Hematopoietic cell transplantation for older acute myeloid leukemia patients in first complete remission: results of a randomized phase III study

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Supplemental material

Supplemental material to methods

Observation arm:

Patients with no-matched donor (n=26), patients with a mismatched donor (n=15) and patients with a matched donor refusing to be randomized or treated before randomization (n=10) were allocated to an observation group and treated at the discretion of the local investigator including HCT with mismatched donors (Figure S10).

Inclusion and exclusion criteria:

Inclusion criteria at registration were age ≥60 and ≤75 years, *de novo* or secondary AML or refractory anemia with excess blasts 5-20% in bone marrow (RAEB), ≤2 induction chemotherapies to reach CR1, Karnofsky Index >70%, and written informed consent. Patients with acute promyelocytic leukemia and Human Immunodeficiency Virus (HIV) positivity were ineligible. Inclusion criteria at randomization were previous registration in the trial, CR after first consolidation and availability of an HLA-identical related or 10/10 unrelated donor. Excluded were patients with more than one consolidation, an interval of >5 months after diagnosis, creatinine clearance <50 ml/min, cardiac ejection fraction <40%, severe pulmonary dysfunction or poorly controlled hypertension (Table S1).

Statistical Analysis

In the initial protocol, the analysis relied on the proportional hazard assumption by specifying a Cox regression adjusting for randomization strata. Assuming a 5-year LFS rate of 45% with HCT versus 25% with non-HCT and requiring 90% power with a two-sided significance level of 5%, the target sample size was 231 patients in order to observe 135 events with a 2:1 randomization. Two interim analyses after 1/3 and 2/3 of the expected events were scheduled using the O'Brien-Fleming sequential design. The time horizon was set at 5 years as initially planned. A conditional power analysis showed that with RM-LFS, reasonable power would be achieved already with a reduced target sample size of 150 randomized patients. The final analysis was performed using a nominal alpha = 5% significance level. The false positive error of the final analysis is practically not affected (Haybittle-Peto) since the first interim analysis was carried out at an alpha =0.0002 level. The changes were proposed to, and approved by, the DMC on occasion of the first planned interim analysis from 78 patients in 2014.

RM-LFS estimation and regression analyses for LFS and OS were performed using the R-package "pseudo".[21–26] As a supportive analysis, we present plots of the difference in RM-LFS as a function of

the time horizon in order to illustrate how the preference for the treatment options depends on the chosen time horizon.

Legend to Figures

Figure S1: Study design

Figure S2: Accrual of patients to the study according to registration, assignment and randomization

Figure S3: A: Time from diagnosis to randomization for all patients (n=125)

B: Time from diagnosis to hematopoietic cell transplantation (HCT; n=66)

Figure S4: Cumulative incidence of Non Relapse mortality (NRM) according to an integrated risk score combining the most dominant parameter from the HCT-CI and the EBMT score (Versluis et al [25]) in the 66 patients with HCT

Figure S5: Cumulative incidence of acute GvHD

Figure S6: Cumulative incidence of chronic GvHD

Figure S7: Leukemia Free Survival (LFS) in the control group after relapse according to related or unrelated HCT

Figure S8: RM-LFS (A) and RM-OS (B) according to HCT vs. non-HCT. RM LFS quantifies the expected number of years alive in CR up to the time horizon with a given therapy; similarly, RM -OS gives the expected years alive at 5 years. The figure makes this phenomenon explicit depicting the difference in RM-LFS (A) and RM-OS (B) varying the time horizon. Due to early NRM, non-HCT is beneficial short term compared to HCT. For RM-LFS, HCT becomes beneficial after about 4 years.

Figure S9: Overall Survival (OS) in the non-HCT group according to HCT vs. non-HCT after relapse

Figure S10: Flow chart of the observation group

Figure S11: OS according to age groups in patients <65, 65-70 and 70+ years.

Table S1: Eligibility criteria at registration and at randomization

a) at registration		b) at randomization
	inclusion criteria	
• Age ≥60 and ≤75 years • *De novo* or *sec.* AML or RAEB • CR1 ≤2 induction chemotherapies • Karnofsky Index >70% • Written informed consent		• Patient registered in the trial • CR after first consolidation • Matching related or unrelated donor (10/10)
	exclusion criteria	
• AML FAB M3 • HIV positivity		• >1 consolidation cycle • >5 months (>150 days) after diagnosis • Creatinine clearance <50 ml/min • Cardiac ejection fraction <40% • Severe pulmonary dysfunction or O_2 support • Poorly controlled hypertension

Table S2: Randomization by trial site

Ntotal=245	Randomised	%	Observation	%	Registered Only	%
UK Leipzig	35	45.5	21	27.3	21	27.3
UK Muenster	21	47.7	17	38.6	6	13.6
Erasmus MC Rotterdam	14	50	1	3.6	13	46.4
Hopitaux universitaires de Geneve	12	85.7	2	14.3	0	0
University Hospital Maastricht	8	61.5	0	0	5	38.5
VU University Medical Center Amsterdam	6	46.2	2	15.4	5	38.5
UK Dresden	9	75	2	16.7	1	8.3
Isala Klinieken, Locatie Sophia, Zwolle	2	28.6	3	42.9	2	28.6
UK Rostock	4	57.1	0	0	3	42.9
Klinikum Chemnitz gGmbH	4	100	0	0	0	0
UK Jena	1	25	0	0	3	75
UK Magdeburg	1	25	1	25	2	50
Academisch Ziekenhuis bij de Universiteit Amsterdam	3	100	0	0	0	0
Charite Berlin	2	66.7	0	0	1	33.3
University Hospital Basel	1	33.3	2	66.7	0	0
Klinikum E. v. Bergmann gGmbH, Potsdam	2	100	0	0	0	0
Centre Hospitalier Sud Amiens	0	0	0	0	1	100
CHU de Nantes	0	0	0	0	1	100
Kantonsspital Luzern	0	0	1	100	0	0
Med. UK Tuebingen	0	0	1	100	0	0
The Alfred Hospital, Melbourne Victoria	0	0	0	0	1	100
UK Aachen	0	0	0	0	1	100
University Medical Centre Utrecht	0	0	1	100	0	0
Nvalid	125	51	54	22	66	26.9

Table S3: Molecular alterations in randomized patients and according to treatment allocation

		TOTAL			HCT		non-HCT		
Variable		n tested	% total	% positive	n=83	% positive	n=42	% positive	p-value
Molecular alterations	*BCR::ABL1*	41	32.8	0.0	29	0.0	12	0.0	n.a.
	PML::RARalpha	66	52.8	0.0	45	0.0	21	0.0	n.a.
	AML1::ETO	82	65.6	2.4	55	1.8	27	3.7	1
	FLT3-ITD	111	88.8	19.8	75	21.3	36	16.7	0.747
	FLT3-TKD	31	24.8	0.0	20	0.0	11	0.0	n.a.
	NPM1 mutation	109	87.2	33.9	74	28.4	35	45.7	0.117
	MLL-PTD	36	28.8	8.3	25	8.0	11	9.1	1
	inv 16;CBF-beta::NYH11	59	47.2	3.4	40	5.0	19	0.0	1
	CEBPA mutation	80	64.0	2.5	55	1.8	25	4.0	0.53
	EVI	27	21.6	3.7	19	0.0	8	12.5	0.296
	JAK2	24	19.2	8.3	17	11.8	7	0.0	1
	WT1	27	21.6	33.3	18	27.8	9	44.4	0.423
	ABL1	16	12.8	0.0	11	0.0	5	0.0	n.a.
	ASXL1	25	20.0	0.0	18	0.0	7	0.0	n.a.
	ATRX	25	20.0	0.0	18	0.0	7	0.0	n.a.
	BCOR	25	20.0	8.0	18	5.6	7	14.3	0.49
	BCORL1	25	20.0	4.0	18	5.6	7	0.0	1
	BRAF	16	12.8	0.0	11	0.0	5	0.0	n.a.
	CALR	25	20.0	4.0	18	0.0	7	14.3	0.28
	CBL	25	20.0	4.0	18	0.0	7	14.3	0.28

