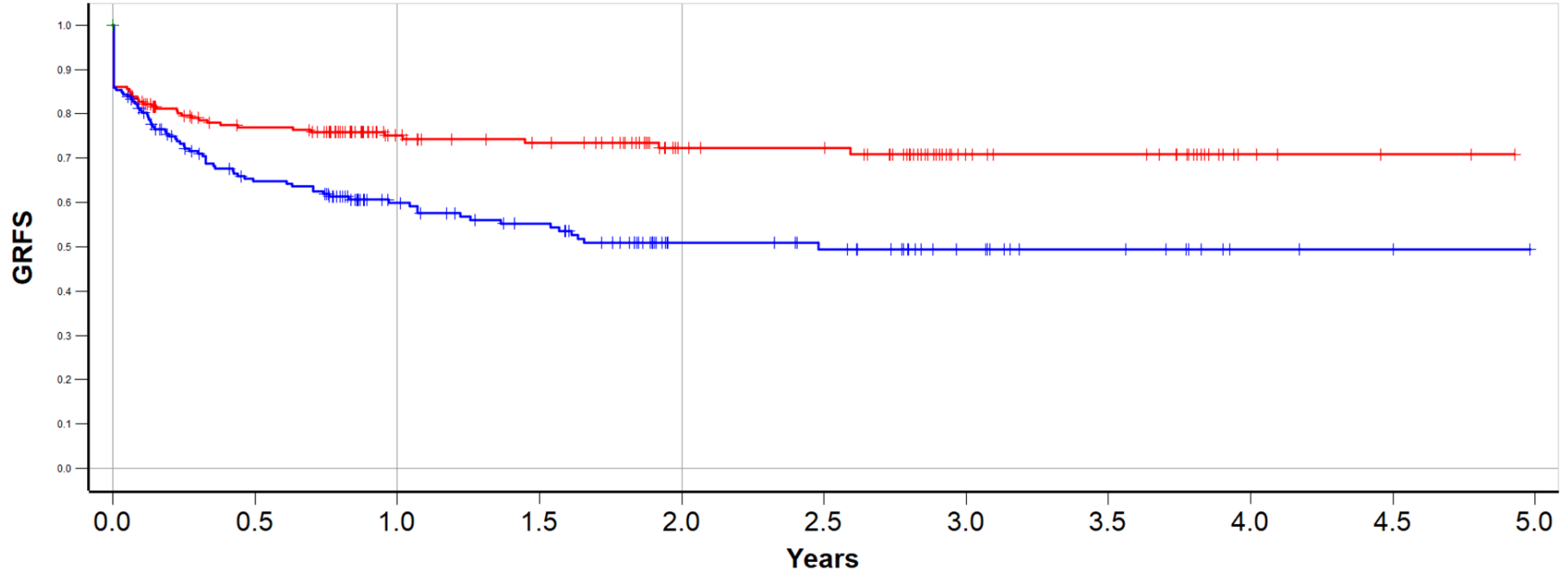
Figure S1. Post-relapse Overall Survival According to Conditioning Regimen (Modified As-Treated Population).



	Patients	Deaths	1-year OS	2-year OS	p value
TBI	23	12	0.49 (0.25−0.69)	0.26 (0.06−0.53)	0.41
Busulfan	23	15	0.43 (0.21−0.64)	0.16 (0.03−0.38)	
Treosulfan	24	11	0.54 (0.30−0.73)	0.36 (0.13−0.60)	

OS analysis used Kaplan-Meier methodology and the log-rank test. BU = busulfan, CHC = chemo-conditioning, OS = overall survival, and TBI = total body irradiation.

Figure S2. GvHD-Free, Relapse-Free Survival According to Conditioning Regimen (ITT population).



Arm	Patients	Events	1-year GRFS	2-year GRFS	p value
TBI	212	54	0.75 (0.70–0.82)	0.72 (0.65–0.79)	<0.001
CHC	201	87	0.60 (0.54−0.68)	0.51 (0.43−0.59)	

GvHD-free, relapse-free survival was estimated with Kaplan-Meier methodology and compared using the log-rank test. Two-year estimates and 95% CIs using log transformation are given. Events were aGvHD Grade III or IV, extensive cGvHD, relapse and death. Death before day 100 and aGvHD is an event at the start of the interval. BU = busulfan, CHC = chemo-conditioning, GRFS = GvHD-free, relapse-free survival, GvHD = graft-versus-host disease, and TBI = total body irradiation.

Table S1. Number of Randomised Patients According to Country and Year.

