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Predictive Factors for Outcome of First Allogeneic Transplant for Elderly Patients With Acute Lymphoblastic Leukemia

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AlloHCT in elderly ALL patients

1 **Predictive factors for outcome of first allogeneic transplant for elderly patients** 2 **with acute lymphoblastic leukemia**

3
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40 **Running Title:** AlloHCT in elderly ALL patients.

41

42 **MICRO ABSTRACT**

43 Acute lymphoblastic leukemia (ALL) in elderly patients is challenging, and while
44 allogeneic stem cell transplantation (alloHCT) has established benefits in younger
45 candidates, its use in the elderly can be difficult. We identified 84 ALL patients 70
46 years or older in the EBMT registry that underwent alloHCT. Our results
47 demonstrate favorable outcome especially in those achieving first complete
48 remission with >50% 2-year OS. AlloHCT appears feasible in select elderly ALL
49 patients.

50

51 **CLINICAL PRACTICE POINTS**

52 • What is already known about this subject?

53 Acute lymphoblastic leukemia (ALL) has dismal outcome in elderly patients, and
54 while allogeneic stem cell transplantation (alloHCT) has established benefits in
55 younger candidates, its use in the elderly can be difficult.

56 • What are the new findings?

57 AlloHCT appears feasibly in elderly patients and our results demonstrate
58 favorable outcome especially in those achieving first complete remission with
59 >50% 2-year OS.

60 • How might it impact on clinical practice in the foreseeable future?

61 We believe our results can help shift the paradigm of alloHCT usage in elderly
62 patients as it appears to be a valid option especially in carefully selected
63 candidates.

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ABSTRACT

The treatment of acute lymphoblastic leukemia (ALL) in patients older than 70 is extremely challenging with dismal outcome. Allogeneic stem cell transplantation (alloHCT) has seen many advancements in the last decades showing benefits in younger ALL patients, but this treatment modality is decreasingly used with increasing age due to high treatment-related mortality. We identified 84 ALL patients 70-84 years old allografted in 2002-2019 from a matched related (23%), unrelated (58%), haploidentical (17%) or cord blood (2%) donor at EBMT participating centers with a median follow-up of 23 months. The 2-year relapse incidence (RI) and non-relapse mortality (NRM) were 37% and 28%, respectively, and 2-year leukemia-free survival (LFS), overall survival (OS) and GVHD-free, relapse-free survival (GRFS) were 35%, 39% and 23%, respectively. The strongest predictor of outcome was disease status at transplant whereby patients in first complete remission (CR1) had >50% 2-year OS, reflected in multivariate analysis (MVA) with significant improvement in RI, LFS and GRFS (HR 0.23, 0.49 and 0.54, respectively). Furthermore, karnofsky score ≥ 90 reflective of good functional status positively influenced NRM in both univariate and MVA (HR 0.37), and interestingly, donor CMV positivity appeared to negatively affect RI, LFS and OS in univariate analysis and RI in MVA (HR 2.87). Our data suggest that alloHCT is an option for elderly ALL patients, particularly those carefully selected and

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85 transplanted in CR1 especially if failed or without access to novel non-
86 chemotherapy-based approaches.

87

88 **KEYWORDS**

89 Acute lymphoblastic leukemia; allogeneic stem cell transplantation; elderly
90 patients; complete remission; haploidentical transplantation; graft-versus-host
91 disease.

92

93 **ABREVIATIONS**

- 94 - Acute lymphoblastic leukemia (ALL)
- 95 - Overall survival (OS)
- 96 - Allogeneic stem-cell transplantation (alloHCT)
- 97 - Total body irradiation (TBI)
- 98 - Reduced-intensity conditioning (RIC)
- 99 - Acute Leukemia Working Party (ALWP)
- 100 - European Society for Blood and Marrow Transplantation (EBMT)
- 101 - Karnofsky performance status (KPS)
- 102 - Graft-versus-host disease (GVHD)
- 103 - Cytomegalovirus (CMV)
- 104 - Myeloablative conditioning (MAC)
- 105 - Leukemia free survival (LFS)
- 106 - Non-relapse mortality (NRM)

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- 107 - Relapse incidence (RI)
- 108 - GVHD-free, relapse-free survival (GRFS)
- 109 - Complete remission (CR)
- 110 - Hazard ratio (HR)
- 111 - Confidence interval (CI)
- 112 - Philadelphia chromosome (Ph)
- 113 - Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI)
- 114 - T cell depletion (TCD)
- 115 - Chimeric antigen receptor (CAR)
- 116 - Pegylated-asparaginase (PEG-ASP)
- 117 - Tyrosine kinase inhibitor (TKI)
- 118 - Minimal residual disease (MRD)
- 119 - Acute myeloid leukemia (AML)
- 120

121 **INTRODUCTION**

122

123 The management of acute lymphoblastic leukemia (ALL) in elderly patients is
124 challenging with a generally dismal outcome. In fact, while patients above the age
125 of 55 only constitute around a fifth of diagnosed ALL, they account for over half of
126 ALL-related deaths.¹ This striking discrepancy is explained by age-related
127 increased comorbidities and higher-risk genetic alterations leading to lower
128 remission rates, higher relapse rates, and poor overall survival (OS). Patients often
129 do not respond well to chemotherapy, and even those achieving remission have
130 <25% 5-year survival.² While the benefits of allogeneic stem-cell transplantation
131 (alloHCT) in younger ALL patients have been well established, with a long term
132 survival advantage exceeding 4 fold in certain patients,³⁻⁷ its indication for elderly
133 patients is controversial and rarely made due to its concomitant high treatment-
134 related mortality,⁸ and older patients are often excluded from investigational
135 trials. Furthermore, many of the alloHCT for ALL are based on myeloablative total
136 body irradiation (TBI) which cannot be delivered to elderly patients due to high
137 toxicity.⁹⁻¹⁵ Many advancements in reduced-intensity conditioning (RIC) have been
138 made however, which is proving to be a promising option for selected patients
139 and increasing study eligibility.^{15,16} Clinical trials with alloHCT in elderly patients
140 remain extremely rare, and results from both prospective and retrospective
141 studies have so far yielded conflicting results with little evidence for benefit of
142 transplant in such patients.^{17,18} This missing gap in the literature drove us to

143 conduct this retrospective analysis using the European Society for Blood and
144 Marrow Transplantation (EBMT) registry, which we believe will provide better
145 understanding of alloHCT outcome and whether this modality is feasible in this
146 population.

147

148 **MATERIALS AND METHODS**

149 *Study Design and Data Collection*

150 This was a retrospective, registry-based, multicenter analysis. Data were provided
151 and approved by the Acute Leukemia Working Party (ALWP) of the EBMT.¹⁹ The
152 EBMT is a voluntary collaborating working group of more than 600 transplant
153 centers that are required to report all consecutive stem cell transplantations and
154 follow-up once a year, with regularly performed audits to determine the accuracy
155 of the data. Since the 1st of January 2003, all transplantation centers have been
156 required to obtain written informed consent prior to data registration with the
157 EBMT, as per the guidelines of the Declaration of Helsinki of 1975.

