ARTICLE - Bone Marrow Transplant

Allogeneic transplantation in acute myelogenous leukemia: a comprehensive single institution's experience

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Allogeneic transplantation in acute myelogenous leukemia.

A single institution's comprehensive experience

Supplementary material

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Abbreviations in Table and figures are those described in the main manuscript

Supplementary Methods.

The Saint Louis Hospital hosts one of largest facility in hematology in Europe with 4 units dedicated to daily care of AML: adolescent, adult, elderly and the allogeneic HSCT unit, each of these with around dedicated 20 beds. Per French law (Haute Autorité de Santé and the French National Cancer Institute), each newly diagnosed AML must be discussed in a multidisciplinary candidate patient review (PtRv). In addition to this AML-PtRv, all HSCT candidates have a 2nd HSCT-specific PtRv. All patients discussed at the HSCT PtRv are HLA-typed. Only patients deemed suitable by the referring physician are considered, if analyses only begin with HSCT-specific PtRv these would select and not represent the denominator of all patients diagnosed with AML during the study period.

Patients with acute promyelocytic leukemia (M3) were excluded. Primary induction therapy varied according to age with older patients receiving hypomethylating agents (HMA) alone or with other drugs, and younger patients most often received anthracycline plus cytarabine, usually a classical 3+7 schema. Some patients were enrolled in protocols of the ALFA group (ALFA-0702 trial; clinicaltrials.gov, #NCT00932412). Patients were classified as good, intermediate, or high risk according to the ELN 2017 classification. Patients younger than 60 years of age with high or intermediate risk were generally considered eligible for HSCT in CR1, while good risk patients were mostly considered for transplantation in CR2. Only patients diagnosed and treated at Saint Louis Hospital were included. Patients who were referred for transplantation from other centers were excluded since they represented a selected population.

Statistical Analysis

Quantitative variables were described as median, inter-quartile range, minimum and maximum. Differences between groups were tested using Wilcoxon and Kruskal-Wallis tests according to the

number of groups. Differences between groups were tested using chi-square or Fisher exact test (f) for small groups. OS and LFS were estimated using the Kaplan-Meier estimator. The cumulative incidence of RI, NRM, time to HSCT, CR1, CR2, and PtRv were calculated using the cumulative incidence estimator to accommodate competing risks. Competing risk was death for RI, HSCT, CR1, CR2 and PtRv, and relapse for NRM. HSCT was a competing event for the time to CR1 and CR2. Univariate impact on outcomes were done using the log-rank test for OS and LFS, and Gray's test for cumulative incidences.

Supplementary Table 1. Clinical demographics of the entire study population.

Variables	Modalities	N=491	de novo (N=318)	Secondary (N=173)	Test p-value
Patient sex	Male	260 (53)	166 (52.2)	94 (54.3)	0.65
	Female	231 (47)	152 (47.8)	79 (45.7)	
Year of AML diagnosis	median [IQR]	2017 [2016-2018]	2017 [2016-2018]	2018 [2017-2018]	0.009
Age at AML diagnosis	median [IQR]	68.9 [56.9-76.6]	67.3 [52.6-74.5]	72.6 [64.4-79.3]	< 0.001
	(range)	(16.3-95)	(16.3-95)	(25.8-91.9)	
Age at AML diagnosis	(16,57)	124 (25.3)	99 (31.1)	25 (14.5)	< 0.001
	(57,69)	124 (25.3)	82 (25.8)	42 (24.3)	
	(69,77)	127 (25.9)	74 (23.3)	53 (30.6)	
	(77,96)	116 (23.6)	63 (19.8)	53 (30.6)	
Type of secondary / transformed AML	MDS			104 (60.1)	Not done
	MPN			28 (16.2)	
	MDS/MPN			28 (16.2)	
	Other			13 (7.5)	
WBC (G/L)	median [IQR]	6.7 [2.3-38]	11.9 [2.7-48.8]	4.2 [1.9-21.8]	< 0.001
	(range)	(0.3-368)	(0.4-368)	(0.3-308.4)	
	missing	7	0	7	
BM blast (%)	median [IQR]	47 [25.5-78]	60 [34-82]	26 [17.5-45.5]	< 0.001
	(range)	(0-99)	(0-99)	(0-97)	
	missing	28	6	22	
Multi-lineage dysplasia	No	269 (61.7)	198 (69)	71 (47.7)	< 0.001
	Yes	167 (38.3)	89 (31)	78 (52.3)	
	missing	55	31	24	
	M1	26 (5.3)	26 (8.2)		Not done
	M2	43 (8.8)	43 (13.6)		
	M4	33 (6.7)	33 (10.4)		
	M5	16 (3.3)	16 (5)		
	M6	3 (0.6)	3 (0.9)		
	M7	1 (0.2)	1 (0.3)		
	t(9;22)	2 (0.4)	2 (0.6)		
	CEBPA	1 (0.2)	1 (0.3)		
	DML	49 (10)	49 (15.5)		
	NPM1	109 (22.2)	109 (34.4)		
	Sarcoma	2 (0.4)	2 (0.6)		
	t(9;11)	6 (1.2)	6 (1.9)		
	Not otherwise specified	19 (3.9)	19 (6)		
	Secondary AML	173 (35.3)	0 (0)	173 (100)	
	missing	1	1	0	