Country*	Chemo-conditioning	Total	Year of Randomisation					
			2013	2014	2015	2016	2017	2018
Germany	Treosulfan	152	0	12	38	34	25	43
France	Busulfan	108	0	0	21	27	28	32
Italy	Busulfan	33	0	0	0	6	13	14
Austria	Treosulfan	18	3	4	2	1	3	5
Czech Republic	Busulfan	14	0	2	0	2	5	5
Norway	Busulfan	14	0	2	6	0	4	2
Australia + New Zealand	Busulfan	12	0	0	4	3	3	2
Denmark	Busulfan	12	0	0	4	3	0	5
Argentina	Busulfan	10	0	0	0	0	1	9
Finland	Treosulfan	10	0	0	4	4	1	1
Slovakia	Treosulfan	9	0	3	0	2	2	2
Belarus	Treosulfan	5	0	0	0	0	0	5
Israel	Busulfan	5	0	1	1	1	0	2
Switzerland	Busulfan	4	0	0	1	1	1	1
Sweden	Busulfan	4	0	0	0	1	2	1
Canada	Busulfan	2	0	0	0	0	0	2
Spain	Busulfan	1	0	0	0	0	0	1
Total		**413**	**3**	**24**	**81**	**85**	**88**	**132**

*Sites in Malaysia, The Netherlands, and Saudi Arabia did not randomise patients into this part of the study.

Table S2. Key Endpoints by Remission Status.

	Intention-to-treat population			Modified as-treated population		
	TBI	**CHC**	**p value**	**TBI**	**CHC**	**p value**
CR1						
Patients	118	106		**110**	**102**	
Death						
Deaths	9	22		9	22	
2-year OS (95% CI)	0.91 (0.83–0.95)	0.79 (0.68–0.86)	0.004	0.90 (0.81–0.95)	0.78 (0.67–0.85)	0.006
Any failure						
Relapse, second malignancy, or death/patients	11	31/		10	30	
2-year EFS (95% CI)	0.91 (0.83–0.95)	0.67 (0.56–0.76)	<0.001	0.91 (0.83–0.96)	0.67 (0.56–0.76)	<0.001
Relapse						
Relapses/patients	8/118	23/106		7	22	
2-year CIR (95% CI)	0.07 (0.03–0.13)	0.24 (0.16–0.33)	0.001	0.07 (0.03–0.13)	0.24 (0.15–0.33)	0.002
Non-leukaemia death						
Death in CR/patients	3/118	8/106		3	8/106	
2-year TRM (95% CI)	0.02 (<0.01–0.06)	0.09 (0.04–0.16)	0.078	0.02 (<0.01–0.13)	0.09 (0.04–0.17)	0.091
CR2						
Patients	85	79		81	76	
Death						
Deaths	9	22		9	19	
2-year OS (95% CI)	0.91 (0.82–0.69)	0.71 (0.58–0.81)	0.009	0.91 (0.81–0.95)	0.74 (0.59–0.38)	0.035
Any failure						
Relapse, second malignancy or death	18	35		18	32	
2-year EFS (95% CI)	0.76 (0.64–0.85)	0.46 (0.39–0.59)	0.002	0.75 (0.62–0.84)	0.46 (0.32–0.59)	0.009
Relapse						
Relapses	15	28		15	25	0.042
2-year CIR (95% CI)	0.20 (0.11–0.31)	0.45 (0.32–0.57)	0.012	0.22 (0.12–0.33)	0.44 (0.30–0.58)	

	Intention-to-treat population			Modified as-treated population		
	TBI	**CHC**	**p value**	**TBI**	**CHC**	**p value**
Non-leukaemia death						
Death in CR	3	7		3	7	
2-year TRM (95% CI)	0.04 (0.01–0.09)	0.09 (0.04–0.17)	0.18	0.04 (0.01–0.10)	0.09 (0.04–0.18)	0.18

OS and EFS analyses used Kaplan-Meier methodology and the log-rank test. CIR estimates accounted for respective competing events and were compared using Gray's test. CHC = chemo-conditioning, CI = confidence interval, CIR = cumulative incidence of relapse, CR = complete remission, EFS = event-free survival, OS = overall survival, TBI = total body irradiation, and TRM = treatment-related mortality.

Table S3. Key Endpoints in Patients Transplanted in CR2 Stratified by Relapse Within Versus Beyond 18 Months of Diagnosis.

	Intention-to-treat population			Modified as-treated population		
	TBI	**CHC**	**p value**	**TBI**	**CHC**	**p value**
Relapse within 18 months						
Patients	43	34		**40**	**30**	
Death						
Deaths	9	12		9	**10**	0.35
2-year OS (95% CI)	0.83 (0.68–0.92)	0.61 (0.40–0.77)	0.23	0.82 (0.66–0.91)	0.63 (0.40–0.79)	
Any failure						
Relapse, second malignancy, or death/patients	13	18		13	16	0.069
2-year EFS (95% CI)	0.67 (0.49–0.80)	0.37 (0.19–0.55)	0.049	0.65 (0.47–0.79)	0.34 (0.15–0.53)	
Relapse						
Relapses/patients	10	14		10	12	0.16
2-year CIR (95% CI)	0.26 (0.13–0.41)	0.51 (0.30–0.69)	0.095	0.27 (0.13–0.43)	0.52 (0.29–0.71)	
Non-leukaemia death						
Death in CR/patients	3	4		3	**4**	0.40
2-year TRM (95% CI)	0.07 (0.02–0.18)	0.12 (0.04–0.26)	0.47	0.08 (0.02–0.18)	0.14 (0.04–0.29)	

