

1 **Allogeneic haemopoietic transplantation for acute**
2 **myeloid leukaemia in second complete remission: A**
3 **registry report by the Acute Leukaemia Working**
4 **Party of the EBMT**

5

6 Running title: Allograft in second remission acute myeloid
7 leukaemia
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9 Maria H. Gilleece¹, Myriam Labopin², Bipin N. Savani³, Ibrahim
10 Yakoub-Agha⁴, Gerard Socié⁵, Tobias Gedde-Dahl⁶, Didier
11 Blaise⁷, Jennifer L. Byrne⁸, Charles Craddock⁹, Jan J.
12 Cornelissen¹⁰, William Arcese¹¹, Edouard Forcade¹², Charles
13 Crawley¹³, Emmanuelle Polge¹⁴, Mohamad Mohty¹⁵, Arnon
14 Nagler¹⁶.

15

16 **Corresponding Author: Maria H. Gilleece MD(Res)**

17 Department of Haematology, Bexley Wing, St James's

18 University Hospital, Leeds. LS9 7TF. United Kingdom

19 Tel: +441132068433

20 mgilleece@nhs.net

21

22 **Author affiliations**

23 1 Department of Haematology, Leeds Teaching Hospitals

24 Trust, Leeds, UK

25

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leukaemia...**

26 2 EBMT Paris study office/CEREST-TC, Paris, France.

27

28 3 Division of Hematology/Oncology, Vanderbilt University

29 Medical Center, Nashville, TN, USA.

30

31 4 CHU de Lille, LIRIC, INSER U995, Université de Lille,

32 Lille, France.

33

34 5 Hematologie / Transplantation, Hôpital St Louis, Paris

35 CEDEX 10, France

36

37 6 Section for Hematology, Oslo University Hospital,

38 Rikshospitalet, Oslo, Norway.

39

40 7 Programme de Transplantation & Therapie Cellulaire,

41 Centre de Recherche en Cancérologie de Marseille,

42 Institut Paoli Calmettes, Marseille, France.

43

44 8 Faculty of Medicine and Health Sciences, University of

45 Nottingham, Nottingham UK.

46

47 9 Queen Elizabeth Medical Centre, University Hospital

48 Birmingham NHS Trust, Department of Haematology,

49 Birmingham, United Kingdom;

50

**Allograft in second remission acute myeloid
leukaemia...**

- 51 10 Erasmus MC Cancer Institute, University Medical
52 Center Rotterdam, Department of Haematology,
53 Rotterdam, Netherlands
54
- 55 11 Tor Vergata University of Rome, Policlinico
56 Universitario Tor Vergata, Stem Cell Transplant Unit,
57 Rome, Italy
58
- 59 12 Service Hématologie Clinique et Thérapie Cellulaire
60 Hôpital Haut-Lévêque – CHU Bordeaux, France
61
- 62 13 Addenbrookes Hospital, Department of Haematology,
63 Cambridge, United Kingdom
64
- 65 14 Acute Leukemia Working Party, European Society for
66 Blood and Marrow Transplantation Paris Study
67 Office/European Center for Biostatistical and
68 Epidemiological Evaluation in Hematopoietic Cell
69 Therapy (CEREST-TC), Paris, France.
70
- 71 15 Hôpital Saint Antoine, INSERM UMR 938, Paris,
72 France; ⁵Université Pierre et Marie Curie, Paris, France;
73
- 74 16 Hematology Division, Chaim Sheba Medical Center,
75 Tel Hashomer, Israel.

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76

77 **Competing interests statement**

78

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Allograft in second remission acute myeloid leukaemia...

99 **Abstract**

100 Allogeneic haemopoietic cell transplant (allo-HCT) may
101 be curative in acute myeloid leukaemia (AML) in second
102 complete remission (CR2) but the impact of reduced
103 intensity (RIC) versus myeloablative conditioning (MAC)
104 is uncertain. The Acute Leukaemia Working Party of the
105 European Society for Blood and Bone Marrow
106 Transplantation Registry studied an AML CR2 cohort
107 characterised by age ≥ 18 y, first allo-HCT 2007-2016,
108 available cytogenetic profile at diagnosis, donors who
109 were matched family, volunteer unrelated with HLA
110 antigen match 10/10 or 9/10 or haplo-identical. The 1879
111 eligible patients included 1010 (54%) MAC allo-HCT
112 recipients.

113

114 In patients < 50 years (y), two year outcomes for MAC vs
115 RIC allo-HCT were equivalent with leukaemia free
116 survival (LFS) 54% for each, overall survival (OS), 61 vs
117 62%, non-relapse mortality (NRM) 18 vs 15% and graft
118 versus host disease relapse free survival (GRFS) 38 vs
119 42%. In patients ≥ 50 y, 2y outcomes for MAC vs RIC allo-
120 HCT were equivalent for LFS 52 vs 49%, OS 58 vs 55%
121 and GRFS 42.4 vs 36%. However, NRM was significantly
122 inferior after MAC allo-HCT, 27 vs 19% ($P=0.01$) despite
123 worse cGVHD after RIC-allo (32 vs 39%). These data

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124 support the need for ongoing prospective study of
125 conditioning intensity and GVHD mitigation in AML.

126

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128 Society for Blood and Bone Marrow Transplantation
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130 transplant centres.

131

132 **Introduction**

133 Acute myeloid leukaemia (AML) is grouped into good,
134 intermediate and adverse genetic risk categories that
135 may be combined with response rates to induction
136 therapy to predict survival outcomes (1–3). Integration of
137 relapse rates, procedural mortality of allogeneic
138 haemopoietic cell transplant (allo-HCT) and projected
139 success rates of salvage regimens permits an estimate of
140 the potential benefit and optimal timing of an allo-HCT as
141 consolidation therapy (4–6,1). Consequently, for patients
142 achieving first complete remission (CR1) it is
143 conventional to offer allo-HCT in adverse and
144 intermediate risk disease where the relapse risk is more
145 than 45% and there are clear benefits to transplantation
146 (7,8). Allo-HCT is deferred to CR2 for patients with good
147 risk disease despite a relapse risk of up to 35%, since

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148 many will be cured without the hazards of allo-HCT (5).
149 However, management of an individual patient requires a
150 personalised amalgamation of risk of relapse, transplant
151 related mortality and access to a suitable donor
152 (1,6,9,10). Thus, patients with high HCT comorbidity
153 index scores and a mismatched volunteer donor may
154 wish to defer allo-HCT (11,12).