CBLB	25	20.0	0.0	18	0.0	7	0.0	n.a.
CBLC	25	20.0	0.0	18	0.0	7	0.0	n.a.
CDKN2A	25	20.0	0.0	18	0.0	7	0.0	n.a.
CSF3R	25	20.0	0.0	18	0.0	7	0.0	n.a.
CUX1	25	20.0	0.0	18	0.0	7	0.0	n.a.
DNMT3A	26	20.8	34.6	19	31.6	7	42.9	0.661
ETV6/TEL	25	20.0	0.0	18	0.0	7	0.0	n.a.
EZH2	25	20.0	12.0	18	5.6	7	28.6	0.18
FBXW7	25	20.0	0.0	18	0.0	7	0.0	n.a.
FLT3	31	24.8	0.0	22	0.0	9	0.0	n.a.
GATA1	25	20.0	4.0	18	0.0	7	14.3	0.28
GATA2	25	20.0	0.0	18	0.0	7	0.0	n.a.
GNAS	25	20.0	0.0	18	0.0	7	0.0	n.a.
HRAS	27	21.6	0.0	19	0.0	8	0.0	n.a.
IDH1	35	28.0	5.7	26	7.7	9	0.0	1
IDH2	35	28.0	17.1	27	18.5	8	12.5	1
IKZF1	26	20.8	7.7	19	10.5	7	0.0	1
JAK3	25	20.0	0.0	18	0.0	7	0.0	n.a.
KDM6A	25	20.0	0.0	18	0.0	7	0.0	n.a.
KIT	25	20.0	4.0	18	5.6	7	0.0	n.a.
KRAS	25	20.0	4.0	18	0.0	7	14.3	1
MLL	25	20.0	0.0	18	0.0	7	0.0	n.a.
MPL	25	20.0	0.0	18	0.0	7	0.0	n.a.
MYD88	25	20.0	0.0	18	0.0	7	0.0	n.a.
NOTCH1	25	20.0	4.0	18	5.6	7	0.0	1
NRAS	25	20.0	4.0	18	5.6	7	0.0	1

PDGFRA	25	20.0	8.0	18	5.6	7	14.3	0.49
PHF6	25	20.0	12.0	18	16.7	7	0.0	0.534
PTEN	25	20.0	0.0	18	0.0	7	0.0	n.a.
PTPN11	25	20.0	4.0	18	5.6	7	0.0	1
RAD21	25	20.0	0.0	18	0.0	7	0.0	n.a.
RUNX1	25	20.0	16.0	18	16.7	7	14.3	1
SETBP1	25	20.0	0.0	18	0.0	7	0.0	n.a.
SF3B1	25	20.0	4.0	18	0.0	7	14.3	0.28
SMC1A	25	20.0	0.0	18	0.0	7	0.0	n.a.
SMC3	27	21.6	0.0	19	0.0	8	0.0	n.a.
SRSF2	29	23.2	10.3	21	9.5	8	12.5	1
STAG2	27	21.6	0.0	20	0.0	7	0.0	n.a.
TET2	24	19.2	4.2	18	5.6	6	0.0	0.49
TP53	24	19.2	25.0	18	16.7	6	50.0	0.0664
U2AF1	25	20.0	4.0	18	5.6	7	0.0	1
ZRSR2	25	20.0	8.0	18	0.0	7	28.6	0.07

Table S4A: Pretreatment [Induction(s) and 1st consolidation]

Induction 1				Induction 2			consolidation		
drug 1	**drug 2**	**drug 3**	**n (%)**	**drug 1**	**drug 2**	**n (%)**	**drug 1**	**drug 2**	**n (%)**
cytarabine	Dauno	No drug/ Azacitidine/ Lena/Temsirolimus/Tosedostat	99 (40.4)	none		173 (70.6)	cytarabine		93 (38.0)
cytarabine	Mito		73 (29.8)	cytarabine	Mito	30 (12.2)	cytarabine	Mito ± PEG	76 (31.0)
cytarabine	Ida	no drug/ATRA	43 (17.5)	cytarabine		12 (4.9)	cytarabine	Amsacrine±Clofarabine	30 (12.2)
Azacitidine	no	If no response day 14 cytarabine/Mito	21 (8.6)	cytarabine	Dauno ± Azacitidine	11 (4.5)	cytarabine		20 (8.2)
cytarabine			7 (2.8)	cytarabine	± Lena	5 (2.0)	cytarabine	Dauno ± Tosedostat or Azacitidine	8 (3.3)
cytarabine	Thio	Amsacrine	2 (0.8)	cytarabine	Ida	5 (2.0)	cytarabine	Ida	5 (2.0)
				cytarabine	Amsacrin	4 (1.6)	cytarabine	Lena	4 (1.6)
				cytarabine		4 (1.6)	cytarabine	Eto	4 (1.6)
				cytarabine	Tosedostat	1 (0.4)	cytarabine	Tosedostat	3 (1.2)
							cytarabine	Cladribine+Midost	1 (0.4)
							Busulfan	Cyclo	1 (0.4)
Total			245 (100)			245 (100)			245 (100)

Abbreviations: ATRA, all-trans-retinoic acid; Cyclo, cyclophosphamide; Dauno, Daunorubicin; Eto, etoposide; Ida, idarubicin; Lena, Lenalidomide; Midost, midostaurin; Mito, Mitoxantrone; Thio, thioptepa; PEG, pegfilgrastim

Table S4B: Consolidation therapy of the non-HCT arm

Therapy	**n (%)**
High dose Cytarabine ± Mitoxantrone	20 (57.1)
Busulfan+Cyclophosphamide followed by autologous HCT	3 (8.6)
Etoposid and Mitoxantrone	3 (8.6)
Azacytidine	1 (2.9)
Not documented	8 (22.9)
Total	**35 (100)**

Table S5: Multivariate analysis of Restricted Mean LFS up to 5 years

Linear model on RM-LFS up to 5 years adjusting for cytogenetic risk and donor type

	mean RM-LFS in months	95% CI lower	95% CI upper	P Value
(intercept)	27.41	10.73	44.09	0.0013
HCT arm	11.05	2.68	19.41	0.0096
intermediate cytogenetic risk	-11.09	-26.44	4.26	0.157
high cytogenetic risk	-19.16	-35.12	-3.20	0.0186
donor unrelated	0.85	-9.56	11.26	0.873

Table S6: Number of patients in continuous CR, relapse and NRM according to NPM1 mutation

Total	HCT NPM1 mut neg		HCT NPM1 mut pos.		non-HCT NPM1 mut neg.		Non-HCT NPM1 mut pos.	
n= 125	n	%	n	%	n	%	n	%
CCR1	15	28.3	8	38.1	4	21.1	4	25
Relapse	22	41.5	6	28.6	15	78.9	12	75
NRM	16	30.2	7	33.3	0	0	0	0

Abbreviations: CCR, continuous complete remission; NRM, non-relapse mortality

Table S7: Causes of death in all patients and according to treatment allocation

		Total		HCT		Non-HCT	
		n	%	n	%	n	%
Relapse		58	67.4	29 (7)	50.9 (12.3)	29	100.0
Infection	bacterial	11	12.8	11	19.3	0	
	viral	2	2.3	2	3.5	0	
GvHD (acute/chronic)		6	7.0	6	10.5	0	
Hemorrhage		4	4.7	4	7.0	0	
Others		3	3.5	3	5.3	0	
Secondary neoplasm		1	1.2	1	1.8	0	
Graft failure		1	1.2	1	1.8	0	
Total		86	100.0	57	100.0	29	100.0