Relapse between >18–30 months						
Patients	42	45		37	44	
Death						
Deaths	0	10		0	9	0.003
2-year OS (95% CI)	1.0	0.78 (0.59–0.89)	0.001	1.0	0.80 (0.61–0.91)	
Any failure						
Relapse, second malignancy, or death	5	17		4	16	0.013
2-year EFS (95% CI)	0.87 (0.68–0.95)	0.53 (0.34–0.69)	0.004	0.86 (0.65–0.94)	0.54 (0.35–0.70)	
Relapse						0.063
Relapses	3	14		4	13	
2-year CIR (95% CI)	0.13 (0.04–0.28)	0.41 (0.24–0.58)	0.026	0.13 (0.14–0.30)	0.40 (0.22–0.57)	
Non-leukaemia death						
Death in CR	0	3		0	3	0.10
2-year of TRM (95% CI)	0	0.06 (0.01–0.18)	0.097	0	0.06 (0.01–0.19)	

OS and EFS analyses used Kaplan-Meier methodology and the log-rank test. CIR estimates accounted for respective competing events and were compared using Gray's test.
CHC = chemo-conditioning, CI = confidence interval, CIR = cumulative incidence of relapse, CR = complete remission, EFS = event-free survival, OS = overall survival, TBI = total body irradiation, and TRM = treatment-related mortality.

Table S4. Toxicity to Day 100 by Conditioning Regimen and Grade in the Modified As-Treated Population.

	TBI							Busulfan-based CHC							Treosulfan-based CHC							p value
	Eval.	Grade 0		Grade 1–2		Grade 3–4		Eval.	Grade 0		Grade 1–2		Grade 3–4		Eval.	Grade 0		Grade 1–2		Grade 3–4		
		n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Reduced granulocytes	190	13	7%	7	4%	164	86%	93	4	4%	5	5%	84	90%	87	4	5%	3	3%	80	92%	0.77
Reduced haemoglobin	190	10	5%	27	14%	153	81%	95	3	3%	17	18%	75	79%	88	1	1%	12	14%	75	85%	0.52
Reduced leukocytes	190	10	5%	10	5%	170	89%	96	4	4%	7	7%	85	89%	88	3	3%	3	3%	82	93%	0.53
Reduced platelets	190	16	8%	3	2%	171	90%	96	4	4%	1	1%	91	95%	88	4	5%	2	2%	82	93%	0.33
Haemolysis	188	165	88%	8	4%	2	1%	95	91	96%	4	4%	0	0%	82	78	95%	1	1%	3	4%	0.11
Non-Haematologic toxicity	190	1	1%	26	14%	163	86%	96	3	3%	18	19%	75	78%	89	1	1%	13	15%	75	84%	0.25
Allergic reaction/ hypersensitivity (including drug fever)	177	148	84%	28	16%	1	1%	95	88	93%	7	7%	0	0%	82	62	76%	19	23%	1	1%	0.56
Cytokine release syndrome/ acute infusion reaction	188	160	85%	19	10%	1	1%	94	91	97%	2	2%	1	1%	82	71	87%	10	12%	1	1%	0.83
Haemophagocytic lymphohistiocytosis	188	174	93%	2	1%	0	0%	95	95	100%	0	0%	0	0%	79	76	96%	1	1%	2	3%	0.032
PTLD	188	179	95%	0	0%	1	1%	95	93	98%	2	2%	0	0%	84	77	92%	1	1%	6	7%	<0.001
Serum sickness	188	175	93%	1	1%	0	0%	95	94	99%	1	1%	0	0%	81	78	96%	3	4%	0	0%	-
Arrhythmia	190	177	93%	5	3%	3	2%	95	90	95%	4	4%	1	1%	84	79	94%	2	2%	3	4%	0.43
Cardiac function	190	147	77%	4	2%	7	4%	83	81	98%	1	1%	1	1%	70	63	90%	5	7%	2	3%	0.40
DIC	188	179	95%	0	0%	0	0%	95	95	100%	0	0%	0	0%	81	77	95%	3	4%	1	1%	0.18
Thrombotic microangiopathy	188	175	93%	1	1%	4	2%	95	94	99%	1	1%	0	0%	82	78	95%	2	2%	2	2%	0.33
Acute vascular leak syndrome	188	168	89%	7	4%	5	3%	95	92	97%	0	0%	3	3%	84	79	94%	4	5%	1	1%	0.67
Thrombosis/embolism	188	175	93%	4	2%	0	0%	95	94	99%	1	1%	0	0%	85	85	100%	0	0%	0	0%	-
Changes in the skin	190	72	38%	114	60%	4	2%	96	40	42%	53	55%	3	3%	87	37	43%	42	48%	8	9%	0.018
Diarrhoea	189	59	31%	103	54%	24	13%	96	27	28%	55	57%	14	15%	88	21	24%	50	57%	17	19%	0.38
Vomiting	189	44	23%	119	63%	24	13%	96	28	29%	61	64%	7	7%	88	9	10%	61	69%	18	20%	0.030
Stomatitis	190	27	14%	39	21%	124	65%	95	27	28%	26	27%	42	44%	88	12	14%	27	31%	49	56%	0.003
Nausea	189	41	22%	75	40%	70	37%	95	29	31%	39	41%	27	28%	88	12	14%	44	50%	32	36%	0.29
Colitis	188	147	78%	25	13%	5	3%	95	69	73%	23	24%	3	3%	82	67	82%	12	15%	3	4%	0.94