155

156 While it is often assumed that those patients who relapse
157 subsequent to a first CR may be duly salvaged and
158 offered allo-HCT in CR2, this does not square with reality
159 (13–16). Breems *et al* studied a cohort of 1540 patients
160 with newly diagnosed AML enrolled on clinical trials
161 between 1987 and 2001 and established that the duration
162 of CR1, age at relapse, cytogenetic risk factor at
163 diagnosis and a prior allo-HCT could be used to predict
164 the likelihood of CR2 (4). Those patients who did achieve
165 CR2 were shown to have a survival benefit from allo-HCT
166 compared to alternative therapies. Subsequent studies
167 have largely confirmed these findings (Table 1) (17–21).

168

169 Since no other large series address the impact of
170 conditioning regimen intensity on the outcomes of HCT in
171 patients with AML CR2, we have analysed an eligible
172 cohort of patients for whom data had been deposited in

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173 the registry of the European Society for Blood and
174 Marrow Transplantation (EBMT).

175

176 **Methods**

177 **Study design and data collection**

178 This was a multicentre, retrospective registry study by the
179 Acute Leukaemia Working Party (ALWP) of the EBMT.

180 The EBMT is a voluntary group that represents more than
181 600 transplant centers, predominantly European, which
182 are required to report all consecutive HCT and follow-up
183 once a year. EBMT Med A/B standardized data collection
184 forms are completed and submitted to the registry by
185 transplant center personnel following written informed
186 consent from patients in accordance with center ethical
187 research guidelines (22). Accuracy of data is assured by
188 the individual transplant centers and by quality control
189 measures such as regular internal and external audits.

190 Since January 1, 2003, all transplant centers have been
191 required to obtain written informed consent prior to data
192 registration with the EBMT, following the Helsinki
193 Declaration of 1975. The study was approved by the
194 ALWP.

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195 Eligibility criteria

196 Eligibility criteria were: age ≥ 18 y, first allo-HCT 2007-
197 2016, diagnosis of AML CR2, availability of cytogenetic
198 profile at diagnosis.
199 Cytogenetic status was classified using MRC UK criteria
200 while any identified molecular markers at diagnosis were
201 also noted (23). Donors were restricted to a human
202 leukocyte antigen (HLA) matched family donor (MFD),
203 volunteer unrelated donor with HLA match 10/10 (VUD)
204 or 9/10 match (MMVUD) or haplo-identical (Haplo ID)
205 donor. Graft source included peripheral blood stem cells
206 (PBSC) or bone marrow (BM) grafts. Engraftment was
207 assessed by conventional EBMT standards (22).

208

209 Intensity of conditioning was classified in accordance with
210 published criteria while the more recently adopted
211 regimens Treosulfan/Fludarabine (TF) and
212 Thiotepa/Busulfan/Fludarabine (TBF) were considered as
213 myeloablative when the busulfan dose was at least 9.6
214 mg/kg (24–26).

215 Statistical analysis

216 Patient, disease, and transplant-related characteristics for
217 the two cohorts (MAC or RIC) were compared by using χ^2
218 statistics for categorical variables and the Mann-Whitney
219 test for continuous variables. The primary endpoint was

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220 leukemia-free survival (LFS). Secondary endpoints were
221 relapse incidence (RI), non-relapse mortality (NRM),
222 overall survival (OS), acute graft-versus-host disease
223 (aGVHD), chronic graft-versus-host-disease (cGVHD)
224 and GVHD-free/relapse-free survival (GRFS). LFS was
225 defined as survival with no evidence of relapse or
226 progression. Relapse was defined as the presence of 5%
227 BM blasts and/or reappearance of the underlying
228 disease. NRM was defined as death without evidence of
229 relapse or progression. OS was defined as the time from
230 allo-HCT to death, regardless of the cause. GRFS was
231 defined as events excluding grade 3-4 acute GVHD,
232 extensive chronic GVHD, relapse, or death in the first
233 post-HCT year (27–29).

234

235 Cumulative incidence was used to estimate the endpoints
236 of NRM, RI, acute and chronic GVHD to accommodate
237 for competing risks. To study acute and chronic GVHD,
238 we considered relapse and death to be competing
239 events. Probabilities of OS, LFS, and GRFS were
240 calculated using the Kaplan–Meier method. Univariate
241 analyses were done using the Gray’s test for cumulative
242 incidence functions and the log rank test for OS, GRFS,
243 and LFS. Cox proportional hazards model was used for
244 multivariate regression. All variables differing significantly

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245 between the 2 groups or factors associated with one
246 outcome in univariate analysis were included in the Cox
247 model. In order to test for a centre effect, we introduced a
248 random effect or frailty for each center into the model
249 (30,31). We studied 2 different Cox models in patients
250 aged under 50 or 50 years and above at the time of allo-
251 HCT. Results were expressed as the hazard ratio (HR)
252 with a 95% confidence interval (95% CI). Proportional
253 hazards assumptions were checked systematically for all
254 proposed models using the Grambsch-Therneau
255 residual-based test. All tests were 2-sided. The type I
256 error rate was fixed at 0.05 for the determination of
257 factors associated with time-to-event outcomes. Analyses
258 were stratified by age at allo-HCT (less or ≥ 50 years) and
259 declared measurable residual disease (MRD) status at
260 HCT. Statistical analyses were performed with SPSS
261 24.0 (SPSS Inc., Chicago, IL, USA) and R 3.4.0 (R Core
262 Team (2017). R: A language and environment for
263 statistical computing. R Foundation for Statistical
264 Computing; Vienna; Austria. <https://www.R-project.org/>.)