Figure S1

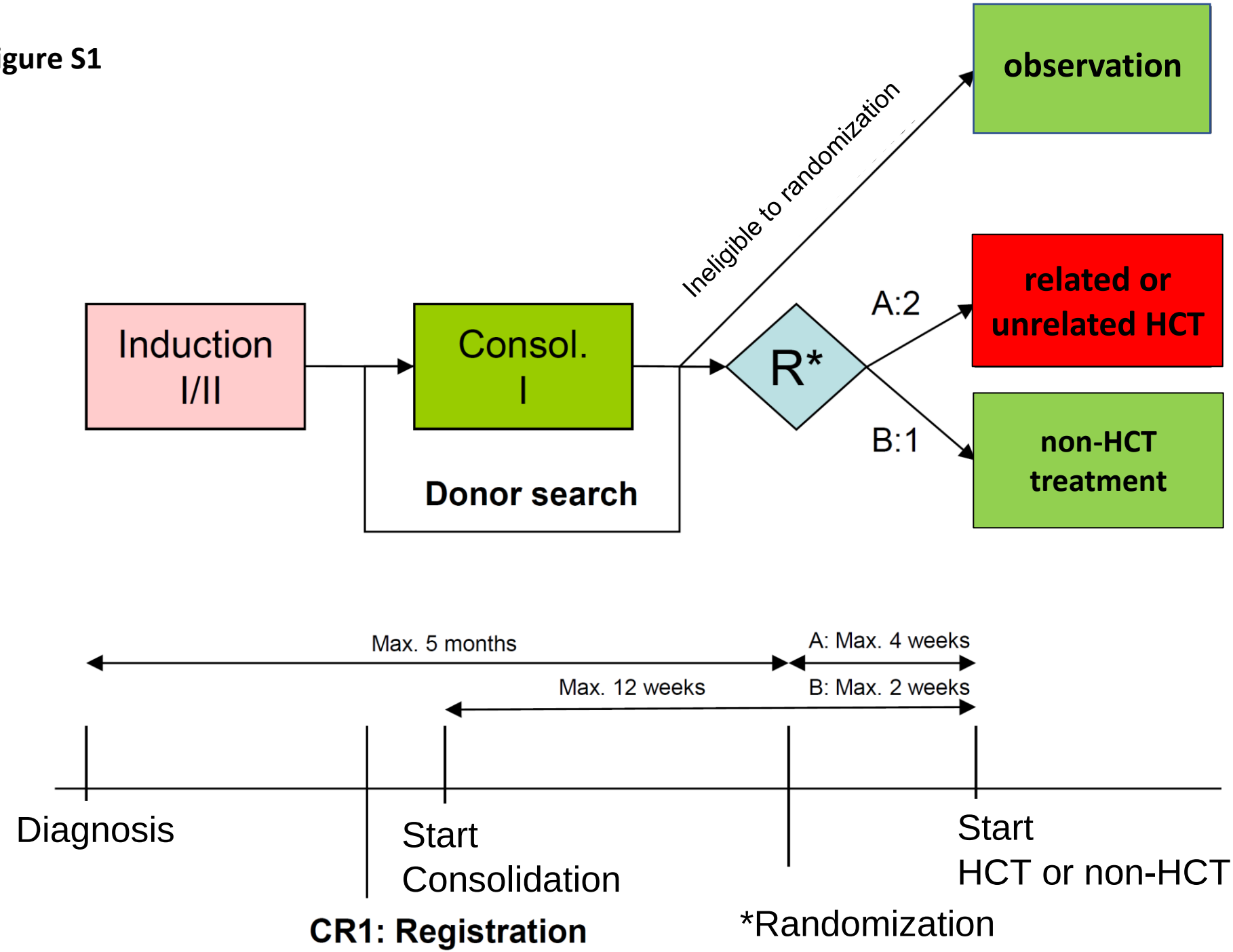

observation
Ineligible to randomization
related or unrelated HCT
A:2
Induction I/II
Consol. I
R*
B:1
non-HCT treatment
Donor search
Max. 5 months
A: Max. 4 weeks
Max. 12 weeks
B: Max. 2 weeks
Diagnosis
Start Consolidation
Start HCT or non-HCT
CR1: Registration
*Randomization

Figure S2

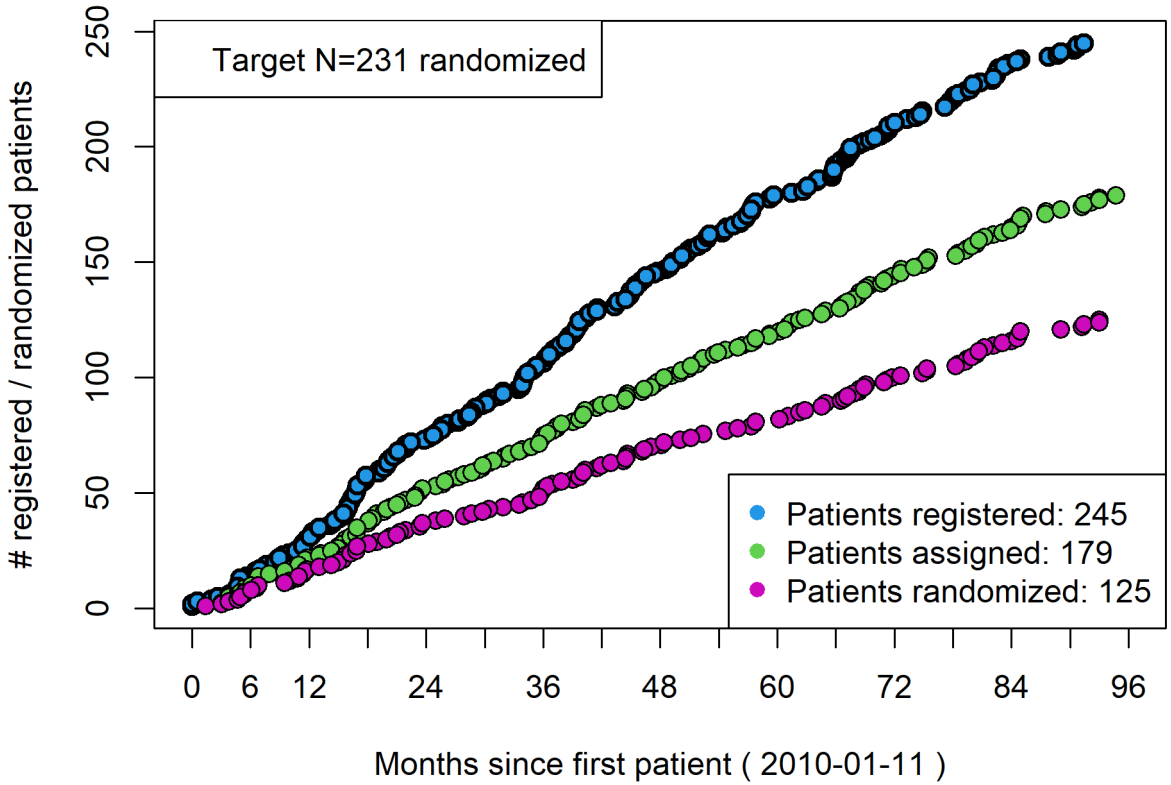

Target N=231 randomized
Patients registered: 245
Patients assigned: 179
Patients randomized: 125
registered / randomized patients
0
50
100
150
200
250
0
6
12
24
36
48
60
72
84
96
Months since first patient (2010-01-11)

Figure S3 A

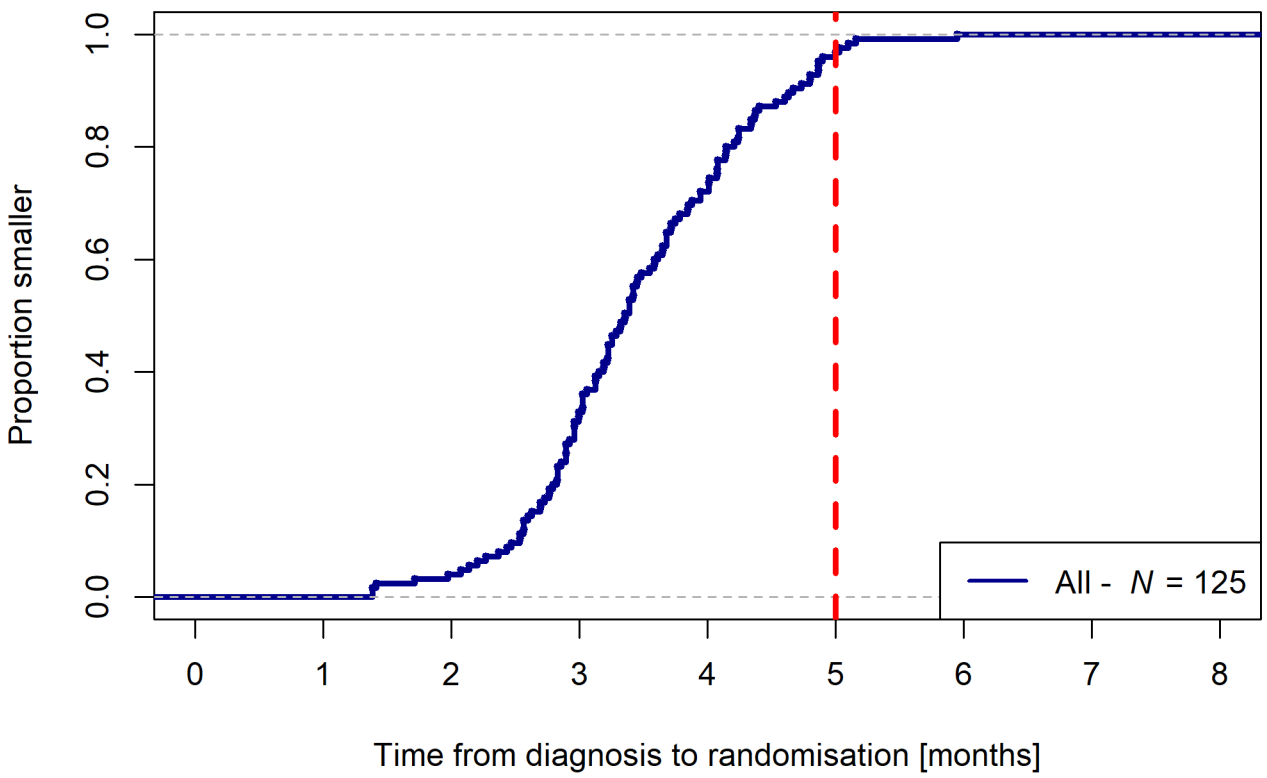

Proportion smaller
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
Time from diagnosis to randomisation [months]
All - N = 125