	TBI							Busulfan-based CHC							Treosulfan-based CHC							p value
	Eval.	Grade 0		Grade 1–2		Grade 3–4		Eval.	Grade 0		Grade 1–2		Grade 3–4		Eval.	Grade 0		Grade 1–2		Grade 3–4		
		n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Ileus, gastrointestinal	188	174	93%	3	2%	3	2%	95	91	96%	2	2%	2	2%	83	78	94%	1	1%	4	5%	0.30
CNS haemorrhage	188	182	97%	0	0%	1	1%	95	95	100%	0	0%	0	0%	84	82	98%	2	2%	0	0%	0.61
Gastrointestinal haemorrhage	188	169	90%	10	5%	2	1%	95	88	93%	3	3%	4	4%	84	76	90%	6	7%	2	2%	0.25
Pulmonary haemorrhage	188	178	95%	2	1%	1	1%	95	93	98%	1	1%	1	1%	84	83	99%	1	1%	0	0%	0.64
Bladder haemorrhage	188	173	92%	7	4%	0	0%	95	87	92%	8	8%	0	0%	84	73	87%	10	12%	1	1%	0.19
Other haemorrhage	188	177	94%	2	1%	1	1%	95	90	95%	4	4%	1	1%	84	82	98%	1	1%	1	1%	0.84
Bilirubin	190	90	47%	79	42%	21	11%	96	44	46%	39	41%	13	14%	88	31	35%	45	51%	12	14%	0.76
Elevated ALT or AST	190	38	20%	105	55%	43	23%	94	23	24%	58	62%	13	14%	87	9	10%	63	72%	15	17%	0.15
VOD	185	175	95%	6	3%	4	2%	95	89	94%	3	3%	3	3%	86	78	91%	7	8%	1	1%	0.66
Liver dysfunction/failure (clinical)	188	171	91%	9	5%	0	0%	95	85	89%	9	9%	1	1%	81	76	94%	4	5%	1	1%	0.35
Pancreatitis	188	178	95%	2	1%	0	0%	95	89	94%	6	6%	0	0%	84	75	89%	9	11%	0	0%	-
Fever	190	21	11%	155	82%	14	7%	96	23	24%	68	71%	5	5%	88	10	11%	70	80%	8	9%	0.59
Infection	190	23	12%	96	51%	71	37%	96	24	25%	39	41%	33	34%	88	6	7%	25	28%	57	65%	<0.0001
Osteonecrosis (avascular necrosis)	188	172	91%	4	2%	1	1%	94	93	99%	0	0%	1	1%	80	77	96%	3	4%	0	0%	0.65
Peripheral neurotoxicity	190	170	89%	16	8%	1	1%	96	90	94%	6	6%	0	0%	88	73	83%	10	11%	5	6%	0.002
Central neurotoxicity	190	174	92%	10	5%	3	2%	96	90	94%	3	3%	3	3%	86	80	93%	4	5%	2	2%	0.70
Leukoencephalopathy	190	154	81%	5	3%	0	0%	93	93	100%	0	0%	0	0%	61	57	93%	3	5%	1	2%	0.13
Encephalopathy	190	179	94%	2	1%	2	1%	95	95	100%	0	0%	0	0%	80	75	94%	2	3%	3	4%	0.096
Seizure	188	178	95%	2	1%	1	1%	95	92	97%	3	3%	0	0%	84	79	94%	4	5%	1	1%	0.57
Hypoxia	190	160	84%	3	2%	21	11%	93	78	84%	1	1%	14	15%	86	64	74%	7	8%	15	17%	0.37
Pneumonitis, pulmonary infiltrates	190	158	83%	10	5%	13	7%	91	78	86%	5	5%	8	9%	81	63	78%	9	11%	9	11%	0.57
ARDS	188	172	91%	3	2%	4	2%	92	88	96%	0	0%	4	4%	82	77	94%	0	0%	5	6%	0.28
Aspiration	188	177	94%	3	2%	0	0%	94	93	99%	1	1%	0	0%	83	78	94%	2	2%	3	4%	0.007
Atelectasis	188	174	93%	5	3%	0	0%	95	93	98%	2	2%	0	0%	81	79	98%	2	2%	0	0%	-
Creatinine	189	106	56%	78	41%	5	3%	96	51	53%	44	46%	1	1%	88	52	59%	34	39%	2	2%	0.67
Haematuria	190	136	72%	42	22%	3	2%	92	66	72%	23	25%	3	3%	82	54	66%	24	29%	4	5%	0.33