265

Results

Patient, disease and transplant characteristics

268 A total of 1879 patients, 1013 male, from 230 transplant
269 centers were eligible. Patient, disease, donor and

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270 transplant characteristics are detailed in Supplementary
271 Table 1 (Table S1).

272 Median follow-up of surviving patients was 26.16 months
273 (m) (0.49 - 124.63). Approximately 95% of patients in
274 each group had *de novo* AML at initial diagnosis.

275 MAC regimens were used in 1010 while 869 received
276 RIC allo-HCT. Time from diagnosis to transplant was
277 marginally longer in RIC allo-HCT recipients at a median
278 of 18.5 m (range 0.8-222.9) vs 17.7m (1.2-239.1)
279 (P=0.017) in MAC recipients.

280 Recipients of RIC allo-HCT compared to MAC allo-HCT
281 recipients were older (median age 57.3y (18.2-75.3) vs
282 42.8y, (18-72y) P<0.001), had a worse Karnofsky
283 performance status (P<0.001) and had a higher
284 proportion of adverse or intermediate cytogenetics at
285 diagnosis (P <10⁻³) (Table S1).

286 Family donors, whether MFD or Haplo-ID, were more
287 commonly available for MAC allo-HCT than RIC allo-HCT
288 recipients and accounted for half of the donors in the
289 MAC allo-HCT group. Conversely, unrelated donors,
290 particularly HLA 10/10 VUDs were more likely than family
291 donors to be used in the RIC allo-HCT setting (P<0.0 01).

292 While PBSC was the preferred source of stem cells in
293 both conditioning groups, this was more pronounced in

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294 the RIC allo-HCT group with only 7.59% cases using BM
295 vs 24.78% in the MAC HCT group ($P<0.001$). A
296 preference for male donors was seen in both groups and
297 particularly so in RIC allo-HCT ($P=0.005$) (Table S1).

298 Transplant characteristics are shown in Table S1. T cell
299 depletion, whether with anti-thymocyte globulin or
300 alemtuzumab was applied in 47.01% MAC HCT and
301 70.59% RIC/NMA HCT ($P<0.001$).

302 Regimens used for GVHD prophylaxis favoured
303 cyclosporine based approaches rather than tacrolimus or
304 post-transplant cyclophosphamide. Cyclosporine was
305 most often used in combination with methotrexate in MAC
306 HCT and alone or with mycophenolate mofetil in
307 RIC/NMA HCT ($P<0.001$).

308

Outcomes of transplantation

310 At 2y, the overall outcomes were LFS 52% (CI: 49.5 -
311 54.5), OS 58.7% (CI: 56.2 - 61.2), RI 28.9% (CI: 26.7 -
312 31.2), NRM 19% (CI: 17.2 - 21), GRFS 38.7% (CI: 36.2 -
313 41.1), cGVHD 37.2% (CI: 34.7 - 39.7) and extensive
314 cGVHD 15.9% (CI: 14.1 - 17.8) (Tables S2 and S3) Non-
315 relapse deaths were predominantly due to GVHD or
316 sepsis (Table S2).

317

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318 Multivariate analysis was performed to examine the
319 impact of conditioning intensity as well as other
320 parameters believed to determine transplant outcomes.
321 Table S4 summarises the MVA for all patients. In this
322 cohort, no transplant outcome differed significantly by
323 conditioning intensity with the notable exception of NRM
324 which favoured RIC Allo-HCT, (HR 0.65 95% CI 0.50-
325 0.84 P=0.001). However, when patients were divided by
326 age range <50y vs ≥50y this advantage to RIC ALLO-
327 HCT retained significance only in patients ≥50y (HR 0.54
328 CI 0.38-0.76 P <0.001) (Tables 2 and 3). Thus, even in
329 patients selected as being fit for MAC Allo-HCT by their
330 transplant team, we found excess NRM in older patients.
331 This is supported by the increase in NRM that is seen
332 with increasing age in the <50y (HR 1.25 CI 1.01-1.53
333 P=0.034) as well as the ≥50y (HR 1.6 CI: 1.21-2.03
334 P=0.001) (Tables 2 and 3).

335

336 The other striking association with conditioning intensity
337 was also seen in patients ≥50y, but not in younger
338 patients, and this was an excess of cGVHD in those
339 undergoing RIC allo-HCT (HR 1.38 CI 1.03-1.85; P=0.03)
340 although this difference did not extend to extensive
341 GVHD (Table 3).

342

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343 A decision to use reduced intensity rather than
344 myeloablative conditioning may be influenced by the age,
345 comorbidity and performance status of the patient (32–
346 34). As well as the impact of increasing age as a
347 continuous variable on NRM, we also found an adverse
348 effect on GRFS which reached significance in patients
349 <50y (HR 1.13 CI 1.01-1.26 P=0.03) while remaining a
350 trend in older patients. Overall, older patients also had
351 worse LFS and OS (31–(32–34)33) (Table S4 and Table
352 3).

353

354 Karnofsky Performance Scores (KPS) >80% were
355 predictive of lower NRM in both age-groups. Additionally,
356 in patients ≥50y, KPS >80 predicted lower rates of
357 aGVHD and superior OS, LFS and GRFS (Table 3).

358 In accordance with other large studies of patients
359 transplanted in AML CR2 that have found better
360 transplant outcomes in those patients with longer duration
361 CR1, probably reflecting the innate aggressiveness of
362 disease, (17–20), we found that patients with longer
363 intervals from diagnosis to allo-HCT had superior RI,
364 LFS, OS and GRFS. (Table S4).

365

366 The distribution of cytogenetic risk groups at diagnosis
367 resembled the MRC and Japanese cohorts (17,18).

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368 Patients with good risk cytogenetics at diagnosis fare
369 better after transplant than those with intermediate and
370 adverse risk cytogenetics (17–20) and our results are
371 confirmatory in a different data set and across all age
372 groups. (Supplementary Tables 4 and 5).