Supplementary Table 2. Initial Treatment for AML

First line	Good (N=145) N (%)	Intermediate (N=117) N (%)	Poor (N=226) N (%)
Supportive Care	6 (4.1)	7 (6)	22 (9.7)
Azacytidine alone	8 (5.5)	20 (17.1)	74 (32.7)
Azacytidine + another drug	5 (3.4)	6 (5.1)	40 (17.7)
IC 3+7*	91 (62.8)	52 (44.4)	42 (18.6)
IC 3+7 GO**	13 (9)	4 (3.4)	3 (1.3)
IC + another drugs	10 (6.9)	15 (12.8)	14 (6.2)
Vyxeos +/- another drug	10 (6.9)	11 (9.4)	22 (9.7)
Other	2 (1.4)	2 (1.7)	9 (4)

* anthracycline/cytarabine as 7/3, GO; gemtuzumab ozogamycin

Supplementary Table 3 Demographics of all patients who underwent HSCT recipients, by ELN 2017 subgroups

Variables	Modalities	HSCT (N=105)	Good (N=27)	Intermediate (N=39)	Poor (N=39)	Test p-value
Patient sex	Male	56 (53.3)	14 (51.9)	20 (51.3)	22 (56.4)	0.89
	Female	49 (46.7)	13 (48.1)	19 (48.7)	17 (43.6)	
Year of AML diagnosis	median [IQR]	2017 [2016-2018]	2017 [2016-2018]	2017 [2016-2018]	2018 [2017-2019]	0.04
	(range)	(2015-2020)	(2015-2019)	(2015-2020)	(2016-2020)	
Age at AML diagnosis	median	54.2	52.6	57.3	54.3	0.75
	[IQR]	[39.2-63.5]	[43.8-58.4]	[35.9-64.5]	[37.2-64.1]	
	(range)	(16.3-71.7)	(25.8-71.1)	(16.8-71.7)	(16.3-71.4)	
Time diagnosis / HSCT (months)	median	6.8	17.6	6.5	6.6	<0.001
	[IQR]	[5.5-16.5]	[7.4-24.4]	[5.4-15.4]	[5.5-7.4]	
	(range)	(3.3-57.3)	(4.4-57.3)	(3.9-37.9)	(3.3-20)	
Age at HSCT	median	54.8	54	58.3	54.8	0.8
	[IQR]	[39.7-64.6]	[44.8-60.9]	[37-65.2]	[37.6-64.5]	
	(range)	(16.7-73.3)	(26.2-72.4)	(17.2-73.3)	(16.7-71.9)	
Age at HSCT	(16.6,45]	33 (31.4)	8 (29.6)	13 (33.3)	12 (30.8)	0.24
	(45,61]	35 (33.3)	12 (44.4)	8 (20.5)	15 (38.5)	
	(61,73.4]	37 (35.2)	7 (25.9)	18 (46.2)	12 (30.8)	
Disease status at HSCT	CR1 (incl. PR1)	61 (58.1)	8 (29.6)	24 (61.5)	29 (74.4)	<0.001
	CR2+ (incl. PR2;CR3)	25 (23.8)	16 (59.3)	8 (20.5)	1 (2.6)	
	Active disease	19 (18.1)	3 (11.1)	7 (17.9)	9 (23.1)	
Disease status at HSCT	CR1	60 (57.1)	8 (29.6)	24 (61.5)	28 (71.8)	ND
	PR1	1 (1)	0 (0)	0 (0)	1 (2.6)	
	CR2	23 (21.9)	15 (55.6)	7 (17.9)	1 (2.6)	
	PR2	1 (1)	0 (0)	1 (2.6)	0 (0)	
	CR3	1 (1)	1 (3.7)	0 (0)	0 (0)	
	PIF	12 (11.4)	0 (0)	5 (12.8)	7 (17.9)	
	Rel 1	4 (3.8)	1 (3.7)	1 (2.6)	2 (5.1)	
	Rel 2	3 (2.9)	2 (7.4)	1 (2.6)	0 (0)	
Donor type	Identical sibling	26 (24.8)	7 (25.9)	10 (25.6)	9 (23.1)	0.62 f
	Haploidentical	22 (21)	4 (14.8)	8 (20.5)	10 (25.6)	
	Matched unrelated	50 (47.6)	16 (59.3)	17 (43.6)	17 (43.6)	
	Mismatched unrelated	7 (6.7)	0 (0)	4 (10.3)	3 (7.7)	
Conditioning regimen	Bu-Flu	65 (61.9)	17 (63)	23 (59)	25 (64.1)	ND
	Bu-Flu + Thiotepa	23 (21.9)	4 (14.8)	8 (20.5)	11 (28.2)	
	Bu + Flamsa	1 (1)	0 (0)	0 (0)	1 (2.6)	
	Bu-Cy + Flamsa	5 (4.8)	3 (11.1)	1 (2.6)	1 (2.6)	