	TBI							Busulfan-based CHC							Treosulfan-based CHC							p value
	Eval.	Grade 0		Grade 1–2		Grade 3–4		Eval.	Grade 0		Grade 1–2		Grade 3–4		Eval.	Grade 0		Grade 1–2		Grade 3–4		
		n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	n	%	
Proteinuria	190	140	74%	31	16%	0	0%	81	71	88%	10	12%	0	0%	74	51	69%	23	31%	0	0%	-

Terminology are National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0, terms modified to meet transplant-specific criteria for toxicity. ALT = alanine aminotransferase, ARDS = acute respiratory distress syndrome, AST = aspartate aminotransferase, CNS = central nervous system, DIC = diffuse intravascular coagulation, PTLD = post-transplant lymphoproliferative disease, VOD = veno-occlusive disease.

Table S5. Causes of Death Unrelated to Relapse in the Modified As-Treated Population.*

	TBI	Busulfan	Treosulfan
Treatment-related mortality	7	7	9
Infection fungal	2	1	
Infection viral	2	2	1
Infection viral + bacterial			3
Infection bacterial			1
Acute graft-versus-host disease	1		1
Chronic graft-versus-host disease	2	2	2
Bleeding		1	
Veno-occlusive disease		1	
Post-transplant lymphoproliferative disease			1

*In addition, one patient randomised to total body irradiation but who received treosulfan-based chemo-conditioning (i.e. protocol violation) had a main cause of death of haemophagocytic lymphohistiocytosis.

Table S6. Incidence of Acute GvHD by Grade, Conditioning Regimen, and Donor Type.

		Intention-to-treat population					Modified as-treated population						
		TBI		CHC		P value*	TBI		Busulfan		Treosulfan		p value*
		n	%	n	%		n	%	n	%	n	%	
MSD	Total patients	54		55			52		34		19		
	Evaluable patients	51		53			49		34		18		
	0 or I	28	55%	35	66%		27	55%	24	71%	11	61%	
	II	12	24%	13	25%		12	24%	7	21%	5	28%	
	III or IV	11	22%	5	9%	0.086	10	20%	3	9%	2	11%	0.40
MD	Total patients	158		146			142		62		71		
	Evaluable patients	152		140			139		62		69		
	0 or I	99	65%	101	72%		88	63%	41	66%	56	81%	
	II	39	26%	26	19%		37	27%	16	26%	6	9%	
	III or IV	14	9%	13	9%	0.98	14	10%	5	8%	7	10%	0.89

*P value for Grade III/IV acute GvHD in the TBI versus CHC arm (chi-square test). aGvHD = acute graft-versus-host disease, MD = human leukocyte antigen (HLA)-compatible (nine or 10 out of 10 allelic matches) related or unrelated matched donor, MRD = minimal residual disease, MSD = HLA-identical sibling donor, TBI = total body irradiation.

Table S7. Univariate evaluation of risk factors.

	Overall Survival					Event-Free Survival				
	n	**Eval.**	**Deaths**	**2-year OS (95% CI)**	**p value (log-rank)**	**n**	**Eval.**	**Deaths**	**2-year OS (95% CI)**	**p value (log-rank)**
Total	**413**	**409**	**68**	**0.83 (0.78–0.87)**		**413**	**409**	**103**	**0.72 (0.67–0.77)**	**–**
Sex (recipient)										
Male	267	264	40	0.85 (0.8–0.89)	0.21	267	264	57	0.77 (0.7–0.82)	0.016
Female	146	145	28	0.79 (0.7–0.86)		146	145	46	0.64 (0.54–0.72)	
Age										
4–6 years	56	55	10	0.82 (0.68–0.9)	0.065	56	55	12	0.77 (0.62–0.86)	0.38
>6–10 years	141	140	17	0.88 (0.8–0.93)		141	140	33	0.73 (0.64–0.81)	
>10–14 years	106	106	15	0.87 (0.77–0.92)		106	106	25	0.77 (0.66–0.85)	
>14 years	110	108	26	0.74 (0.63–0.82)		110	108	33	0.63 (0.52–0.73)	
Immunophenotype										
B-cell precursor	297	294	50	0.84 (0.79–0.88)	0.58	297	294	80	0.71 (0.64–0.76)	0.22
T-cell ALL	94	93	13	0.83 (0.72–0.9)		94	93	16	0.81 (0.7–0.88)	
Other	18	18	4	0.66 (0.31–0.87)		18	18	5	0.56 (0.22–0.8)	
MRD pre-HSCT*										
MRD- (PCR)	135	135	18	0.90 (0.83–0.94)	0.60	135	135	29	0.78 (0.69–0.85)	0.49
MRD+ (PCR)	132	132	24	0.81 (0.72–0.87)		132	132	36	0.70 (0.61–0.78)	
MRD- (flow cytometry)	57	57	9	0.80 (0.65–0.9)		57	57	12	0.75 (0.58–0.85)	
MRD+(flow cytometry	12	12	2	0.69 (0.16–0.93)		12	12	2	0.83 (0.48–0.96)	
Donor										
MSD	108	108	22	0.81 (0.71–0.88)	<0.001	108	108	30	0.69 (0.58–0.77)	<0.001
MD	299	297	43	0.85 (0.8–0.89)		299	297	69	0.75 (0.68–0.8)	
Remission status										
CR1	225	224	31	0.85 (0.79–0.9)	<0.001	225	224	42	0.80 (0.73–0.85)	<0.001
CR2	164	163	31	0.81 (0.73–0.87)		164	163	53	0.61 (0.52–0.69)	
CR3	18	18	3	0.89 (0.62–0.97)		18	18	4	0.89 (0.62–0.97)	
CR2 patients: type of relapse										