373 At 2y, OS following allo-HCT was 67.4, 56.8 and 37.9% in
374 good, intermediate and adverse risk cytogenetic groups
375 respectively. Overall, this compares favourably with the
376 5y OS of 35, 47 and 34% reported by Burnett in which
377 survival curves flattened between 2 and 3 years from
378 transplant, but emphasises the persistently poor outcome
379 due to relapse for patients with adverse karyotypes
380 (17,32,35,36).

381

382 Donor selection has historically had a major impact on
383 the outcomes of transplant, although the increasing use
384 of high resolution HLA typing and novel GVHD
385 prophylaxis strategies may be eroding the differences in
386 outcomes associated with unrelated versus matched or
387 haploidentical family donors (37–40). In this study we
388 found that donor characteristics retained a significant
389 impact upon transplant outcomes (Tables 2 and 3).

390 MMVUD and Haplo-ID donors were associated with
391 increased rates of NRM and aGVHD II-IV and the use of

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392 female donors was associated with higher rates of
393 extensive cGVHD.
394 In general in modern transplant practice PBSC is the
395 preferred stem cell source although faster engraftment
396 may be offset by increased risks of GVHD (41). We found
397 that the use of PBSC was associated with significantly
398 increased rates of cGVHD in both the <50y and the ≥50y
399 (HR 1.784 CI 1.253-2.539, HR 1.683 CI 1.08-2.624) but
400 no improvements in OS or LFS in either group (Tables 2
401 and 3). Similar to our earlier study in AML CR1, (42),
402 TCD led to beneficial effects on GRFS, aGVHD and
403 cGVHD in <50y and to improvements in GRFS and
404 cGVHD in the ≥50y without detriment to RI, OS or LFS
405 suggesting that TCD reduces GVHD without increasing
406 relapse risks (Tables 2 and 3).
407
408 Finally, we looked for the impact of centre and year of
409 transplant but found no significant effect on transplant
410 outcomes (Tables 3 and 4).

411 412 Discussion

413
414 This large registry study tracked the effect of allo-HCT on
415 the post-transplant survival characteristics of 1879
416 patients with AML in CR2 in the modern era (2007-2016)
417 and investigated the impact of conditioning intensity on

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418 outcomes in patients aged <50y or ≥50y. OS, LFS and
419 GRFS at 2y were 58.7%, 52% and 38.7%.

420 We established that in patients aged <50y, 2y OS was
421 61.1% vs 61.8% for MAC vs RIC allo-HCT (P=0.7) while
422 LFS was 53.9% vs 54.1% (P=0.61). Similarly, in patients
423 aged 50y or more at HCT, MAC allo-HCT and RIC allo-
424 HCT were equivalent with 2y OS of 58.3% vs 55.1%
425 (P=0.3) and LFS of 51.5% vs 49.3% (P=0.7). Multivariate
426 analysis confirmed that in patients <50y and ≥50y,
427 intensity of conditioning made no significant difference to
428 OS, LFS or RI. However, in ≥50y, NRM rates were
429 significantly reduced following RIC allo-HCT and while
430 there was an increased risk of cGVHD this did not
431 manifest as extensive cGVHD. These observations
432 suggest overall equivalence of MAC and RIC regimens
433 and a rationale for further prospective study. This is in
434 keeping with our previous observations in AML CR1 but
435 contrasts with the outcomes of the Blood and Marrow
436 Transplant Clinical Trials Network (BMT CTN) 0901
437 prospective study of 272 patients with AML or
438 myelodysplasia in which high relapse rates in patients
439 receiving RIC Allo-HCT compared to MAC Allo-HCT led
440 to premature study closure (42,43). Despite the caveat
441 that our current study is retrospective, it is a larger one,
442 encompassing a wider range of regimens and with longer

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443 follow-up. Additionally, the outcomes of patients with AML
444 CR2 in the BMT CTN study are not specified.

445

446 Similar to earlier studies, we found that adverse factors
447 included increasing age, cytogenetics other than good
448 risk, poor performance status, shorter time intervals from
449 initial diagnosis to transplant and mismatched donor allo-
450 HCT (4,17,20).

451

452 Given the high rates of relapse, with overall 2y RI of
453 28.9%, there is a grave need for more active leukaemia
454 therapy. This might be addressed by sequential
455 chemotherapy approaches such as the FLAMSA based
456 regimens or by combining alkylating agents in the
457 conditioning regimen (26,44–46). Additionally, new agents
458 hold out the promise of higher CR rates and prospects for
459 maintenance therapies which may potentially be used in
460 conjunction with allo-HCT to improve survival in AML(47–
461 50). Immunotherapy approaches, while less advanced
462 than for lymphoid malignancies also hold potential (51).

463

464 Our study is limited since it can only address the
465 outcomes of those patients who achieved CR2 and were
466 transplanted, thus not addressing the larger problem of
467 management of relapse after CR1. Likewise, we may only

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468 speculate as to the reasons why allo-HCT was deferred
469 to CR2. We had insufficient data to draw conclusions
470 about the impact of comorbidity, MRD or molecular sub-
471 groups such as FLT3 ITD with or without NPM1
472 mutations (34,52–54). While MRD status was available in
473 67% patients, equally distributed across conditioning
474 groups, it had no confounding influence on the
475 relationship between conditioning intensity and transplant
476 outcomes.

477
478 However, we show improving survival outcomes after
479 allo-HCT in a large cohort of patients with AML CR2
480 treated in a recent time-frame while confirming that
481 existing prognostic indicators retain their value. These
482 data also provide fresh impetus for the prospective
483 comparison of the impact of conditioning intensity on allo-
484 HCT outcomes in AML CR2.