158

159 Eligibility criteria for this analysis included elderly patients (aged ≥ 70 years) with
160 ALL who received a first alloHCT between 2000 and 2019 from an HLA-matched
161 related, unrelated, haploidentical or cord blood donor with bone marrow,
162 peripheral blood or cord blood stem cells. Variables collected included recipient

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163 and donor age and gender, date of diagnosis, disease status and Karnofsky
164 performance status (KPS) score at the time of transplant. Transplant-related
165 factors included date, conditioning regimen and graft-versus-host disease (GVHD)
166 prophylaxis, *in vivo* T-cell depletion, donor type, and patient and donor
167 cytomegalovirus (CMV) status.

168 *Definitions*

169 Myeloablative conditioning (MAC) was defined as a regimen containing either TBI
170 with a dose ≥ 8 Gy, a total dose of oral busulfan (Bu) > 8 mg/kg, or a total dose of
171 intravenous Bu > 6.4 mg/kg. All other regimens were defined as RIC.²⁰ Diagnosis
172 and grading of acute²¹ and chronic GVHD²² were performed by transplant centers
173 using standard criteria. High-resolution HLA allele typing at loci A, B, C, DRB1 and
174 DQ was retrieved from the EBMT registry for both the patient and the donor.

175 *Endpoints*

176
177 Endpoints included leukemia free survival (LFS), OS, non-relapse mortality (NRM),
178 relapse incidence (RI), acute and chronic GVHD, and GVHD-free, relapse-free
179 survival (GRFS), with all outcomes measured from the time of alloHCT. LFS was
180 defined as survival without leukemia relapse or progression, with patients
181 censored at the time of last contact. OS was defined as the time until death from
182 any cause. NRM was defined as being alive until death with no previous leukemia
183 relapse. GRFS was defined as being alive with neither grade III-IV acute GVHD,

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184 extensive chronic GVHD, nor relapse.²³ Surviving patients were censored at the
185 time of last contact.

186

187 *Statistical analysis*

188

189 The Kaplan-Meier method was used to calculate the probabilities of OS and LFS.
190 Cumulative incidence functions were used to estimate RI and NRM in a competing
191 risk setting. Death and relapse were considered as competing events for acute and
192 chronic GVHD.

193 Univariate analyses were done using the Gray's test for cumulative incidence
194 functions and the log rank test for OS, GRFS, and LFS. A Cox proportional
195 hazards model was used for multivariate regression, including status of the
196 disease at HSCT (first complete remission [CR1] vs other), donor type (MSD vs
197 other), year of HSCT and factors associated with the outcome in univariate.

198 Results were expressed as hazard ratio (HR) with a 95% confidence interval (CI).

199 All tests were two sided. The type-1 error rate was fixed at 0.05 for

200 determination of factors associated with time-to-event outcomes. All analyses

201 were performed using SPSS 24.0 (SPSS Inc, Chicago, IL, USA) and R version 3.4.0

202 (R Core Team. R: a language for statistical computing. 2014. R Foundation for

203 Statistical Computing, Vienna, Austria).

204

205 **RESULTS**

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206 *Patient and Transplantation Characteristics*

207 Eighty-four patients (43% female; median age 72 years; range 70-84) met the
208 eligibility criteria and were included in this study (Tables 1 & 2) with a median
209 follow-up for alive patients of 23 months (IQR 6-46). More than half (53%) of the
210 patients were in CR1, 26% were in second or subsequent remission (CR2+), and
211 21% had advanced disease. Thirteen % had T-cell acute lymphoblastic leukaemia
212 (T-ALL), 35% were Philadelphia chromosome positive, 21% were Philadelphia
213 chromosome (Ph) negative, and 31% had B-cell acute lymphoblastic leukemia (B-
214 ALL) with unknown Ph status. The KPS score was ≥ 90 in 59% of the patients and
215 the Hematopoietic Cell Transplantation-Comorbidity Index (HCT-CI) was 1-2, and
216 ≥ 3 in 11% and 17% of patients, respectively. Conditioning was MAC in 22.6% of
217 the patients (Supplementary Table 1) and 40.5% received TBI. *In vivo* T cell
218 depletion (TCD) was used in 55% of patients. Sixty-eight % of the patients and 57%
219 of the donors were CMV positive. Sixteen percent of patients were males who
220 received a graft from a female donor. Patients were allografted from a matched
221 related (23%), matched unrelated (58%), haploidentical (17%) or cord blood donor
222 (2%).

223

224 *Transplant outcomes*

225

226 Median time from diagnosis to alloHCT was 8.8 months (IQR 5.7-16.3). Day +180
227 acute GVHD grades II-IV and III-IV were encountered in 30% and 10% of patients,

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228 respectively, whereas the 2-year cumulative incidence of chronic and extensive
229 GVHD were 34% and 23%, respectively. The 2-year RI was 37% and NRM 28%. The
230 2-year LFS, OS and GRFS were 35%, 39% and 23%, respectively. (Tables 3 & 4) The
231 main causes of death of the 46 deceased patients were primary disease (45%),
232 infections (29%) and GVHD (10%) (Table 5).

233 In the univariate analysis (Tables 3 & 4), patient age, ALL subtype, conditioning
234 intensity, TBI use, patient and donor gender, female to male donor, and *in vivo*
235 TCD did not affect any of the transplant outcomes. On the other hand, at least one
236 outcome was affected by the status at transplant, donor type, KPS score and HCT-
237 CI, year of transplant, and patient and donor CMV serology. In fact, patients in CR1
238 had a significantly better 2-year outcomes compared to CR2+ and advanced
239 disease with relapse rates of 14% versus 54% and 64% respectively ($p=0.001$), LFS
240 of 52% versus 21% and 18% respectively ($p=0.009$), OS of 53% versus 33% and 21%
241 respectively ($p=0.029$), and GRFS of 36% versus 8% and 13% respectively ($p=0.01$).
242 (Table 3) (Figure 1). Patients with a KPS score ≥ 90 had a significantly lower NRM
243 (17%) compared to 44% in those with a KPS < 90 ($p=0.016$), and those transplanted
244 from CMV positive donors had a higher RI of 50% versus 21% in CMV negative
245 donors ($p=0.007$), and worse LFS (23% versus 49%; $p=0.012$) and OS (25% versus
246 55%; $p=0.024$) (Table 3). On the other hand, patients undergoing haploidentical
247 transplants and those with HCT-CI scores ≥ 3 had significantly higher rates of day
248 +180 grade III-IV acute GVHD (29% $p=0.04$ and 36% $p=0.015$ respectively). Patients
249 transplanted before 2015 (median) had lower rates of day +180 grade II-IV acute

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250 GVHD (14% versus 41%; $p=0.016$) and 2-year chronic GVHD (13% versus 46%;
251 $p=0.018$), whereas patients with a positive CMV serology had lower rates of
252 chronic (23% versus 55%; $p=0.007$) and extensive chronic GVHD (11% versus 57%;
253 $p=0.001$) (Table 4).

254 In multivariate analysis (Table 6), CR1 was significantly associated with improved
255 RI, LFS and GRFS with HR of 0.23 ($p = 0.007$), 0.49 ($p = 0.034$) and 0.54 ($p = 0.027$)
256 respectively. KPS above 90 was significant for improved NRM with a HR of 0.37 (p
257 $= 0.025$), and donor CMV positivity negatively affected RI with HR of 2.87 ($p =$
258 0.039) but was no longer a predictor of LFS (HR 1.86; $p = 0.062$) and OS (HR 1.96;
259 $p = 0.057$).