	Overall Survival					Event-Free Survival				
	n	**Eval.**	**Deaths**	**2-year OS (95% CI)**	**p value (log-rank)**	**n**	**Eval.**	**Deaths**	**2-year OS (95% CI)**	**p value (log-rank)**
Bone marrow isolated	111	110	22	0.81 (0.71–0.88)	0.93	111	110	37	0.60 (0.48–0.7)	0.80
Other isolated	14	14	2	0.85 (0.51–0.96)		14	14	5	0.62 (0.31–0.82)	
Combined	38	38	7	0.82 (0.63–0.92)		38	38	11	0.65 (0.44–0.8)	
CR2 patients: time of relapse										
<18 months	22	22	5	0.77 (0.53–0.9)	0.012	22	22	9	0.59 (0.36–0.76)	0.025
18–30 months	55	54	16	0.71 (0.54–0.83)		55	54	22	0.5 (0.33–0.65)	
>30 months	87	87	10	0.89 (0.78–0.95)		87	87	22	0.69 (0.56–0.79)	

*Defined as $>10^{-3}$ for flow cytometry and $>10^{-4}$ for PCR. For the univariate evaluation of risk factors, OS and EFS were estimated with Kaplan-Meier methodology and compared using the log-rank test. Two-year estimates and 95% CIs using log transformation are given. ALL = acute lymphoblastic leukaemia, CR1 = first complete remission (below 5% of morphological blasts in bone marrow; no active extramedullary disease), CR2 = second complete remission, CR3 = third complete remission, HSCT = haematopoietic stem cell transplantation, MD = human leukocyte antigen (HLA)-compatible (nine or 10 out of 10 allelic matches) related or unrelated matched donor, MRD = minimal residual disease, MSD = HLA-identical sibling donor, PCR = polymerase chain reaction, and TBI = total body irradiation.

Table S8. Sub-group Analyses of Overall Survival by Risk Factor and Conditioning Regimen (ITT Population).