Figure S3 B

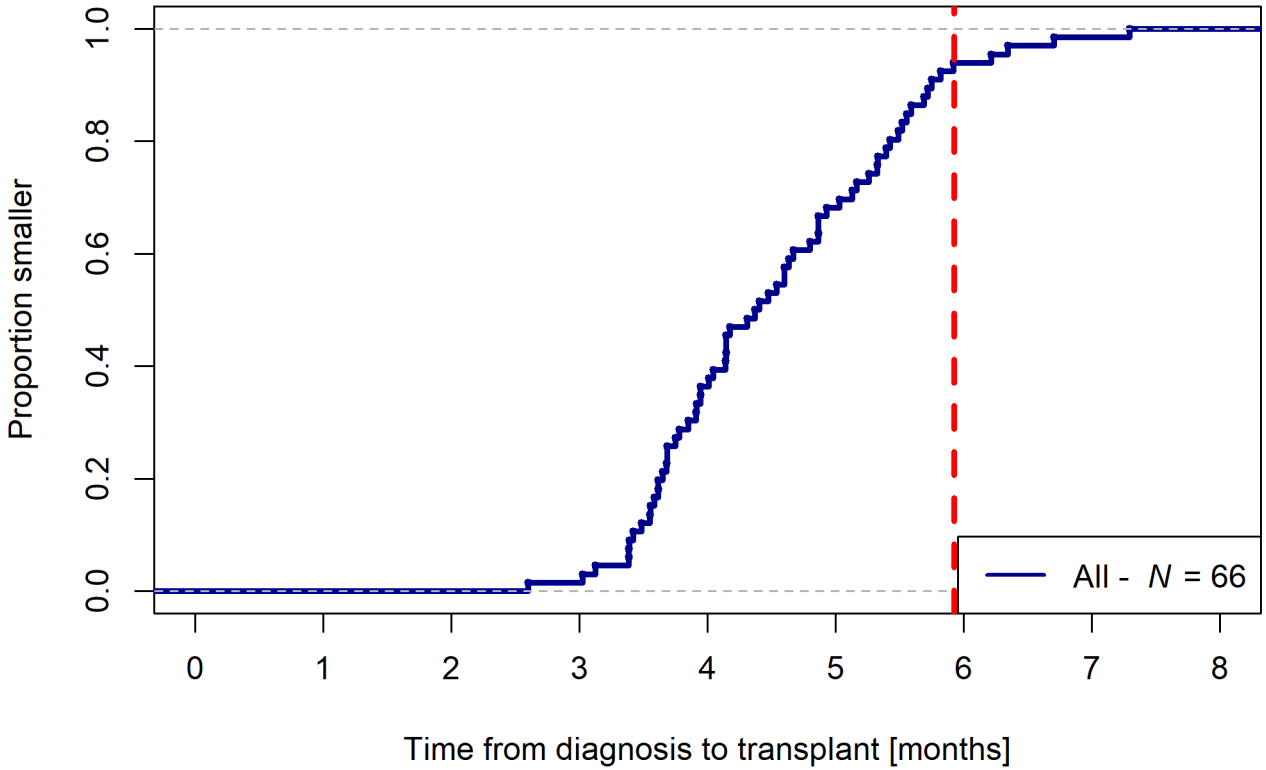

Proportion smaller
0.0
0.2
0.4
0.6
0.8
1.0
0
1
2
3
4
5
6
7
8
Time from diagnosis to transplant [months]
All - N = 66

Figure S4

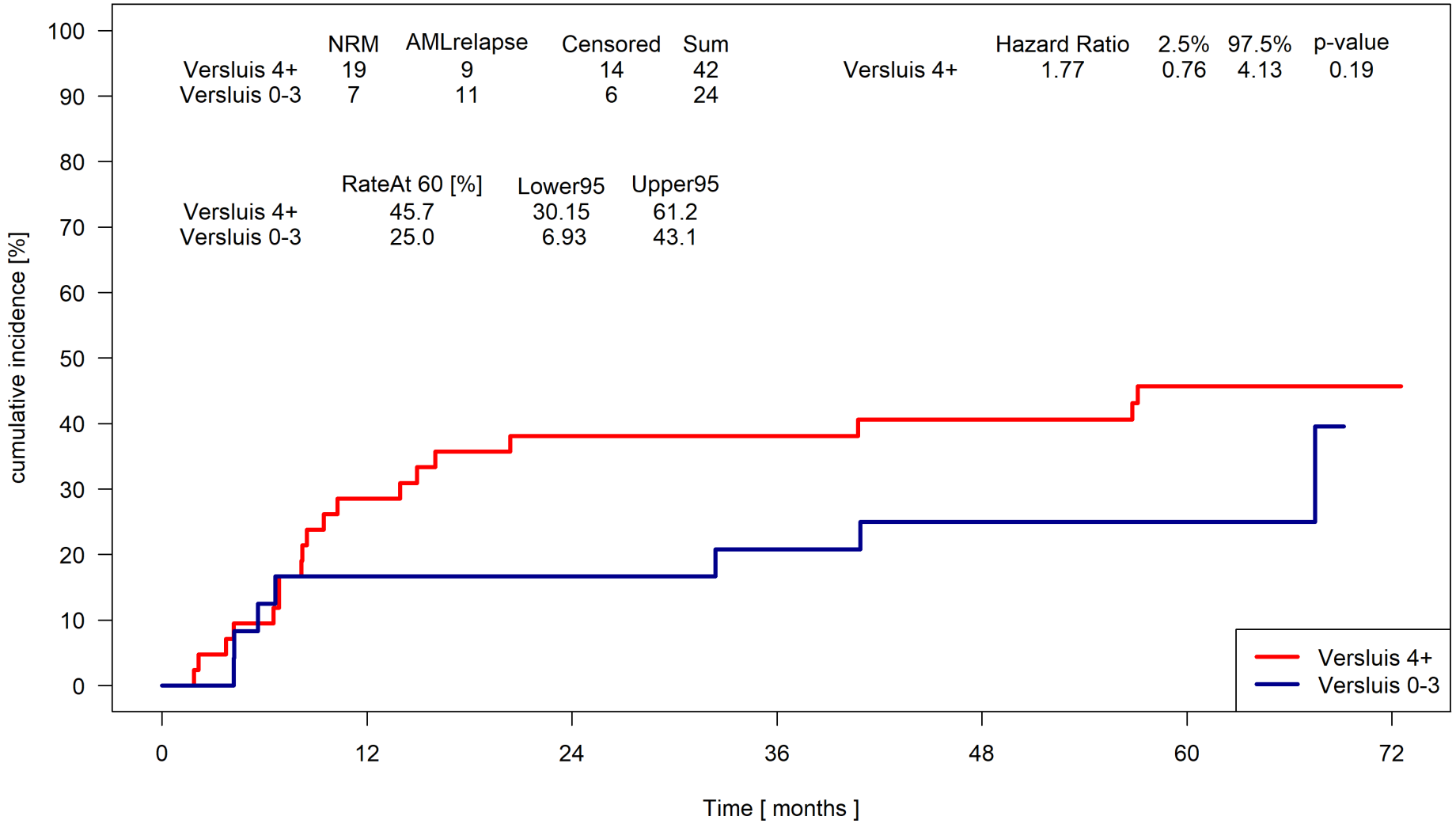

NRM AMLrelapse Censored Sum
Versluis 4+ 19 9 14 42
Versluis 0-3 7 11 6 24
Hazard Ratio 2.5% 97.5% p-value
Versluis 4+ 1.77 0.76 4.13 0.19
RateAt 60 [%] Lower95 Upper95
Versluis 4+ 45.7 30.15 61.2
Versluis 0-3 25.0 6.93 43.1
cumulative incidence [%]
100
90
80
70
60
50
40
30
20
10
0
0
12
24
36
48
60
72
Time [months]
Versluis 4+
Versluis 0-3