485

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495 **Competing interests statement**

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501 Ibrahim Yakoub-Agha - Nil

502 Gerard Socié - Nil

503 Tobias Gedde-Dahl - Nil

504 Didier Blaise- Nil

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512 Charles Crawley - Nil

513 Emmanuelle Polge - Nil

514 Mohamad Mohty - Nil

515 Arnon Nagler - Nil

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764 **Legends**

765 **Main text tables**

766 **Table 1 Large Studies of outcome of haemopoietic cell**
767 **transplant in second complete remission**

768

769 **Table 2 Multivariate analysis of outcomes of haemopoietic**
770 **cell transplant in patients aged under 50 years.**

771 aGVHD acute graft versus host disease

772 Allo-HCT allogeneic hematopoietic cell transplant

773 AML acute myeloid leukemia

774 cGVHD chronic graft versus host disease

775 CI confidence interval

776 GRFS graft versus host disease and relapse free survival

777 Haplo haploidentical

778 HR hazard ratio

779 KPS Karnofsky performance status

780 LFS Leukaemia free survival

781 MFD matched family donor

782 MMVUD mismatched volunteer unrelated donor

783 NRM Non-relapse mortality

784 OS Overall survival

785 PBSC peripheral blood stem cells

786 RI relapse incidence

787 TCD T cell depletion

788 VUD volunteer unrelated donor

789

790 **Table 3 Multivariate analysis of outcomes of haemopoietic**
791 **cell transplant in patients aged 50 years or above.**

792 aGVHD acute graft versus host disease

793 Allo-HCT allogeneic hematopoietic cell transplant

794 AML acute myeloid leukemia

795 cGVHD chronic graft versus host disease

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809 VUD volunteer unrelated donor

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812

813 **Figure 1**

814 Outcomes of reduced intensity conditioning (RIC) versus
815 myeloablative conditioning (MAC) allogeneic
816 haemopoietic cell transplant in patients aged 50 or older.

817 (a) Non-relapse mortality (NRM)

818 (b) Relapse incidence

819 (c) Chronic Graft versus Host disease

820 (d) Overall survival (OS)

821 (e) Leukaemia-free survival (LFS)

822 (f) Graft versus host and relapse free survival (GRFS)

823

Table 1

Author, Group & Study type	Study population	Outcomes	Conclusions and limitations
Burnet et al (reference 17) UK Medical Research Council	n=1160 Age 16-49y AML patients in first relapse (excluding APL and any prior transplant) Risk stratification by MRC criteria (Grimwade et al 2001 reference 23) Era: 1988-2009	642 (55%) achieved CR2. 314 (27%) had allo-HCT Allo-HCT 5Y OS from CR2 by MRC risk category: Good: 35% overall, t(8;21) 29% and inv16 39% Intermediate: 47% Adverse: 34% Unknown: 53%	Post-trial analysis with centre defined relapse and reinduction. The benefits of allo-HCT were seen only in those with intermediate or adverse cytogenetic risk groups at diagnosis. Multivariate analysis found that only CR1 duration was significantly associated with survival. Conditioning intensity did not determine outcome. Era coincides with significant changes in HCT practice such as the introduction of reduced intensity conditioning and improvements in supportive care and high resolution HLA typing.
Kurosawa et al(reference 18) Japan retrospectivenational study,	n=931 Age 16-70y AML patients in first relapse (excluding APL and any with prior transplant) Risk stratification by South-West Oncology Group (SWOG) criteria(reference 21). Era 1994-2006	463 (50%) achieved CR2 242 (26%) had allo-HCT in CR2 Allo-HCT 3Y OS from relapse by SWOG cytogenetic risk criteria Overall: 59% Good: t(8;21) 64% and inv16 70% Intermediate: 58% Adverse:67%	The benefits of allo-HCT were only seen in those with intermediate or adverse risk cytogenetic risk groups at diagnosis. Multivariate analysis found that CR1 duration $\geq 1y$, cytogenetic risk group at diagnosis, white cell count at diagnosis $\leq 20 \times 10^9/L$ and CR1 status achieved with first cycle of induction therapy all predicted survival after relapse. Era coincides with significant changes in HCT practice such as the introduction of reduced intensity conditioning and improvements in supportive care and high resolution HLA typing.
Hospital et al,(reference 19) French AML Intergroup retrospective study	n=145 Age 16-76y AML patients with core-binding factor mutations in first relapse (excluding any with prior transplant). Era 1994-2011	127 (88%) achieved CR2 77 (53%) had allo-HCT in CR2 Allo-HCT 5Y OS 59% and DFS 57% from relapse Incorporation of gemtuzumab ozogamycin (GO) into salvage regimen yielded superior 5Y OS of 82 vs 48% and DFS of 83 vs 44%.	Multivariate analysis found that the benefits of allo-HCT were greater in younger patients, those with inv16/t(16;16), longer duration CR1 and use of GO as part of salvage therapy at relapse. Era spans 17 years during which confounders such as experience of RIC-Allo-HCT, supportive care and resolution of HLA matching made significant advances. Residual disease status by molecular and/or immunophenotype was unavailable.
Weisdorf et al(reference 20) Center for International Blood Marrow Transplant Research retrospective study	n=4682 Age $\geq 18y$ AML patients with disease status primary induction failure (PIF) n=1440, median age 52y, relapse failing ≥ 1 reinduction cycle (RI) n = 1256, median age 49y and CR2 n = 1986, median age 47y. All patients received an allo-HCT Era 2000-2013	Allo-HCT 5Y OS: PIF 21%, RI 18% CR2 39%	Multivariate analysis found that the superior outcomes of allo-HCT in AML CR2 were associated with better performance scores (≥ 90), longer duration CR1 (>12 months), a history of <i>de novo</i> AML and non-adverse cytogenetics (SWOG criteria). Era spans 13 years during which confounders such as experience of RIC-Allo-HCT, supportive care and resolution of HLA matching made significant advances. Residual disease status by molecular and/or immunophenotype was unavailable.