260

261 **DISCUSSION**

262 In this study we evaluated the predictive factors for post-transplant outcome in
263 elderly ALL patients above the age of 70 years using 84 patients from the EBMT
264 registry. We found that RI, LFS, OS and GRFS were significantly better in patients
265 transplanted after achieving CR1, and that RI (and possibly LFS and OS) were
266 significantly worse if donors were CMV positive. A KPS score ≥ 90 at transplant
267 was associated with better NRM but gave no overall survival benefit. These
268 results may help guide treatment choice for this particularly challenging
269 population.

270 The main challenges when treating elderly ALL patients are centered around the
271 lack of options and effective treatment strategies. In fact, conventional

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272 chemotherapy has so far yielded suboptimal results in this population, and while
273 younger counterparts are often offered more intensive therapies such as alloHCT
274 and chimeric antigen receptor (CAR) T-cells, the more elderly are often left
275 behind, as it can be difficult selecting those eligible and deciding on whether to
276 use full-intensity regimens such as MAC and TBI.

277 Ph-negative ALL is drug-resistant by nature, and elderly patients often require
278 reduction of key administered drugs throughout the course of therapy which
279 reflects in poor outcome using conventional chemotherapy alone.^{9,11,12,24,25}

280 Conversely, the proportion of Ph-positive ALL increases with increasing age,
281 historically considered high-risk disease, the introduction of tyrosine kinase
282 inhibitors (TKIs) led to better CR rates and lower induction mortality.^{26,27} This has
283 yet to reflect on long-term survival, as 5-year OS remains around 14% for
284 patients older than 60 years receiving imatinib with full intensity regimens.²⁸

285 High subsequent relapse rates could be overcome with the use of second and
286 third generation TKIs owing to their higher potency.²⁹⁻³⁴

287 AlloHCT is considered a standard of care for high-risk ALL patients and offered as
288 consolidation for all fit candidates when suitable donors are available. Elderly
289 patients can be particularly challenging as they often present with high-risk
290 disease and often lack the required fitness to undergo such intensive therapy.

291 Studies investigating alloHCT in older patients have reported a 3-year OS of
292 around 40% with NRM from matched donors of approximately 25%.^{15,35} While
293 prospective randomized trials have yet to establish a definitive answer, our data

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294 suggest that alloHCT is feasible in patients above 70 years of age, with almost
295 40% surviving beyond 2 years, especially if transplanted in CR1 where survival
296 exceeds 50%. It is important to note that although a bad KPS score was
297 associated with higher NRM, there was no impact on LFS, OS, nor GRFS, likely
298 because of small numbers.

299 An important aspect and possible setback when considering alloHCT is donor
300 availability and optimal selection. Physicians are often torn between proceeding
301 with the first available donor or waiting for a more optimally matched one to
302 maximize outcome. Matched related donors are traditionally favored, but
303 advancements in haploidentical alloHCT has significantly improved outcomes for
304 candidates lacking such donors,³⁶⁻³⁸ a challenge particularly faced with elderly
305 patients. There are data that even suggest better outcomes compared to
306 matched sibling donor for minimal residual disease (MRD)-positive disease.³⁹ It
307 has been also recently published that all donor choices provide comparable
308 results in certain ALL patients,^{37,40,41} which appears to apply to elderly patients as
309 donor type had no measurable impact on outcome suggesting that the first
310 available donor should be used regardless of compatibility.

311 While data from alloHCT in elderly ALL patients remain scarce, results can also be
312 extrapolated from elderly acute myeloid leukemia (AML) patients. Recently
313 published data from the ALWP comparing outcomes between 713 patients ≥ 70
314 years and 16,161 patients age 50 to 69 years with AML who underwent alloHCT
315 between 2004 and 2014 have shown worse outcomes in elderly patients except

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316 those with active disease.⁴² In fact, survival at 2 years was 38% (95% CI 34%-42%)
317 in elderly group compared to 50% (95% CI 49%-50%) in the younger patients ($p <$
318 0.001). In patients with active disease, corresponding percentages were 35%
319 (95% CI 29%-41%) in the elderly and 33% (95% CI 31%-34%) in younger patients
320 ($p = 0.36$).

321 There is mounting interest for earlier use of novel agents such as inotuzumab
322 and blinatumomab in ALL treatment given their impressive activity and
323 tolerability which has also been reflected in the elderly population. Inotuzumab
324 in combination with low-dose cyclophosphamide, dexamethasone and
325 methotrexate in newly diagnosed elderly Ph-negative ALL patients (median age
326 68 years) was shown to be safe and highly efficacious with CR rates reaching
327 98%.⁴³ This was reflected by a 3-year OS of 56%, far superior to standard
328 chemotherapy. Blinatumomab is currently being investigated both as frontline
329 and relapse therapy in combination with the POMP regimen (mercaptopurine,
330 vincristine, methotrexate, and prednisone) (ClinicalTrials.gov identifier:
331 NCT02143414), dasatinib and corticosteroids (ClinicalTrials.gov identifier:
332 NCT02143414, NCT02744768), and tyrosine kinase inhibitors in Ph-positive
333 patients (ClinicalTrials.gov identifier: NCT03263572). Patients with T-ALL
334 however, lack the availability of such novel drugs and currently remain with an
335 unmet treatment need. A sequential-based conditioning for these patients can
336 therefore be an option, especially in the relapsed/refractory RR setting.⁴⁴

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337 CAR T-cells are also emerging for the treatment of ALL especially in the RR
338 setting. The CD19-directed CAR T Isagenlecleucel yielded impressive results with
339 80% CR rates in heavily pretreated ALL mostly in pediatric patients.⁴⁵ This led to
340 its approval as salvage therapy by the FDA for young (≤ 25 years) fit RR-ALL
341 patients.⁴⁶ The ZUMA-3 study is a phase I trial investigating the use of KTE-X19,
342 an autologous anti-CD19 CAR T in RR adult ALL patients.⁴⁷ Recently published
343 interim analysis of 45 patients ranging from 18 to 77 years of age over 16
344 months median follow-up showed acceptable safety and encouraging efficacy
345 with up to 84% of patients achieving CR or CR with incomplete bone marrow
346 recovery and a median survival of 15 months. Phase II results are still awaited.

347

348 **LIMITATIONS**

349 Many challenges were faced during the design and data analysis of this study,
350 and results should be interpreted with caution. Firstly, this study was limited by
351 its retrospective registry-based nature, and by the inclusion of only transplant-
352 eligible patients. The authors acknowledge that there is a probable selection bias
353 whereby only relatively fit elderly patients were deemed eligible for transplant,
354 not necessarily reflective of all elderly ALL patients above 70. Similarly, the
355 patient group was treated over an 18-year period which accounts for a relatively
356 narrow subgroup of all ALL transplants, again putting into question the data
357 generalizability. While multivariate analysis was performed, the small sample
358 size was underpowered to show significant results, whereby models were limited

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359 in both size and significance. Finally, other limitations also included missing data
360 such as MRD status, comorbidities index for all patients and the use of TKIs as
361 part of treatment course.