Figure S5

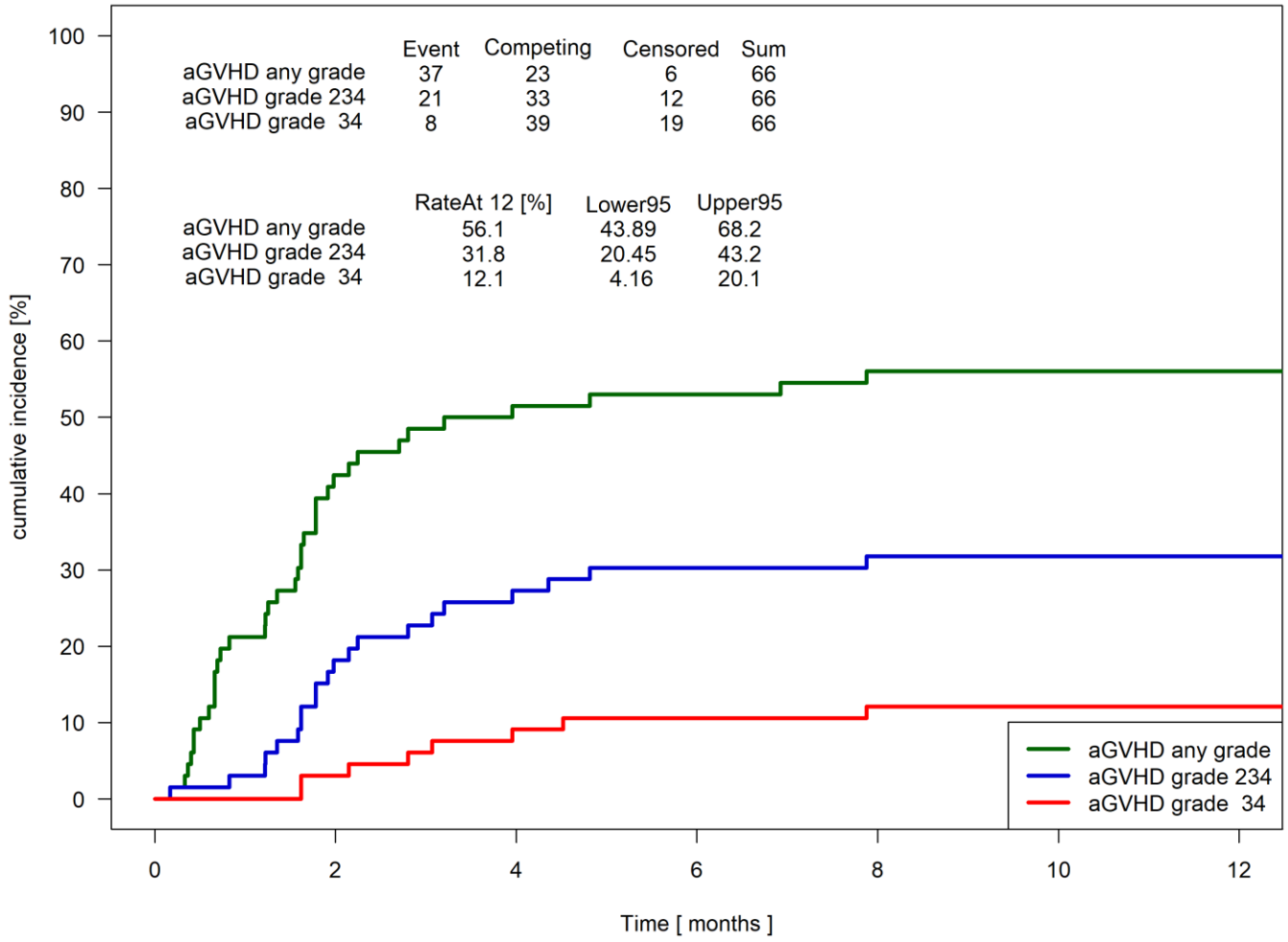

Event Competing Censored Sum
aGVHD any grade 37 23 6 66
aGVHD grade 234 21 33 12 66
aGVHD grade 34 8 39 19 66
RateAt 12 [%] Lower95 Upper95
aGVHD any grade 56.1 43.89 68.2
aGVHD grade 234 31.8 20.45 43.2
aGVHD grade 34 12.1 4.16 20.1
cumulative incidence [%]
Time [months]
aGVHD any grade
aGVHD grade 234
aGVHD grade 34

Figure S6

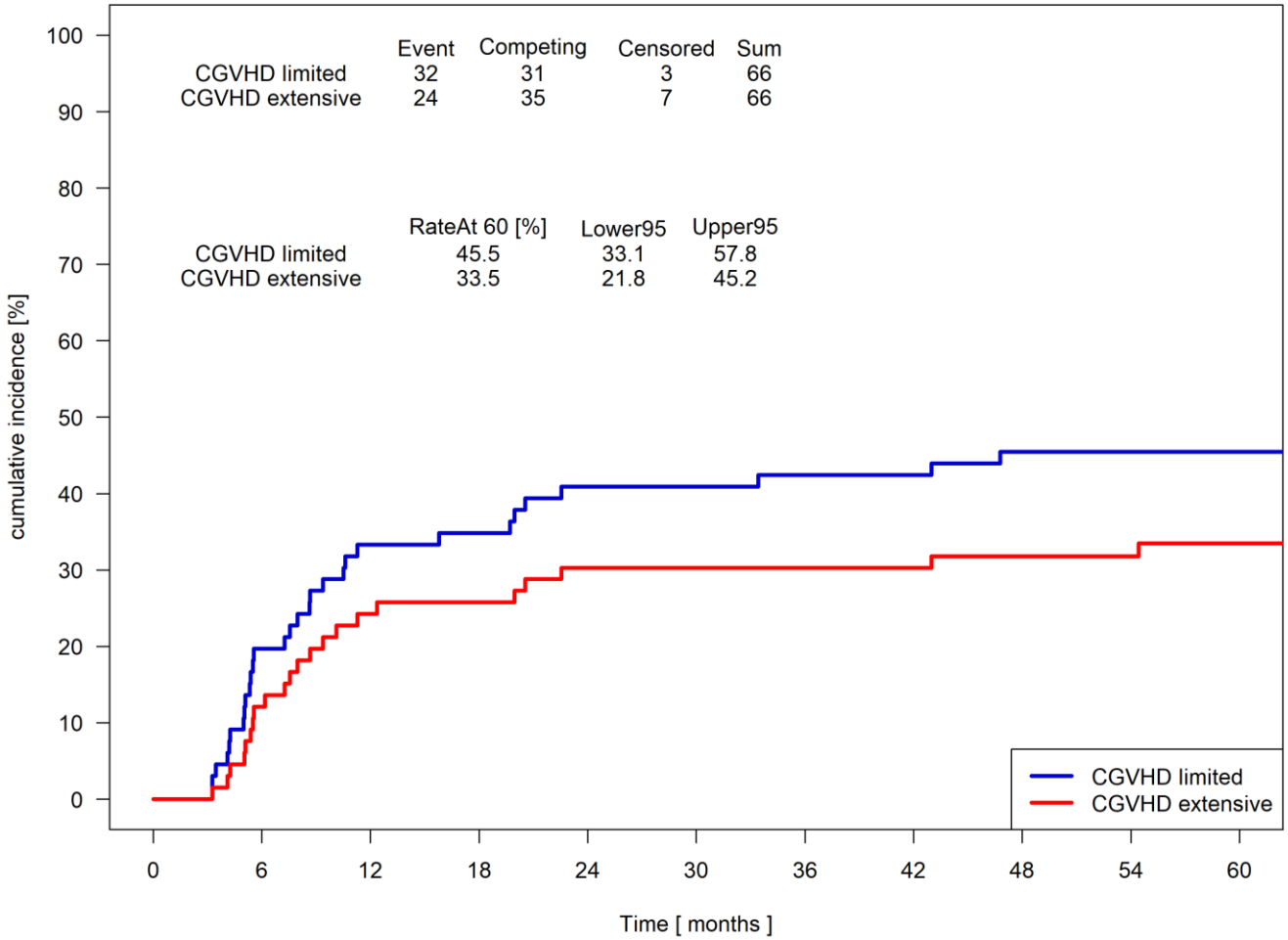
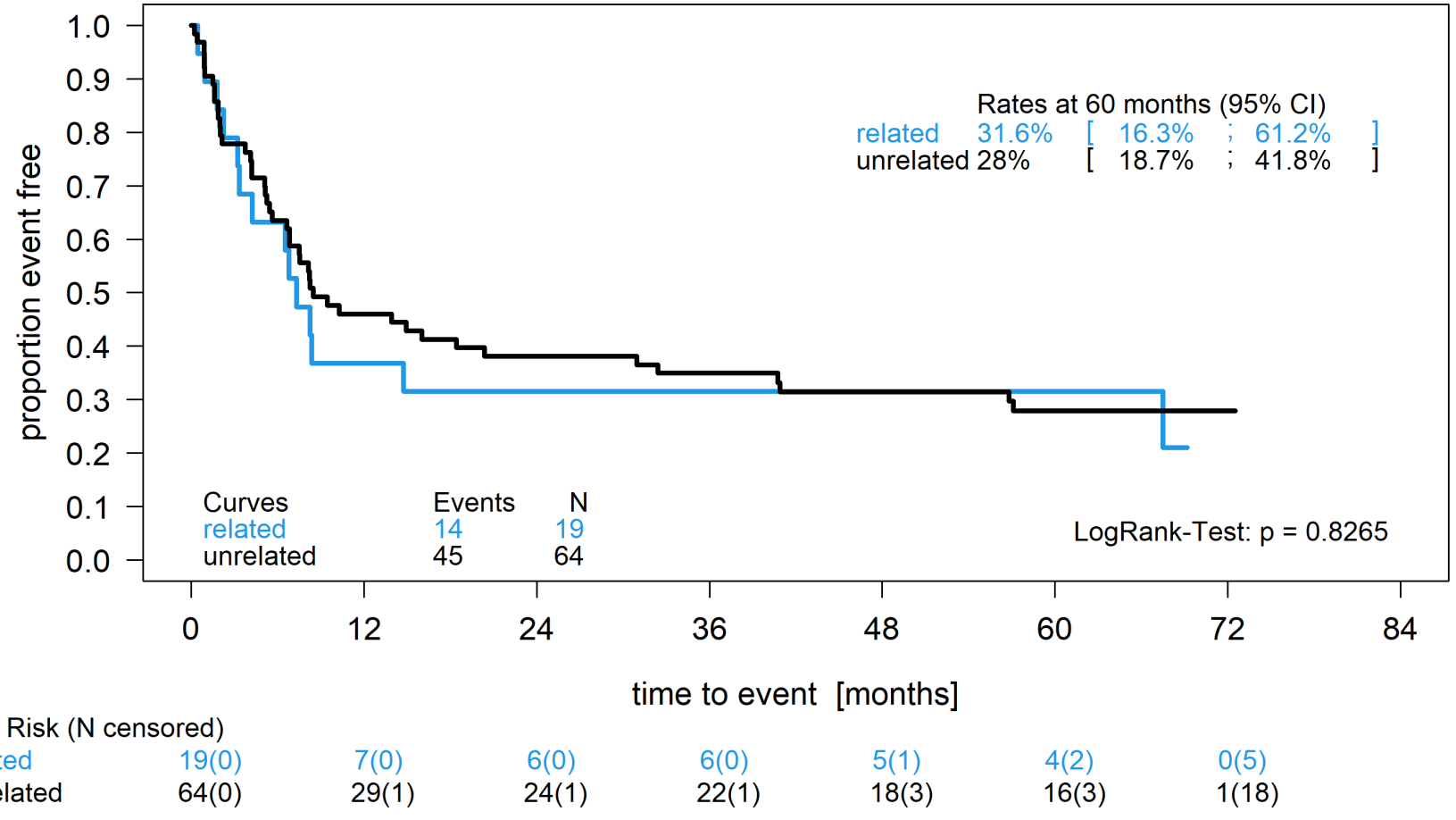