	TBI				CHC				HR (CHC vs. TBI)		p value
	n	Eval.	Events	2-year OS (95% CI)	n	Eval.	Events	2-year OS (95% CI)	HR (95% CI)	p value	(Interaction)
Total	**212**	**209**	**19**	**0.91 (0.86–0.95)**	**201**	**200**	**49**	**0.75 (0.67–0.81)**	**2.96 (1.74–5.03)**	**<0.001**	
Sex (recipient)											
Male	145	143	12	0.93 (0.87–0.97)	122	121	28	0.76 (0.66–0.84)	2.94 (1.49–5.79)	0.002	0.96
Female	67	66	7	0.88 (0.75–0.94)	79	79	21	0.72 (0.59–0.82)	2.85 (121–6.71)	0.016	
Age											
4–6 years	34	33	5	0.85 (0.65–0.94)	22	22	5	0.77 (0.53–0.9)	1.54 (0.45–5.33)	0.49	0.039
>6–10 years	66	65	3	0.95 (0.86–0.98)	75	75	14	0.81 (0.69–0.89)	4.71 (1.35–16.41)	0.015	
>10–14 years	64	64	2	1	42	42	13	0.67 (0.48–0.8)	13.24 (2.96–59.24)	0.001	
>14 years	48	47	9	0.79 (0.61–0.89)	62	61	17	0.71 (0.56–0.82)	1.32 (0.59–2.96)	0.51	
Immunophenotype											
B-cell precursor	153	150	15	0.91 (0.84–0.95)	144	144	35	0.77 (0.68–0.84)	2.54 (1.39–4.65)	0.003	0.60
T-cell ALL	48	48	3	0.92 (0.77–0.97)	46	45	10	0.73 (0.55–0.85)	4.07 (1.12–14.78)	0.033	
Other	11	11	1	0.91 (0.51–0.99)	7	7	3	0.28 (0.01–0.7)	5.5 (0.57–53.28)	0.14	
MRD pre-HSCT*											
MRD- (PCR)	72	72	7	0.95 (0.86–0.98)	63	63	11	0.84 (0.7–0.92)	2.18 (0.84–5.63)	0.11	0.75
MRD+ (PCR)	61	61	5	0.90 (0.78–0.96)	71	71	19	0.73 (0.59–0.83)	3.76 (1.4–10.08)	0.009	
MRD- (flow cytometry)	32	32	2	0.93 (0.75–0.98)	25	25	7	0.65 (0.39–0.82)	4.9 (1.02–23.61)	0.047	
MRD+ (flow cytometry)	9	9	1	0.67 (0.05–0.95)	3	3	1	0.67 (0.05–0.95)	3 (0.19–47.96)	0.44	
Donor											
MSD	54	54	7	0.89 (0.75–0.95)	54	54	15	0.74 (0.58–0.84)	2.28 (0.93–5.59)	0.072	0.60
MD	156	155	12	0.92 (0.86–0.96)	143	142	31	0.77 (0.68–0.84)	3.06 (1.57–5.96)	0.001	
Remission status											
CR1	118	118	9	0.91 (0.83–0.95)	107	106	22	0.79 (0.68–0.86)	2.99 (1.38–6.5)	0.006	0.89
CR2	85	84	9	0.91 (0.82–0.96)	79	79	22	0.71 (0.58–0.81)	2.69 (1.24–5.84)	0.013	

	TBI				CHC				HR (CHC vs. TBI)		p value
	n	Eval.	Events	2-year OS (95% CI)	n	Eval.	Events	2-year OS (95% CI)	HR (95% CI)	p value	(Interaction)
CR3	7	7	1	1	11	11	2	0.82 (0.45–0.95)	1.86 (0.16–21.68)	0.62	
CR2 patients: type of relapse											
Bone marrow isolated	53	52	6	0.92 (0.8–0.97)	58	58	16	0.72 (0.56–0.83)	2.48 (0.97–6.34)	0.058	1.0
Other isolated	7	7	0		7	7	2				
Combined	24	24	3	0.87 (0.65–0.96)	14	14	4	0.68 (0.25–0.9)	2.51 (0.56–11.26)	0.23	
CR2 patients: time of relapse											
<18 months	16	16	2	0.88 (0.59–0.97)	6	6	3	0.50 (0.11–0.80)	4.46 (0.75–26.75)	0.10	0.50
18–30 months	27	26	7	0.80 (0.59–0.91)	28	28	9	0.63 (0.39–0.8)	1.16 (0.43–3.13)	0.77	
>30 months†	42	42	0	1	45	45	10	0.78 (0.59–0.89)	22.5 (1.1-442	0.041	

*Defined as $>10^{-3}$ for flow cytometry and $>10^{-4}$ for PCR. OS was estimated with Kaplan-Meier methodology. Two-year estimates and 95% CIs using log transformation are given. To explore potential interaction between conditioning type and these risk factors, subgroup analyses were performed, and the statistical significance of these interaction was explored with Cox regression (†using Firth correction). ALL = acute lymphoblastic leukaemia, CR1 = first complete remission (below 5% of morphological blasts in bone marrow; no active extramedullary disease), CR2 = second complete remission, CR3 = third complete remission, HSCT = haematopoietic stem cell transplantation, MD human leukocyte antigen (HLA)-compatible (nine or 10 out of 10 allelic matches) related or unrelated matched donor, MRD = minimal residual disease, MSD = HLA-identical sibling donor, OS = overall survival, PCR = polymerase chain reaction, and TBI = total body irradiation.

Table S9. Sub-group Analysis of Event-Free Survival by Risk Factor and Conditioning Regimen (ITT Population).