362

363 **CONCLUSION**

364 AlloHCT has seen many advancements over the last decades allowing for
365 significant improvements in acute leukemia patients outcome. The elderly
366 population however has yet to take full advantage of these advancements, as
367 treating physicians are sometimes reluctant to subject these patients to alloHCT
368 due to their usual frailty, more aggressive disease with short life expectancy, and
369 higher treatment-related mortality. We propose that alloHCT is feasible in this
370 subgroup with over 50% 2-year OS in patients with favorable outcome
371 predictive-factors such as achieving CR1, good functional status and donor CMV
372 negativity. Interestingly, donor choice did not have a notable impact on
373 outcome, albeit CMV positivity might confer worse survival, making any available
374 donor a suitable candidate. These results can hopefully help guide decision-
375 making regarding undergoing alloHCT in older patients pending prospective trials
376 to confirm these findings. It is worth noting that non-chemotherapy-based novel
377 immunotherapies such as BITE antibodies, inotuzumab, and CAR T-cells are
378 potentially good alternatives to alloHCT when available and should also be
379 considered in such patients.

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REFERENCES

- 392 1. National Cancer Institute: Cancer Stat Facts: Leukemia: Acute lymphocytic leukemia
393 (ALL).
- 394 2. Yilmaz M, Kantarjian H, Jabbour E. Treatment of acute lymphoblastic leukemia in older
395 adults: now and the future. *Clin Adv Hematol Oncol* 2017;15:266-74.
- 396 3. Thiebaut A, Vernant JP, Degos L, et al. Adult acute lymphocytic leukemia study testing
397 chemotherapy and autologous and allogeneic transplantation. A follow-up report of the French
398 protocol LALA 87. *Hematol Oncol Clin North Am* 2000;14:1353-66, x.
- 399 4. Thomas X, Boiron JM, Hugué F, et al. Outcome of treatment in adults with acute
400 lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol* 2004;22:4075-86.
- 401 5. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute
402 lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic
403 transplantation in first complete remission, and an autologous transplantation is less effective
404 than conventional consolidation/maintenance chemotherapy in all patients: final results of the
405 International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood* 2008;111:1827-33.
- 406 6. Pidala J, Djulbegovic B, Anasetti C, Kharfan-Dabaja M, Kumar A. Allogeneic
407 hematopoietic cell transplantation for adult acute lymphoblastic leukemia (ALL) in first
408 complete remission. *Cochrane Database Syst Rev* 2011:CD008818.
- 409 7. Santoro N, Ruggeri A, Labopin M, et al. Unmanipulated haploidentical stem cell
410 transplantation in adults with acute lymphoblastic leukemia: a study on behalf of the Acute
411 Leukemia Working Party of the EBMT. *J Hematol Oncol* 2017;10:113.
- 412 8. DeFilipp Z, Advani AS, Bachanova V, et al. Hematopoietic Cell Transplantation in the
413 Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review
414 from the American Society for Transplantation and Cellular Therapy. *Biol Blood Marrow*
415 *Transplant* 2019;25:2113-23.
- 416 9. Sive JI, Buck G, Fielding A, et al. Outcomes in older adults with acute lymphoblastic
417 leukaemia (ALL): results from the international MRC UKALL XII/ECOG2993 trial. *Br J*
418 *Haematol* 2012;157:463-71.
- 419 10. Akahoshi Y, Nishiwaki S, Arai Y, et al. Reduced-intensity conditioning is a reasonable
420 alternative for Philadelphia chromosome-positive acute lymphoblastic leukemia among elderly
421 patients who have achieved negative minimal residual disease: a report from the Adult Acute
422 Lymphoblastic Leukemia Working Group of the JSHCT. *Bone Marrow Transplant*
423 2020;55:1317-25.
- 424 11. Sancho JM, Ribera JM, Xicoy B, et al. Results of the PETHEMA ALL-96 trial in elderly
425 patients with Philadelphia chromosome-negative acute lymphoblastic leukemia. *Eur J Haematol*
426 2007;78:102-10.
- 427 12. Ribera JM, Garcia O, Chapchap EC, et al. Treatment of Frail Older Adults and Elderly
428 Patients With Philadelphia Chromosome-negative Acute Lymphoblastic Leukemia: Results of a
429 Prospective Trial With Minimal Chemotherapy. *Clin Lymphoma Myeloma Leuk* 2020.
- 430 13. Giebel S, Labopin M, Socie G, et al. Improving results of allogeneic hematopoietic cell
431 transplantation for adults with acute lymphoblastic leukemia in first complete remission: an
432 analysis from the Acute Leukemia Working Party of the European Society for Blood and
433 Marrow Transplantation. *Haematologica* 2017;102:139-49.

AlloHCT in elderly ALL patients

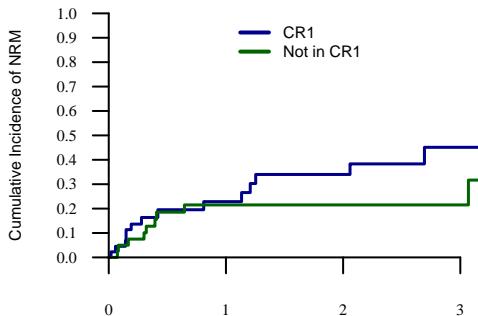
- 434 14. Cahu X, Labopin M, Giebel S, et al. Impact of conditioning with TBI in adult patients
435 with T-cell ALL who receive a myeloablative allogeneic stem cell transplantation: a report from
436 the acute leukemia working party of EBMT. *Bone Marrow Transplant* 2016;51:351-7.
- 437 15. Rosko A, Wang HL, de Lima M, et al. Reduced intensity conditioned allograft yields
438 favorable survival for older adults with B-cell acute lymphoblastic leukemia. *Am J Hematol*
439 2017;92:42-9.
- 440 16. Peric Z, Labopin M, Peczynski C, et al. Comparison of reduced-intensity conditioning
441 regimens in patients with acute lymphoblastic leukemia >45 years undergoing allogeneic stem
442 cell transplantation-a retrospective study by the Acute Leukemia Working Party of EBMT. *Bone*
443 *Marrow Transplant* 2020.
- 444 17. Fathi AT, DeAngelo DJ, Stevenson KE, et al. Phase 2 study of intensified chemotherapy
445 and allogeneic hematopoietic stem cell transplantation for older patients with acute
446 lymphoblastic leukemia. *Cancer* 2016;122:2379-88.
- 447 18. Wolach O, Stevenson KE, Wadleigh M, et al. Allogeneic transplantation is not superior
448 to chemotherapy in most patients over 40 years of age with Philadelphia-negative acute
449 lymphoblastic leukemia in first remission. *American Journal of Hematology* 2016;91:793-9.
- 450 19. Kanate AS, Nagler A, Savani B. Summary of Scientific and Statistical Methods, Study
451 Endpoints and Definitions for Observational and Registry-Based Studies in Hematopoietic Cell
452 Transplantation. *Clinical Hematology International* 2019;2:2-4.
- 453 20. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens:
454 working definitions. *Biol Blood Marrow Transplant* 2009;15:1628-33.
- 455 21. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease
456 in human recipients of marrow from HL-A-matched sibling donors. *Transplantation*
457 1974;18:295-304.
- 458 22. Terwey TH, Vega-Ruiz A, Hemmati PG, et al. NIH-defined graft-versus-host disease
459 after reduced intensity or myeloablative conditioning in patients with acute myeloid leukemia.
460 *Leukemia* 2012;26:536-42.
- 461 23. Ruggeri A, Labopin M, Ciceri F, Mohty M, Nagler A. Definition of GvHD-free, relapse-
462 free survival for registry-based studies: an ALWP-EBMT analysis on patients with AML in
463 remission. *Bone Marrow Transplant* 2016;51:610-1.
- 464 24. O'Brien S, Thomas DA, Ravandi F, Faderl S, Pierce S, Kantarjian H. Results of the
465 hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in
466 elderly patients with acute lymphocytic leukemia. *Cancer* 2008;113:2097-101.
- 467 25. Enrico M, Francesco S, Francesco L. Treatment of Adult Patients with
468 Relapsed/Refractory B-Cell Philadelphia-Negative Acute Lymphoblastic Leukemia. *Clinical*
469 *Hematology International* 2019;1:85-93.
- 470 26. Ribera JM, Garcia O, Oriol A, et al. Feasibility and results of subtype-oriented protocols
471 in older adults and fit elderly patients with acute lymphoblastic leukemia: Results of three
472 prospective parallel trials from the PETHEMA group. *Leuk Res* 2016;41:12-20.
- 473 27. Ottmann OG, Wassmann B, Pfeifer H, et al. Imatinib compared with chemotherapy as
474 front-line treatment of elderly patients with Philadelphia chromosome-positive acute
475 lymphoblastic leukemia (Ph+ALL). *Cancer* 2007;109:2068-76.
- 476 28. Daver N, Thomas D, Ravandi F, et al. Final report of a phase II study of imatinib
477 mesylate with hyper-CVAD for the front-line treatment of adult patients with Philadelphia
478 chromosome-positive acute lymphoblastic leukemia. *Haematologica* 2015;100:653-61.