Event Competing Censored Sum
CGVHD limited 32 31 3 66
CGVHD extensive 24 35 7 66
RateAt 60 [%] Lower95 Upper95
CGVHD limited 45.5 33.1 57.8
CGVHD extensive 33.5 21.8 45.2
cumulative incidence [%]
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
30
36
42
48
54
60
Time [months]
CGVHD limited
CGVHD extensive

Figure S7



N at Risk (N censored)							
related	19(0)	7(0)	6(0)	6(0)	5(1)	4(2)	0(5)
unrelated	64(0)	29(1)	24(1)	22(1)	18(3)	16(3)	1(18)

Figure S8 A

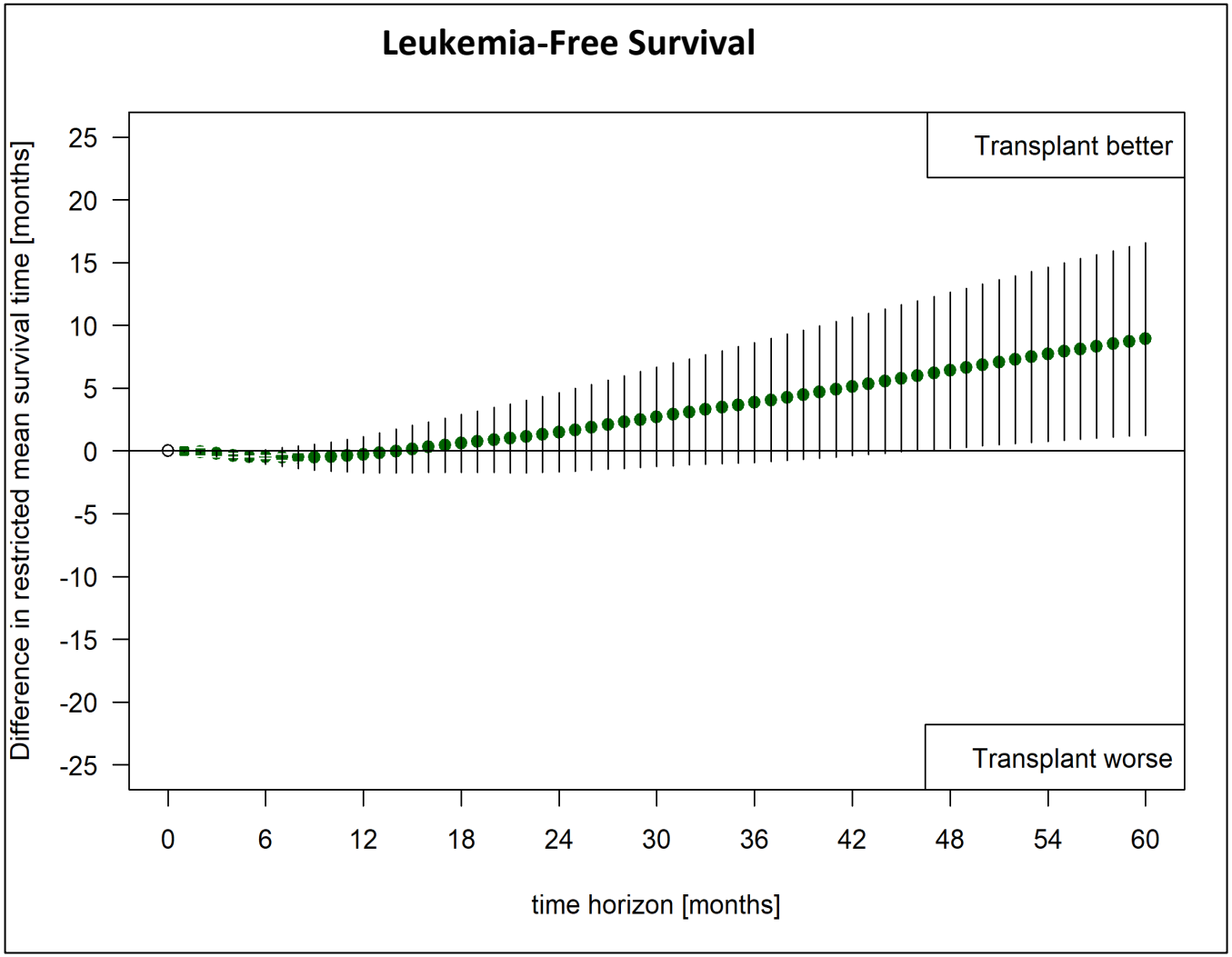

Leukemia-Free Survival
Transplant better
Transplant worse
Difference in restricted mean survival time [months]
25
20
15
10
5
0
-5
-10
-15
-20
-25
0
6
12
18
24
30
36
42
48
54
60
time horizon [months]