Table 2

	Relapse			NRM			LFS		
	HR	CI	p	HR	CI	p	HR	CI	p
Age <50y									
RIC vs MAC	1.00	0.724 - 1.38	1.00	0.779	0.513 - 1.182	0.24	0.903	0.7 - 1.166	0.43
Age (per 10 y)	1.05	0.898 - 1.219	0.56	1.245	1.014 - 1.529	0.04	1.114	0.986 - 1.259	0.08
Time Diagnosis to allo-HCT (m)	0.96	0.948 - 0.975	<10-5	0.999	0.991 - 1.007	0.78	0.982	0.974 - 0.99	10-5
Cytogenetics									
Good risk group (reference data)	1.00			1.00			1.00		
Intermediate	1.52	1.115 - 2.071	0.01	0.922	0.638 - 1.331	0.66	1.266	1.001 - 1.603	0.05
Adverse	3.347	2.26 - 4.958	<10-5	0.917	0.463 - 1.816	0.80	2.326	1.675 - 3.23	<10-5
Donor									
MFD (reference data)	1.00			1.00			1.00		
VUD 10/10	0.809	0.578 - 1.131	0.21	1.271	0.802 - 2.014	0.31	0.97	0.74 - 1.27	0.82
MMUD 9/10	0.842	0.546 - 1.3	0.44	1.986	1.168 - 3.377	0.01	1.189	0.854 - 1.657	0.31
Haplo	0.576	0.312 - 1.065	0.08	2.096	1.097 - 4.002	0.02	0.944	0.61 - 1.462	0.80
KPS>80%	1.084	0.497 - 2.362	0.84	0.447	0.219 - 0.914	0.03	0.716	0.424 - 1.207	0.21
PBSC vs BM	0.714	0.51 - 0.999	0.05	1.599	0.97 - 2.636	0.07	0.957	0.725 - 1.264	0.76
Year of allo-HCT	1.005	0.953 - 1.06	0.86	0.987	0.922 - 1.057	0.72	1.002	0.961 - 1.045	0.93
Patient female	0.865	0.659 - 1.135	0.29	0.981	0.693 - 1.389	0.92	0.894	0.723 - 1.107	0.31
Donor female	0.76	0.574 - 1.006	0.06	1.089	0.77 - 1.539	0.63	0.87	0.701 - 1.081	0.21
in vivo TCD	1.064	0.767 - 1.475	0.71	0.853	0.564 - 1.289	0.45	0.972	0.752 - 1.256	0.83
centre			0.25			0.25			0.18

	OS			GRFS			acute GVHD II-IV		
	HR	CI	p	HR	CI	p	HR	CI	p
Age <50y									
RIC vs MAC	0.914	0.7 - 1.192	0.507	0.863	0.683 - 1.091	0.217	0.863	0.62 - 1.201	0.381
Age (per 10 y)	1	0.965 - 1.25	0.155	1.129	1.012 - 1.259	0.030	1.017	0.869 - 1.189	0.838
Time Diagnosis to allo-HCT (m)	0.982	0.974 - 0.991	<10-4	0.991	0.985 - 0.997	0.003	0.999	0.992 - 1.006	0.763
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.318	1.026 - 1.692	0.031	1.14	0.926 - 1.403	0.217	0.91	0.678 - 1.222	0.531
Adverse	2.417	1.708 - 3.421	<10-5	1.822	1.344 - 2.471	<10-3	0.804	0.484 - 1.337	0.401
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.044	0.784 - 1.389	0.770	1.049	0.825 - 1.334	0.698	2.057	1.439 - 2.939	<10-4
MMUD 9/10	1.406	0.997 - 1.983	0.052	1.195	0.881 - 1.622	0.252	2.679	1.721 - 4.17	<10-4
Haplo	1.217	0.776 - 1.908	0.393	0.692	0.46 - 1.039	0.076	1.595	0.949 - 2.683	0.078
KPS>80%	0.62	0.371 - 1.035	0.067	0.955	0.574 - 1.588	0.859	0.701	0.356 - 1.378	0.303
PBSC vs BM	1.087	0.809 - 1.46	0.581	1.252	0.97 - 1.615	0.084	1.203	0.849 - 1.705	0.298
Year of allo-HCT	0.989	0.946 - 1.035	0.643	1.021	0.983 - 1.06	0.288	0.974	0.927 - 1.023	0.291
Patient female	0.838	0.667 - 1.053	0.129	0.917	0.758 - 1.109	0.371	0.88	0.668 - 1.161	0.367
Donor female	0.941	0.749 - 1.183	0.603	0.953	0.787 - 1.154	0.623	0.811	0.613 - 1.074	0.144
in vivo TCD	0.901	0.692 - 1.173	0.439	0.622	0.492 - 0.786	<10-4	0.479	0.346 - 0.663	<10-4
centre			0.291			0.090			0.912

	acute GVHD III-IV			chronic GVHD			ext. chronic GVHD		
	HR	CI	p	HR	CI	p	HR	CI	p
Age <50y									
RIC vs MAC	0.773	0.414 - 1.443	0.418	0.959	0.698 - 1.317	0.795	1.024	0.638 - 1.644	0.922
Age (per 10 y)	1.129	0.841 - 1.515	0.418	1.049	0.907 - 1.213	0.519	0.999	0.803 - 1.242	0.993
Time Diagnosis to allo-HCT (m)	1.004	0.993 - 1.014	0.499	1.005	1 - 1.011	0.067	0.997	0.988 - 1.007	0.564
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.011	0.589 - 1.735	0.969	1.011	0.77 - 1.328	0.936	0.904	0.604 - 1.351	0.621
Adverse	1.03	0.423 - 2.506	0.949	1.354	0.846 - 2.167	0.206	1.187	0.564 - 2.495	0.652
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.844	1.002 - 3.395	0.049	1.205	0.879 - 1.652	0.247	1.27	0.816 - 1.977	0.290
MMUD 9/10	1.529	0.657 - 3.559	0.324	1.072	0.689 - 1.669	0.758	0.963	0.481 - 1.926	0.914
Haplo	0.881	0.29 - 2.672	0.823	0.771	0.446 - 1.332	0.351	0.501	0.199 - 1.264	0.143
KPS>80%	0.477	0.169 - 1.345	0.162	1.608	0.633 - 4.083	0.318	4.276	0.563 - 32.455	0.160
PBSC vs BM	1.504	0.765 - 2.958	0.237	1.784	1.253 - 2.539	0.001	3.131	1.738 - 5.64	<10-3
Year of allo-HCT	0.971	0.886 - 1.064	0.528	0.974	0.924 - 1.026	0.315	1.052	0.971 - 1.14	0.213
Patient female	0.821	0.492 - 1.369	0.450	1.04	0.802 - 1.348	0.768	0.849	0.578 - 1.247	0.404
Donor female	0.825	0.493 - 1.381	0.465	1.719	1.331 - 2.22	<10-4	1.515	1.047 - 2.194	0.028
in vivo TCD	0.429	0.24 - 0.769	0.004	0.562	0.411 - 0.77	<10-3	0.27	0.167 - 0.435	<10-5
centre			0.779			0.076			0.016