- 479 29. Ravandi F, O'Brien SM, Cortes JE, et al. Long-term follow-up of a phase 2 study of
480 chemotherapy plus dasatinib for the initial treatment of patients with Philadelphia chromosome-
481 positive acute lymphoblastic leukemia. *Cancer* 2015;121:4158-64.
- 482 30. Rousselot P, Coude MM, Gokbuget N, et al. Dasatinib and low-intensity chemotherapy in
483 elderly patients with Philadelphia chromosome-positive ALL. *Blood* 2016;128:774-82.
- 484 31. Kim DY, Joo YD, Lim SN, et al. Nilotinib combined with multiagent chemotherapy for
485 newly diagnosed Philadelphia-positive acute lymphoblastic leukemia. *Blood* 2015;126:746-56.
- 486 32. Ottmann OG, Pfeifer H, Cayuela J-M, et al. Nilotinib (Tasigna®) and Chemotherapy for
487 First-Line Treatment in Elderly Patients with De Novo Philadelphia Chromosome/BCR-ABL1
488 Positive Acute Lymphoblastic Leukemia (ALL): A Trial of the European Working Group for
489 Adult ALL (EWALL-PH-02). *Blood* 2014;124:798-.
- 490 33. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia
491 chromosome-positive leukemias. *N Engl J Med* 2013;369:1783-96.
- 492 34. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. Ponatinib efficacy and safety in Philadelphia
493 chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. *Blood*
494 2018;132:393-404.
- 495 35. Roth-Guepin G, Canaani J, Ruggeri A, et al. Allogeneic stem cell transplantation in acute
496 lymphoblastic leukemia patients older than 60 years: a survey from the acute leukemia working
497 party of EBMT. *Oncotarget* 2017;8:112972-9.
- 498 36. Srouf SA, Milton DR, Bashey A, et al. Haploidentical Transplantation with Post-
499 Transplantation Cyclophosphamide for High-Risk Acute Lymphoblastic Leukemia. *Biol Blood*
500 *Marrow Transplant* 2017;23:318-24.
- 501 37. Brissot E, Labopin M, Russo D, et al. Alternative donors provide comparable results to
502 matched unrelated donors in patients with acute lymphoblastic leukemia undergoing allogeneic
503 stem cell transplantation in second complete remission: a report from the EBMT Acute
504 Leukemia Working Party. *Bone Marrow Transplant* 2020.
- 505 38. Wang Y, Liu QF, Xu LP, et al. Haploidentical versus Matched-Sibling Transplant in
506 Adults with Philadelphia-Negative High-Risk Acute Lymphoblastic Leukemia: A Biologically
507 Phase III Randomized Study. *Clin Cancer Res* 2016;22:3467-76.
- 508 39. Chang YJ, Wang Y, Xu LP, et al. Haploidentical donor is preferred over matched sibling
509 donor for pre-transplantation MRD positive ALL: a phase 3 genetically randomized study.
- 510 40. Shem-Tov N, Peczynski C, Labopin M, et al. Haploidentical vs. unrelated allogeneic
511 stem cell transplantation for acute lymphoblastic leukemia in first complete remission: on behalf
512 of the ALWP of the EBMT. *Leukemia* 2020;34:283-92.
- 513 41. Al Malki MM, Yang D, Labopin M, et al. Comparing transplant outcomes in ALL
514 patients after haploidentical with PTCy or matched unrelated donor transplantation. *Blood Adv*
515 2020;4:2073-83.
- 516 42. Ringden O, Boumendil A, Labopin M, et al. Outcome of Allogeneic Hematopoietic Stem
517 Cell Transplantation in Patients Age >69 Years with Acute Myelogenous Leukemia: On Behalf
518 of the Acute Leukemia Working Party of the European Society for Blood and Marrow
519 Transplantation. *Biol Blood Marrow Transplant* 2019;25:1975-83.
- 520 43. Kantarjian H, Ravandi F, Short NJ, et al. Inotuzumab ozogamicin in combination with
521 low-intensity chemotherapy for older patients with Philadelphia chromosome-negative acute
522 lymphoblastic leukaemia: a single-arm, phase 2 study. *Lancet Oncol* 2018;19:240-8.
- 523 44. Bazarbachi AH, Al Hamed R, Labopin M, et al. Allogeneic stem-cell transplantation with
524 sequential conditioning in adult patients with refractory or relapsed acute lymphoblastic

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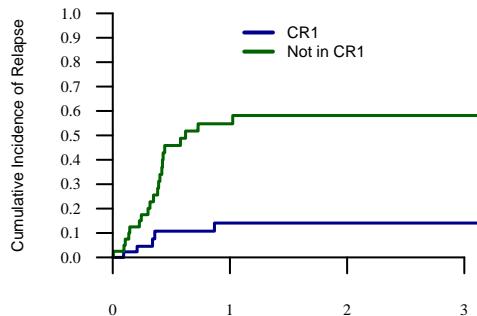
- 525 leukemia: a report from the EBMT Acute Leukemia Working Party. *Bone Marrow Transplant*
526 2020;55:595-602.
- 527 45. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in Children and Young
528 Adults with B-Cell Lymphoblastic Leukemia. *N Engl J Med* 2018;378:439-48.
- 529 46. O'Leary MC, Lu X, Huang Y, et al. FDA Approval Summary: Tisagenlecleucel for
530 Treatment of Patients with Relapsed or Refractory B-cell Precursor Acute Lymphoblastic
531 Leukemia. *Clin Cancer Res* 2019;25:1142-6.
- 532 47. Shah BD, Bishop MR, Oluwole OO, et al. End of phase I results of ZUMA-3, a phase 1/2
533 study of KTE-X19, anti-CD19 chimeric antigen receptor (CAR) T cell therapy, in adult patients
534 (pts) with relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL). *Journal of Clinical*
535 *Oncology* 2019;37:7006-.
- 536