Figure S8 B

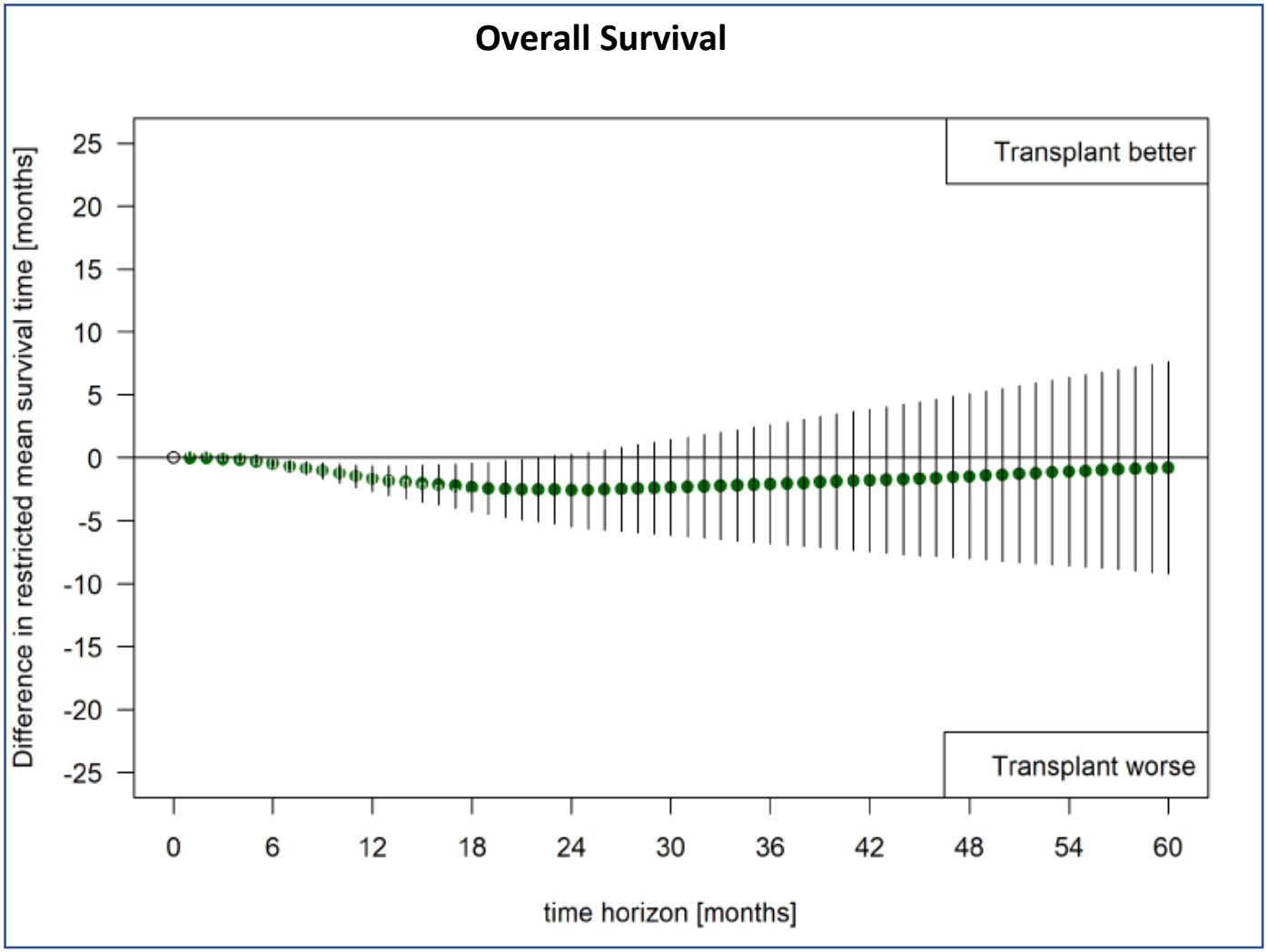

Overall Survival
Transplant better
Transplant worse
Difference in restricted mean survival time [months]
25
20
15
10
5
0
-5
-10
-15
-20
-25
0
6
12
18
24
30
36
42
48
54
60
time horizon [months]

Figure S9

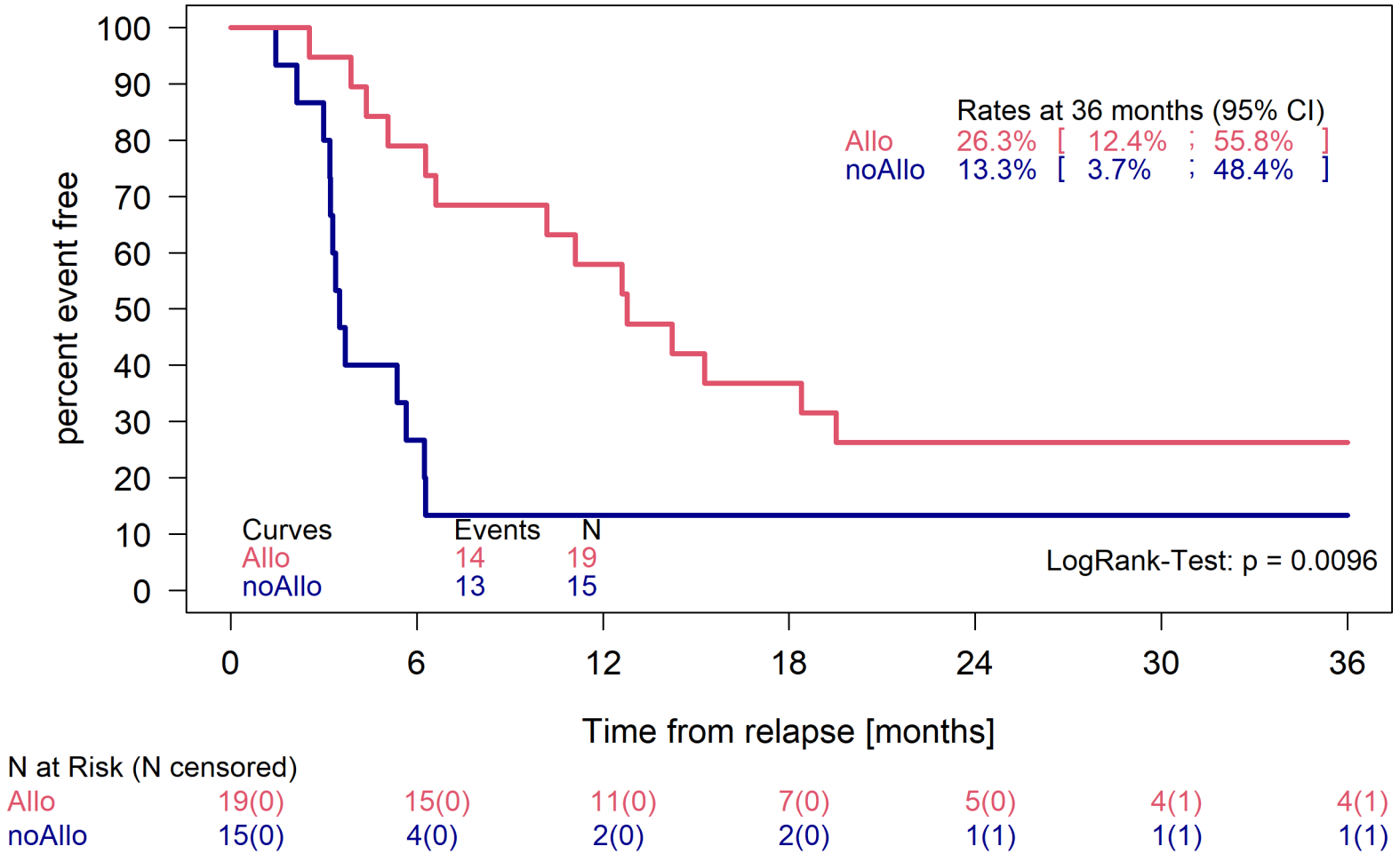

100
90
80
70
60
50
40
30
20
10
0
percent event free
Rates at 36 months (95% CI)
Allo 26.3% [12.4% ; 55.8%]
noAllo 13.3% [3.7% ; 48.4%]
Curves Events N
Allo 14 19
noAllo 13 15
LogRank-Test: p = 0.0096
0
6
12
18
24
30
36
Time from relapse [months]
N at Risk (N censored)
Allo 19(0) 15(0) 11(0) 7(0) 5(0) 4(1) 4(1)
noAllo 15(0) 4(0) 2(0) 2(0) 1(1) 1(1) 1(1)