Table 3

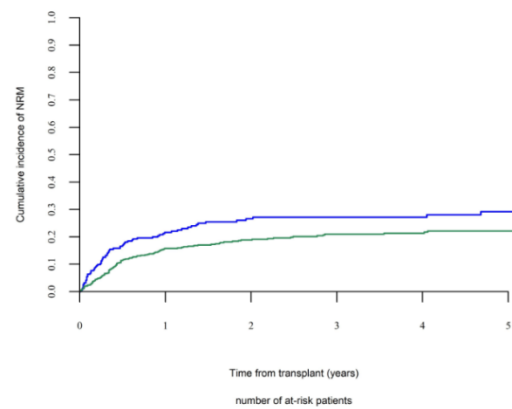
	HR	Relapse CI	p	HR	NRM CI	p	HR	LFS CI	p
Age ≥50y									
RIC vs MAC	1.261	0.912 - 1.743	0.161	0.535	0.378 - 0.758	<10-3	0.883	0.695 - 1.122	0.310
Age (per 10 y)	0.981	0.781 - 1.232	0.868	1.567	1.211 - 2.027	0.001	1.205	1.013 - 1.432	0.035
Secondary AML	0.857	0.521 - 1.41	0.543	0.99	0.564 - 1.737	0.971	0.916	0.63 - 1.333	0.647
Time Diagnosis to allo-HCT (m)	0.974	0.963 - 0.986	10-5	1.001	0.992 - 1.01	0.786	0.987	0.98 - 0.995	0.001
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.436	1.006 - 2.049	0.046	0.869	0.585 - 1.292	0.488	1.163	0.892 - 1.518	0.265
Adverse	1.79	1.035 - 3.096	0.037	1.108	0.579 - 2.121	0.756	1.465	0.961 - 2.234	0.076
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.097	0.805 - 1.495	0.558	1.237	0.822 - 1.859	0.308	1.146	0.894 - 1.469	0.281
MMUD 9/10	0.93	0.614 - 1.409	0.733	2.241	1.419 - 3.539	0.001	1.338	0.987 - 1.814	0.061
Haplo	0.577	0.298 - 1.117	0.103	1.948	1.069 - 3.552	0.029	1.017	0.657 - 1.574	0.941
KPS >80%	0.867	0.472 - 1.592	0.646	0.265	0.162 - 0.435	<10-5	0.486	0.331 - 0.715	<10-3
PBSC vs BM	0.998	0.635 - 1.568	0.992	1.325	0.825 - 2.128	0.244	1.117	0.804 - 1.553	0.509
Year of allo-HCT	0.985	0.935 - 1.037	0.556	0.943	0.889 - 1.001	0.054	0.968	0.93 - 1.007	0.104
Patient female	0.747	0.575 - 0.971	0.029	0.825	0.608 - 1.12	0.218	0.774	0.633 - 0.945	0.012
Donor female	0.909	0.687 - 1.203	0.505	1.027	0.745 - 1.415	0.869	0.95	0.768 - 1.174	0.634
in vivo TCD	1.028	0.761 - 1.389	0.859	1.047	0.746 - 1.468	0.792	1.042	0.826 - 1.315	0.727
centre			0.228			0.256			0.188

	HR	OS CI	p	HR	GRFS CI	p	HR	acute GVHD II-IV CI	p
Age ≥50y									
RIC vs MAC	0.915	0.713 - 1.175	0.489	1.04	0.832 - 1.299	0.733	0.921	0.648 - 1.307	0.644
Age (per 10 y)	1.265	1.056 - 1.516	0.011	1.017	0.865 - 1.196	0.840	0.927	0.717 - 1.197	0.559
Secondary AML	0.955	0.646 - 1.412	0.819	1.061	0.755 - 1.491	0.734	1.506	0.92 - 2.467	0.104
Time Diagnosis to allo-HCT (m)	0.988	0.98 - 0.996	0.002	0.993	0.986 - 1	0.037	1.004	0.996 - 1.012	0.357
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.202	0.903 - 1.6	0.206	1.192	0.934 - 1.521	0.159	1.031	0.685 - 1.552	0.883
Adverse	1.607	1.042 - 2.479	0.032	1.31	0.879 - 1.954	0.185	0.833	0.403 - 1.724	0.623
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.183	0.909 - 1.54	0.210	1.137	0.906 - 1.426	0.267	1.68	1.118 - 2.525	0.013
MMUD 9/10	1.511	1.098 - 2.081	0.011	1.516	1.146 - 2.004	0.004	2.685	1.692 - 4.26	<10-4
Haplo	1.321	0.842 - 2.074	0.226	1.016	0.681 - 1.517	0.937	2.434	1.341 - 4.417	0.003
KPS >80%	0.437	0.297 - 0.645	<10-4	0.363	0.254 - 0.518	0.000	0.562	0.322 - 0.982	0.043
PBSC vs BM	1.167	0.827 - 1.649	0.379	1.172	0.863 - 1.593	0.309	1.331	0.809 - 2.191	0.260
Year of allo-HCT	0.968	0.927 - 1.01	0.133	0.97	0.936 - 1.007	0.108	0.986	0.932 - 1.043	0.622
Patient female	0.828	0.672 - 1.022	0.078	0.884	0.735 - 1.062	0.188	1.044	0.779 - 1.4	0.771
Donor female	1.008	0.808 - 1.259	0.941	1.065	0.88 - 1.29	0.516	0.919	0.669 - 1.261	0.599
in vivo TCD	1.082	0.853 - 1.371	0.516	0.764	0.617 - 0.945	0.013	0.93	0.659 - 1.312	0.679
centre			0.312			0.120			0.263