NRM



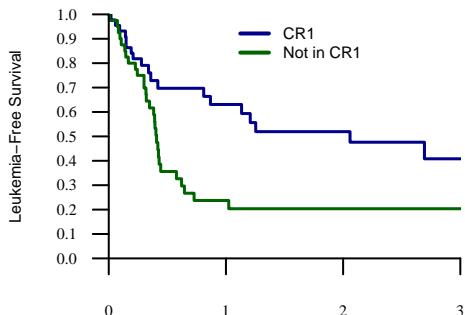
Time from transplant (years)				
number of at-risk patients				
44	18	12	6	
40	8	3	2	

RI



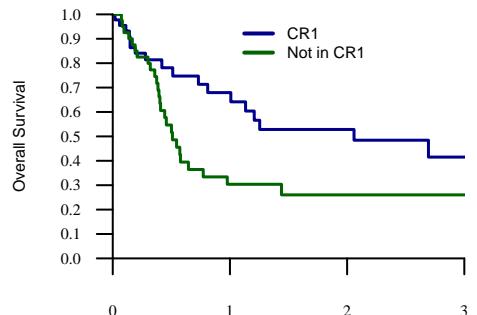
Time from transplant (years)				
number of at-risk patients				
44	18	12	6	
40	8	3	2	

LFS



Time from transplant (years)				
number of at-risk patients				
44	18	12	6	
40	8	3	2	

OS



Time from transplant (years)				
number of at-risk patients				
44	19	12	6	
40	10	4	3	

n=84	
Patient Characteristics	N (%) / Median (Range) [IQR]
Age (years)	71.5 (70-83.8) [70.5-72.9]
Year of Transplant	2015 (2002-2019)
Follow-up (months)	23.2 [6.1-45.8]
Gender	
Male	48 (57.1%)
Female	36 (42.9%)
Diagnosis	
Ph- B-ALL	18 (21.4%)
Ph+ B-ALL	29 (34.5%)
Ph-unknown B-ALL	26 (31.0%)
T-ALL	11 (13.1%)
missing	13 (15.5%)
Status at transplant	
First CR	44 (52.4%)
CR2+	22 (26.2%)
Advanced	18 (21.4%)
Karnofsky score	
<90	32 (38.1%)
>=90	46 (54.8%)
missing	6 (7.1%)
HCT-CI	
HCT-CI = 0	31 (36.9%)
HCT-CI = 1 or 2	9 (10.7%)
HCT-CI >=3	14 (16.7%)
missing	30 (35.7%)
Patient CMV serology	
CMV-	27 (32.1%)
CMV+	57 (67.9%)

Table 1: Patient characteristics. Ph= Philadelphia; CR= Complete remission; HCT-CI= Hematopoietic Cell Transplantation-Comorbidity Index; CMV= Cytomegalovirus.

Transplant Characteristics	n=84	
	N (%) / Median (Range) [IQR]	
Diagnosis to transplant (months)	8.8 (2.1-101) [5.7-16.3]	
Donor		
Matched sibling	19 (22.6%)	
Unrelated	49 (58.3%)	
Haploidentical	14 (16.7%)	
Cord blood	2 (2.4%)	
Source of stem cells		
Bone marrow	13 (15.5%)	
Peripheral blood	69 (82.1%)	
Cord blood	2 (2.4%)	
Donor Gender		
Male	55 (65.5%)	
Female	25 (29.8%)	
missing	4 (4.8%)	
Female to male		
No	69 (82.1%)	
Yes	13 (15.5%)	
missing	2 (2.4%)	
Donor CMV serology		
CMV-	36 (42.9%)	
CMV+	47 (56.0%)	
missing	1 (1.1%)	
In vivo T-Cell Depletion		
No	38 (45.2%)	
Yes	46 (54.8%)	
Conditioning		
MAC	19 (22.6%)	
RIC	65 (77.4%)	
MAC Chemo	3 (3.6%)	
RIC Chemo	47 (55.9%)	
MAC TBI	16 (19.0%)	
RIC TBI	18 (21.5%)	
Post-transplant cyclophosphamide		
No	67 (79.8%)	
Yes	16 (19.0%)	
missing	1 (1.2%)	

Table 2: Transplant characteristics. CMV= Cytomegalovirus;
MAC= Myeloablative conditioning; RIC= Reduced intensity

Cause of death	n=46 N (%)
Original disease	19 (41.3%)
Infection	12 (26.1%)
GVHD	4 (8.7%)
Interstitial pneumonitis	3 (6.5%)
Multi-organ failure	2 (4.3%)
Other transplant related	1 (2.2%)
Failure/Rejection	1 (2.2%)
Missing	4 (8.7%)

Table 3: Cause of death.