Figure S10

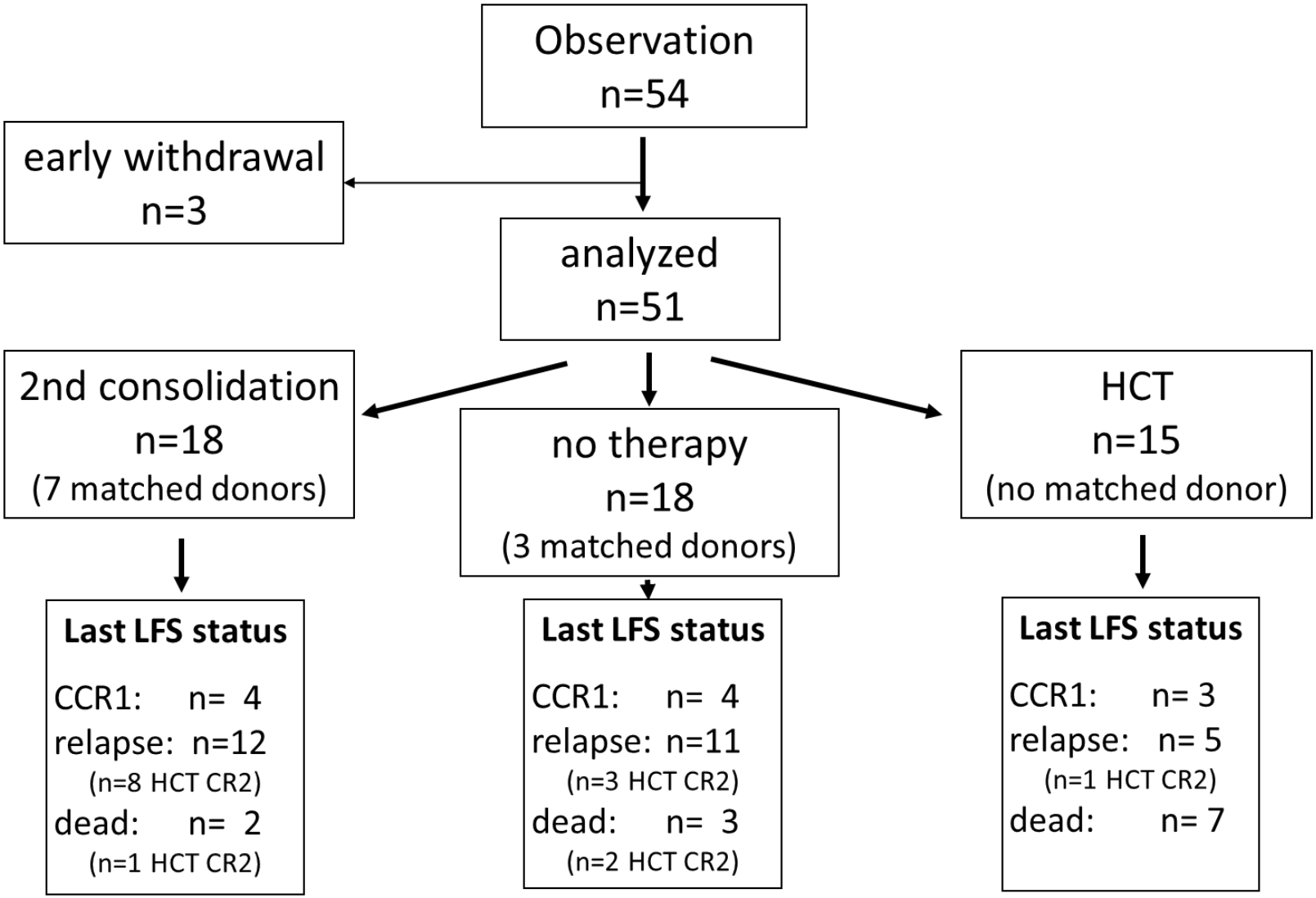
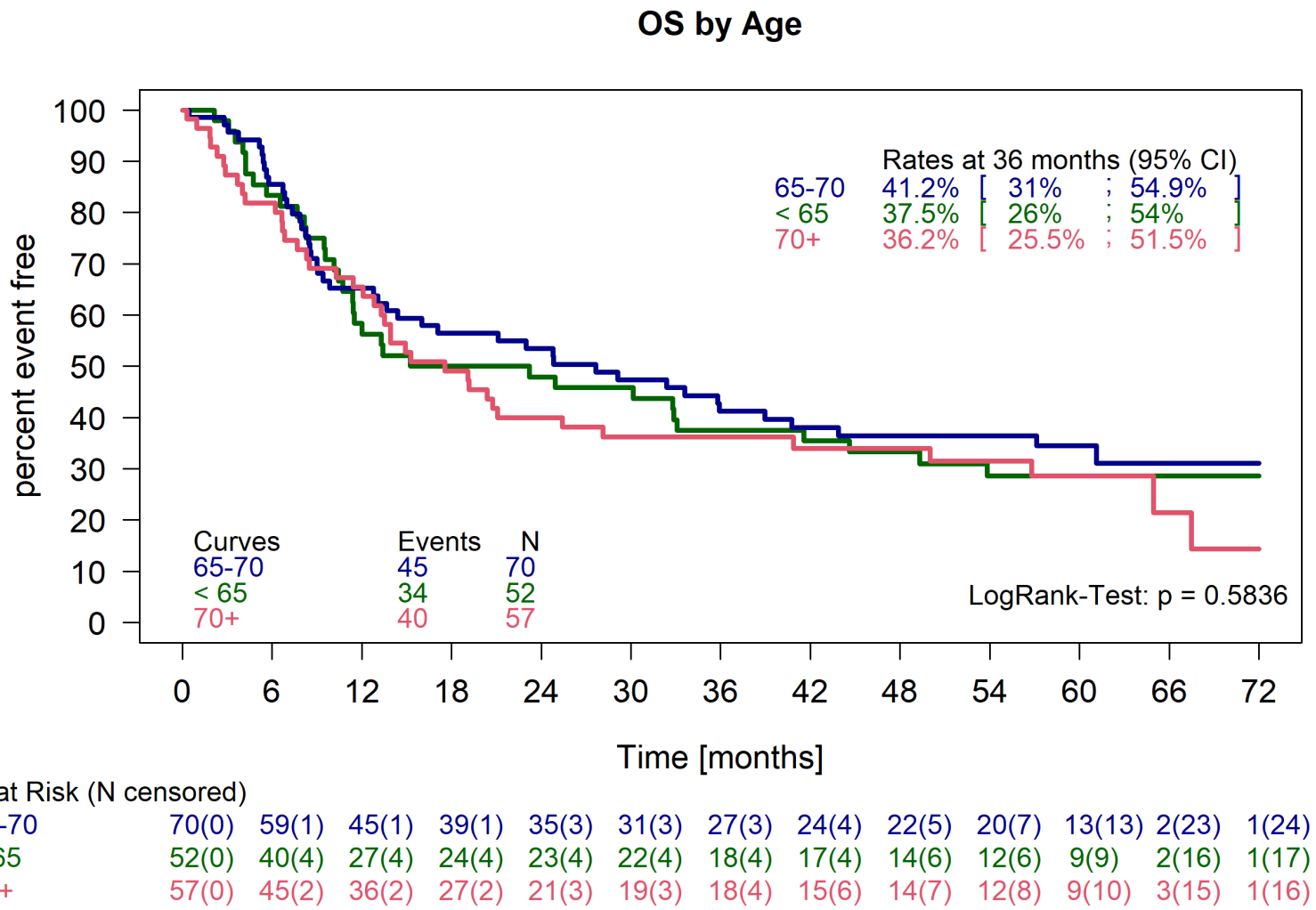

Observation
n=54
early withdrawal
n=3
analyzed
n=51
2nd consolidation
n=18
(7 matched donors)
no therapy
n=18
(3 matched donors)
HCT
n=15
(no matched donor)
Last LFS status
CCR1: n= 4
relapse: n=12
(n=8 HCT CR2)
dead: n= 2
(n=1 HCT CR2)
Last LFS status
CCR1: n= 4
relapse: n=11
(n=3 HCT CR2)
dead: n= 3
(n=2 HCT CR2)
Last LFS status
CCR1: n= 3
relapse: n= 5
(n=1 HCT CR2)
dead: n= 7

Figure S11



N at Risk (N censored)

65-70	70(0)	59(1)	45(1)	39(1)	35(3)	31(3)	27(3)	24(4)	22(5)	20(7)	13(13)	2(23)	1(24)
< 65	52(0)	40(4)	27(4)	24(4)	23(4)	22(4)	18(4)	17(4)	14(6)	12(6)	9(9)	2(16)	1(17)
70+	57(0)	45(2)	36(2)	27(2)	21(3)	19(3)	18(4)	15(6)	14(7)	12(8)	9(10)	3(15)	1(16)