	HR	acute GVHD III-IV CI	p	HR	chronic GVHD CI	p	HR	ext. chronic GVHD CI	p
Age ≥50y									
RIC vs MAC	0.729	0.428 - 1.242	0.245	1.377	1.027 - 1.845	0.032	1.352	0.869 - 2.102	0.181
Age (per 10 y)	0.71	0.469 - 1.075	0.106	0.863	0.698 - 1.067	0.173	0.79	0.571 - 1.093	0.155
Secondary AML	1.669	0.78 - 3.573	0.187	0.933	0.57 - 1.527	0.782	1.45	0.741 - 2.838	0.279
Time Diagnosis to allo-HCT (m)	1.008	0.997 - 1.02	0.143	0.996	0.988 - 1.003	0.249	1.005	0.995 - 1.015	0.316
Cytogenetics									
Good risk group (reference data)	1			1			1		
Intermediate	1.082	0.574 - 2.043	0.807	1.161	0.843 - 1.599	0.359	1.064	0.667 - 1.7	0.794
Adverse	0.357	0.079 - 1.614	0.181	1.583	0.917 - 2.732	0.099	1.071	0.435 - 2.639	0.881
Donor									
MFD (reference data)	1			1			1		
VUD 10/10	1.293	0.669 - 2.5	0.445	0.983	0.738 - 1.311	0.909	1.388	0.892 - 2.159	0.146
MMUD 9/10	4.167	2.125 - 8.173	<10-4	1.006	0.678 - 1.493	0.975	1.741	0.992 - 3.056	0.054
Haplo	1.811	0.717 - 4.572	0.209	0.86	0.508 - 1.455	0.575	0.585	0.234 - 1.464	0.252
KPS >80%	0.338	0.152 - 0.748	0.007	0.758	0.432 - 1.33	0.333	0.66	0.261 - 1.671	0.381
PBSC vs BM	1.441	0.679 - 3.06	0.341	1.683	1.08 - 2.624	0.021	1.599	0.814 - 3.144	0.173
Year of allo-HCT	0.994	0.909 - 1.086	0.886	0.985	0.939 - 1.034	0.543	1.004	0.933 - 1.081	0.905
Patient female	1.114	0.704 - 1.762	0.644	1.137	0.886 - 1.458	0.313	1.08	0.743 - 1.571	0.686
Donor female	1.107	0.686 - 1.787	0.676	1.034	0.795 - 1.344	0.804	1.558	1.065 - 2.28	0.022
in vivo TCD	0.747	0.44 - 1.269	0.281	0.484	0.373 - 0.627	0.000	0.266	0.18 - 0.393	<10-5
centre			0.283			0.271			0.921

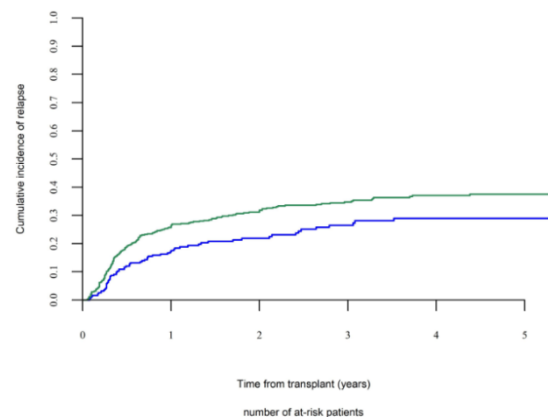
A

NRM



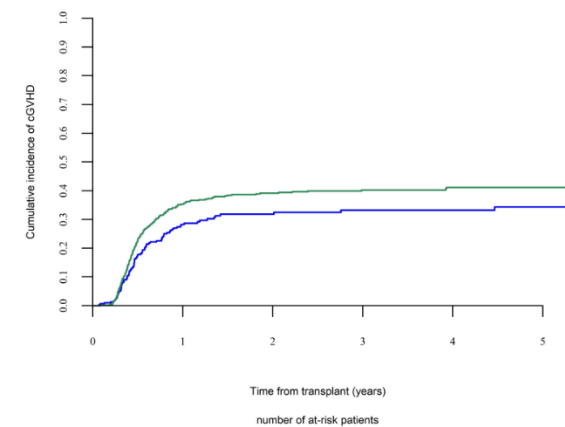
B

Relapse



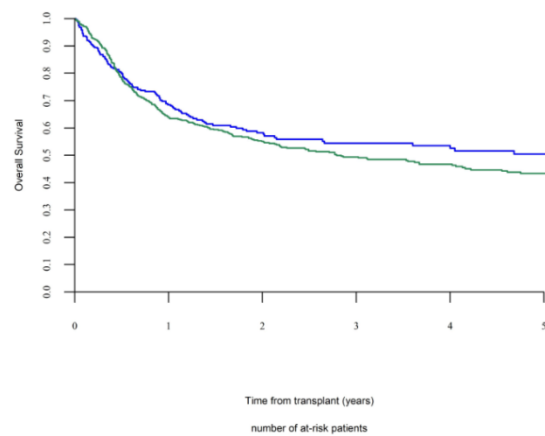
C

cGVHD



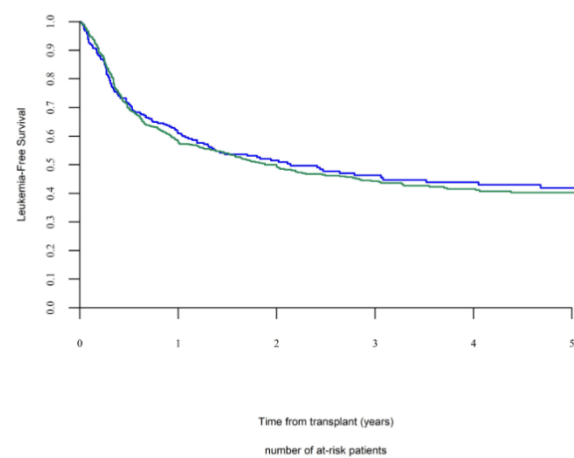
D

OS



E

LFS



F

GRFS