		2 year				
		Relapse	NRM	LFS	OS	GRFS
Whole population		36.6%[25.3-48]	28%[17.8-39.1]	35.4%[24-47]	38.6%[26.6-50.5]	23.1%[13.5-34.2]
Status at transplant	CR1	14.1%[4.9-27.9]	34%[18.2-50.5]	51.9%[33.6-67.5]	52.8%[33.9-68.6]	36%[19.7-52.7]
	CR2+	53.9%[27-74.7]	24.8%[8.4-45.6]	21.3%[6.1-42.7]	33.1%[13.8-54]	7.5%[0.6-27.5]
	Advanced	64.4%[34.9-83.2]	17.2%[3.8-38.7]	18.3%[4.6-39.4]	20.6%[5.2-43]	12.7%[2.2-33]
	P value	0.001	0.5	0.009	0.029	0.01
Diagnosis	Ph- B ALL	24.2%[6.7-47.6]	37.9%[14-61.9]	37.9%[14.9-61]	37.2%[14.4-60.4]	29.5%[8.7-54.3]
	Ph+ B ALL	30.7%[14.1-49]	27.8%[11.6-46.6]	41.6%[22.2-59.9]	41.9%[21.7-60.8]	25.6%[9.9-44.8]
	T ALL	68.8%[15.3-92.8]	0%	31.2%[4.6-64.3]	30.3%[4.4-63.3]	17.7%[1-52.2]
	P value	0.28	0.11	0.73	0.55	0.13
Age at transplant	All B ALL	28.9%[15.8-43.4]	32.9%[18.3-48.3]	38.2%[22.8-53.4]	37.5%[21.8-53.3]	24.5%[11.3-40.3]
	< Median	35.8%[20.2-51.7]	15%[5.9-28]	49.2%[31.9-64.3]	49.3%[31.5-64.8]	28.4%[13.8-45]
	> Median	37.7%[21.4-53.9]	40.4%[23.2-57]	22%[9.4-37.8]	27.8%[13.2-44.5]	18.4%[7.3-33.4]
P value	0.8	0.06	0.2	0.3	0.92	
Donor	Matched sibling	18.4%[3.9-41.3]	30.8%[7.5-58.7]	50.8%[21.1-74.4]	48.3%[19.5-72.3]	47.8%[20.2-71.2]
	Unrelated	38.7%[24.2-53]	29.2%[16.4-43.2]	32.1%[18.8-46.3]	36.2%[21.7-50.8]	15.5%[6.1-29]
	Haploidentical	55.9%[18.5-81.8]	11%[0.4-41.2]	33.1%[8.1-61.4]	40.2%[10.9-68.7]	21.4%[3.5-49.3]
	P value	0.21	0.64	0.42	0.52	0.08
Karnofsky	<90	24.2%[10.2-41.2]	44.3%[25.1-62]	31.5%[15.4-49.1]	34.4%[17.3-52.2]	19.3%[7.3-35.6]
	>=90	45.5%[29.4-60.3]	16.7%[7-30]	37.8%[22.7-52.7]	40.7%[24.7-56.2]	27.7%[14.7-42.4]
	P value	0.07	0.016	0.61	0.42	0.92
HCT-CI	0	29.8%[13.6-48]	28.6%[13-46.4]	41.6%[22.9-59.4]	44.3%[24.9-62.1]	24.6%[10.3-42.1]
	1 or 2	38.9%[6-72.9]	36.1%[1.1-79.6]	25%[1.4-63.9]	25%[1.4-63.9]	26.7%[1.5-65.9]
	>=3	42.7%[10.1-72.9]	22.9%[2.8-54.4]	34.4%[8.2-63.4]	29.6%[5.2-60.7]	21.4%[3.5-49.3]
	P value	0.64	0.68	0.87	0.88	0.86
Year of transplant	< Median	38.4%[20.5-56.1]	36.1%[18.2-54.3]	25.5%[11-42.9]	29.9%[13.8-47.8]	25.9%[11.4-43.2]
	> Median	36%[21.4-50.8]	22.7%[11.3-36.5]	41.3%[25.9-56.1]	44.6%[28.5-59.4]	20%[8.3-35.4]
	P value	0.47	0.55	0.12	0.3	0.7
Conditioning	MAC	37.4%[13.9-61.3]	15.8%[3.7-35.6]	46.8%[21.7-68.5]	44.2%[19.3-66.7]	43.7%[20.2-65.2]
	RIC	36%[23.4-48.8]	30.7%[18.8-43.5]	33.3%[20.9-46.1]	37.6%[24.2-51]	19.5%[9.9-31.5]
	P value	0.72	0.65	1	0.85	0.74
TBI	No	32.7%[18.9-47.2]	30.4%[17-44.9]	36.9%[22.3-51.6]	37.2%[22.2-52.1]	27.4%[15-41.2]
	Yes	43.7%[23.9-62]	24.4%[9.9-42.4]	31.9%[14.8-50.5]	41.5%[22-59.9]	14.7%[3.1-34.7]
	P value	0.41	0.88	0.52	0.87	0.47
Patient sex	Male	36.4%[20.9-52.1]	26.1%[13.6-40.4]	37.5%[22.1-53]	38%[22-53.9]	21.8%[9.5-37.2]
	Female	37.1%[20.6-53.6]	29.1%[14-46.2]	33.8%[17.8-50.6]	39.6%[21.9-56.8]	24.3%[10.9-40.6]
	P value	0.99	0.72	0.6	0.4	0.9
Donor sex	Male	30.1%[17.3-43.9]	29.3%[16.8-43.1]	40.6%[26-54.7]	44.3%[29.3-58.3]	29.8%[17-43.6]
	Female	46.1%[23.6-66.1]	24.1%[7.8-45.2]	29.8%[11.7-50.4]	28.6%[10.2-50.4]	9.5%[0.8-31.3]
	P value	0.2	0.45	0.63	0.57	0.37
Female to male transplant	No	33.8%[21.9-46.1]	28.7%[17.4-40.9]	37.6%[24.9-50.2]	42.3%[28.8-55.1]	26.1%[15.3-38.3]
	Yes	58.2%[17.7-84.5]	15.4%[2.2-40.1]	26.4%[4.6-56.1]	17.3%[1.1-50.2]	24.6%[4.8-52.4]
	P value	0.09	0.42	0.34	0.25	0.33
Patient CMV	CMV-	35.8%[13.3-59.2]	25.3%[7.6-48]	38.9%[15.9-61.7]	47.3%[20.9-69.9]	18.5%[3.6-42.4]
	CMV+	38.1%[24.8-51.2]	28.7%[17-41.6]	33.2%[20.7-46.2]	35.2%[22.2-48.5]	26.5%[15.2-39.2]
	P value	0.37	0.81	0.23	0.25	0.9
Donor CMV	CMV-	20.8%[8.1-37.5]	30.1%[14.3-47.7]	49%[29.5-66]	54.6%[33.8-71.3]	25.1%[9.8-43.9]
	CMV+	49.9%[33-64.7]	26.9%[14-41.6]	23.2%[11.1-37.9]	25.2%[12.5-40.2]	18.8%[8.2-32.6]
	P value	0.007	0.65	0.012	0.024	0.27
In vivo T-cell depletion	No	39.2%[21.2-56.9]	23.9%[9.9-41.2]	36.9%[19.2-54.7]	47.3%[27.2-65]	29%[13.7-46.3]
	Yes	34.4%[20-49.2]	31.6%[17.7-46.5]	34.1%[19.7-49]	32.8%[18.5-47.9]	19.8%[8.8-33.9]
	P value	0.54	0.92	0.75	0.65	0.92

Table 4 : Univariate analysis. CR= Complete remission; Ph= Philadelphia; MAC= Myeloablative conditioning; RIC= Reduced intensity conditioning; CMV= Cytomegalovirus; TBI=Total Body Irradiation.