	TBI				CHC				HR (CHC vs. TBI)		p value
	n	Eval.	Events	2-year EFS (95% CI)	n	Eval.	Events	2-year EFS (95% CI)	HR (95% CI)	p value	(Inter-action)
	212	**209**	**31**	**0.86 (0.79–0.9)**	**201**	**200**	**72**	**0.58 (0.5–0.66)**	**2.79 (1.83–4.25)**	**<0.001**	
Sex (recipient)											
Male	145	143	19	0.88 (0.81–0.93)	122	121	38	0.64 (0.54–0.73)	2.57 (1.48–4.46)	0.001	0.76
Female	67	66	12	0.81 (0.68–0.89)	79	79	34	0.48 (0.35–0.61)	2.95 (1.53–5.71)	0.001	
Age											
4–6 years	34	33	6	0.79 (0.58–0.90)	22	22	6	0.73 (0.49–0.87)	1.6 (0.52–4.97)	0.41	0.29
>6–10 years	66	65	7	0.90 (0.80–0.96)	75	75	26	0.58 (0.44–0.70)	4 (1.73–9.24)	0.001	
>10–14 years	64	64	8	0.91 (0.78–0.97)	42	42	17	0.55 (0.36–0.70)	4.45 (1.9–10.38)	0.001	
>14 years	48	47	10	0.77 (0.61–0.87)	62	61	23	0.55 (0.4–0.68)	1.78 (0.85–3.74)	0.13	
Immunophenotype											
B-cell precursor	153	150	26	0.84 (0.76–0.89)	144	144	54	0.58 (0.48–0.66)	2.42 (1.52–3.87)	0.000	0.45
T-cell ALL	48	48	4	0.90 (0.75–0.96)	46	45	12	0.71 (0.54–0.82)	3.69 (1.19–11.44)	0.024	
Other	11	11	1	0.91 (0.51–0.99)	7	7	4		9.58 (1.03–89.14)	0.047	
MRD pre-HSCT*											
MRD- (PCR)	72	72	11	0.88 (0.77–0.94)	63	63	18	0.66 (0.51–0.78)	2.21 (1.04–4.68)	0.039	0.75
MRD+ (PCR)	61	61	9	0.86 (0.73–0.93)	71	71	27	0.56 (0.42–0.68)	3.23 (1.51–6.88)	0.002	
MRD- (flow cytometry)	32	32	3	0.87 (0.62–0.96)	25	25	9	0.59 (0.33–0.77)	4.4 (1.19–16.27)	0.026	
MRD+ (flow cytometry)	9	9	1	0.89 (0.43–0.98)	3	3	1	0.67 (0.05–0.95)	3.67 (0.23–59.59)	0.36	
Donor											
MSD	54	54	10	0.81 (0.67–0.9)	54	54	20	0.57 (0.41–0.7)	2.17 (1.01–4.63)	0.046	0.58
MD	156	155	21	0.87 (0.8–0.92)	143	142	48	0.61 (0.51–0.7)	2.87 (1.72–4.8)	0.000	
Remission status											
CR1	118	118	11	0.91 (0.83–0.95)	107	106	31	0.67 (0.56–0.76)	3.56 (1.79–7.09)	0.000	0.28

	TBI				CHC				HR (CHC vs. TBI)		p value
	n	Eval.	Events	2-year EFS (95% CI)	n	Eval.	Events	2-year EFS (95% CI)	HR (95% CI)	p value	(Inter-action)
CR2	85	84	18	0.76 (0.64–0.85)	79	79	35	0.46 (0.33–0.59)	2.36 (1.34–4.17)	0.003	
CR3	7	7	2		11	11	2	0.82 (0.45–0.95)	1.1 (0.15–8.35)	0.92	
CR2-patients: type of relapse											
Bone marrow isolated	53	52	11	0.77 (0.61–0.87)	58	58	26	0.45 (0.3–0.6)	2.49 (1.23–5.04)	0.011	0.65
Other isolated	7	7	2	0.69 (0.21–0.91)	7	7	3	0.57 (0.17–0.84)	1.3 (0.22–7.78)	0.78	
Combined	24	24	5	0.76 (0.49–0.9)	14	14	6	0.42 (0.11–0.71)	2.47 (0.74–8.19)	0.14	
CR2 patients: time of relapse											
<18 months	16	16	5	0.69 (0.4–0.86)	6	6	4	0.33 (0.05–0.68)	2.49 (0.67–9.32)	0.17	0.67
18–30 months	27	26	8	0.65 (0.41–0.82)	28	28	14	0.37 (0.16–0.57)	1.94 (0.81–4.63)	0.14	
>30 months	42	42	5	0.87 (0.68–0.95)	45	45	17	0.53 (0.34–0.69)	3.85 (1.42–10.45)	0.008	

*Defined as $>10^{-3}$ for flow cytometry and $>10^{-4}$ for PCR. EFS was estimated with Kaplan-Meier methodology and compared using the log-rank test. Two-year estimates and 95% CIs using log transformation are given. To explore potential interaction between conditioning type and these risk factors, subgroup analyses were performed, and the statistical significance of these interaction was explored with Cox regression. ALL = acute lymphoblastic leukaemia; CR1 = first complete remission (below 5% of morphological blasts in bone marrow; no active extramedullary disease), CR2 = second complete remission, CR3 = third complete remission, EFS = event-free survival, HSCT = haematopoietic stem cell transplantation, MD = human leukocyte antigen (HLA)-compatible (nine or 10 out of 10 allelic matches) related or unrelated matched donor, MRD = minimal residual disease, MSD = HLA-identical sibling donor, PCR = polymerase chain reaction, and TBI = total body irradiation.

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