		180 days		2 year	
		Acute GVHD II-IV	Acute GVHD III-IV	chronic GVHD	ext. chronic GVHD
Whole population		29.6%[20.1-39.8]	9.9%[4.6-17.6]	33.6%[21.7-46]	23.3%[12.9-35.4]
Status at transplant	CR1	29.2%[16.1-43.6]	4.8%[0.8-14.3]	33.3%[16-51.7]	29.3%[13.2-47.4]
	CR2+	36.4%[16.9-56.3]	18.2%[5.5-36.8]	55.6%[27.4-76.7]	34.1%[10.3-60.2]
	Advanced	29.4%[10.1-52]	11.8%[1.8-32]	7%[0.3-28.8]	0%
	P value	0.9	0.24	0.013	0.08
Diagnosis	Ph- B ALL	27.8%[9.6-49.7]	5.6%[0.3-23.1]	13.9%[1.8-37.9]	9.5%[0.3-37.7]
	Ph+ B ALL	29.6%[13.8-47.4]	11.1%[2.7-26.2]	41.7%[19.5-62.7]	27.8%[10.5-48.5]
	T ALL	45.5%[14.9-72.2]	18.2%[2.4-45.7]	44.3%[4-81.3]	44.3%[4-81.3]
	P value	0.53	0.55	0.18	0.09
Age at transplant	All B ALL	28.9%[16.4-42.6]	8.9%[2.8-19.5]	30.9%[16-47.1]	20.8%[8.7-36.5]
	< Median	33.2%[18.8-48.2]	12.5%[4.5-24.8]	34.4%[17.6-51.8]	27.5%[12.6-44.8]
	> Median	29.3%[16.2-43.6]	7.3%[1.9-18]	32.6%[16.1-50.2]	18.3%[6.2-35.5]
P value	0.69	0.42	0.76	0.54	
Donor	Matched sibling	22.2%[6.5-43.6]	5.6%[0.3-23.2]	16.3%[2.1-42.6]	10.2%[0.4-38.5]
	Unrelated	29.6%[17.2-43.1]	6.2%[1.6-15.6]	41.9%[25.2-57.7]	31.7%[17.1-47.4]
	Haploidentical	42.9%[16.6-67.1]	28.6%[8.2-53.3]	21.8%[1.8-56]	0%
	P value	0.45	0.04	0.28	0.11
Karnofsky	<90	29%[14.2-45.6]	6.5%[1.1-18.9]	44.8%[24.9-62.8]	31.5%[14.4-50.2]
	>=90	32.4%[19.7-45.7]	12%[4.8-22.7]	21.6%[9.8-36.3]	14%[4.9-27.7]
	P value	0.84	0.41	0.18	0.26
HCT-CI	0	33.8%[17.3-51.2]	6.7%[1.1-19.5]	49.6%[28-67.9]	33.8%[15.6-53.2]
	1 or 2	22.2%[2.8-53]	0%	19%[0.3-62.4]	19%[0.3-62.4]
	>=3	50%[21.5-73.2]	35.7%[12.2-60.4]	14.9%[2.2-38.9]	0%[NaN-NaN]
	P value	0.35	0.015	0.32	0.13
Year at transplant	< Median	13.8%[4.2-28.9]	3.4%[0.2-15.3]	13%[3-30.7]	8.7%[1.3-25.1]
	> Median	40.9%[27.2-54]	13.5%[5.9-24.3]	46%[27.8-62.5]	32.7%[16.6-50]
	P value	0.016	0.15	0.018	0.054
Conditioning	MAC	38.9%[16.8-60.7]	16.7%[3.9-37.2]	26.5%[5-55.4]	7.4%[0.4-29.8]
	RIC	28.9%[18.2-40.6]	7.9%[2.9-16.3]	35.5%[21.9-49.3]	27.2%[14.8-41.2]
	P value	0.31	0.25	0.62	0.24
Patient sex	Male	37%[23.1-50.8]	8.7%[2.7-19.1]	33.5%[17.6-50.2]	20.9%[8-37.9]
	Female	23.2%[10.7-38.4]	11.4%[3.5-24.5]	33.3%[16.1-51.7]	26.2%[11.1-44.3]
	P value	0.19	0.66	0.76	0.4
TBI	No	25%[13.8-38]	8.3%[2.6-18.3]	36.6%[21.3-52]	24.7%[11.9-39.8]
	Yes	39.8%[22.9-56.3]	12.1%[3.7-25.8]	30.8%[10.6-54]	21.2%[5.3-43.9]
	P value	0.14	0.55	0.32	0.64
Donor sex	Male	31.5%[19.6-44.1]	7.4%[2.3-16.4]	37.3%[22.3-52.3]	22.8%[10.9-37.2]
	Female	33.7%[15.6-52.9]	16.7%[5-34.1]	30.7%[9-56]	27.8%[6.7-54.5]
	P value	0.78	0.21	0.38	0.93
Female to male transplant	No	30%[19.5-41.3]	7.5%[2.7-15.4]	35.6%[22.4-48.9]	24.5%[13.3-37.4]
	Yes	41.7%[13.9-67.8]	25%[5.4-51.7]	10%[0.4-38.2]	0%
	P value	0.34	0.07	0.49	0.48
Patient CMV	CMV-	41.7%[22.4-60]	11.1%[2.7-26.2]	55.4%[24.3-78.2]	56.7%[16.2-83.7]
	CMV+	25.9%[15.1-38.2]	9.3%[3.4-18.8]	22.6%[11.5-36]	11.1%[4-22.4]
	P value	0.18	0.82	0.007	0.001
Donor CMV	CMV-	37.7%[21.6-53.8]	11.4%[3.5-24.5]	43.4%[21.6-63.5]	36.9%[16.3-57.7]
	CMV+	24.4%[13-37.8]	8.9%[2.8-19.5]	25.2%[12.2-40.5]	14.4%[5-28.6]
	P value	0.27	0.73	0.29	0.1
In vivo T-cell depletion	No	41.1%[24.8-56.7]	13.5%[4.8-26.6]	38.3%[18.1-58.4]	17.8%[5.1-36.9]
	Yes	22.7%[11.6-36.1]	6.8%[1.7-16.9]	30.4%[16-46.2]	25.2%[12.1-40.5]
	P value	0.11	0.33	0.33	0.82

Table 5 : Univariate analysis. CR= Complete remission; Ph= Philadelphia; MAC= Myeloablative conditioning; RIC= Reduced intensity conditioning; CMV= Cytomegalovirus; TBI=Total Body Irradiation.

Outcome	Variables	HR (95% CI)	p value
Relapse	CR1 vs other	0.23 (0.08-0.67)	0.007
	MSD vs other	0.48 (0.13-1.77)	0.27
	Donor CMV positivity	2.87 (1.06-7.77)	0.039
	Year of HSCT	0.96 (0.84-1.10)	0.55
NRM	CR1 vs other	1.05 (0.43-2.58)	0.91
	MSD vs other	0.60 (0.20-1.85)	0.38
	KPS \geq 90	0.37 (0.15-0.88)	0.025
	Year of HSCT	0.91 (0.79-1.05)	0.18
LFS	CR1 vs other	0.49 (0.26-0.95)	0.034
	MSD vs other	0.54 (0.23-1.26)	0.16
	Donor CMV positivity	1.86 (0.97-3.58)	0.062
	Year of HSCT	0.95 (0.87-1.05)	0.3
OS	CR1 vs other	0.61 (0.32-1.20)	0.15
	MSD vs other	0.61 (0.26-1.41)	0.25
	Donor CMV positivity	1.96 (0.98-3.91)	0.057
	Year of HSCT	1.0 (0.91-1.11)	0.95
GRFS	CR1 vs other	0.54 (0.31-0.93)	0.027
	MSD vs other	0.54 (0.25-1.14)	0.1
	Year of HSCT	0.99 (0.91-1.08)	0.77
Acute GVHD II-IV	CR1 vs other	0.85 (0.39-1.86)	0.67
	MSD vs other	0.70 (0.24-2.06)	0.52
	Year of HSCT	1.10 (0.95-1.27)	0.22
Chronic GVHD	CR1 vs other	0.81 (0.32-2.04)	0.65
	MSD vs other	0.50 (0.11-2.21)	0.36
	Patient CMV positivity	0.44 (0.17-1.11)	0.08
	Year of HSCT	1.01 (0.82-1.23)	0.96

Table 6: Multivariate Analysis. HR: Hazard ratio. CI: Confidence interval. CR1: First complete remission. MSD: Matched sibling donor. HSCT: Hematopoietic stem-cell transplantation. NRM: Non-relapse mortality. KPS: Karnofsky score. LFS: Leukemia-free survival. OS: Overall survival. GRFS: GRFS and relapse free survival. GVHD: Graft-vs-host disease.