	Bu-Cy + Arac + Clofa	1 (1)	1 (3.7)	0 (0)	0 (0)	
	Bu-Cy	9 (8.6)	2 (7.4)	6 (15.4)	1 (2.6)	
	Treosulfan + Flu	1 (1)	0 (0)	1 (2.6)	0 (0)	
Myeloablative regimen	No	73 (69.5)	20 (74.1)	25 (64.1)	28 (71.8)	0.64
	Yes	32 (30.5)	7 (25.9)	14 (35.9)	11 (28.2)	
Type of AML	de novo	75 (71.4)	22 (81.5)	29 (74.4)	24 (61.5)	0.19
	Secondary AML	30 (28.6)	5 (18.5)	10 (25.6)	15 (38.5)	
Type of secondary AML	MDS	14 (46.7)	2 (40)	5 (50)	7 (46.7)	ND
	MPN	4 (13.3)	1 (20)	1 (10)	2 (13.3)	
	MDS/MPN	4 (13.3)	0 (0)	1 (10)	3 (20)	
	Therapy related	8 (26.7)	2 (40)	3 (30)	3 (20)	
Extra medullary involvement at diagnosis	No	75 (73.5)	22 (81.5)	27 (73)	26 (68.4)	0.5
	Yes	27 (26.5)	5 (18.5)	10 (27)	12 (31.6)	
	missing	3	0	2	1	
AML WHO2016	M0	3 (2.9)	0 (0)	0 (0)	3 (7.7)	ND
	M1	5 (4.8)	0 (0)	4 (10.3)	1 (2.6)	
	M2	13 (12.4)	3 (11.1)	4 (10.3)	6 (15.4)	
	M4	8 (7.6)	4 (14.8)	3 (7.7)	1 (2.6)	
	M5	4 (3.8)	0 (0)	2 (5.1)	2 (5.1)	
	M6	2 (1.9)	0 (0)	2 (5.1)	0 (0)	
	M7	1 (1)	0 (0)	0 (0)	1 (2.6)	
	t(9;22)	1 (1)	0 (0)	0 (0)	1 (2.6)	
	DML	11 (10.5)	0 (0)	4 (10.3)	7 (17.9)	
	NPM1	21 (20)	14 (51.9)	7 (17.9)	0 (0)	
	Sarcoma	1 (1)	0 (0)	0 (0)	1 (2.6)	
	t(9;11)	3 (2.9)	0 (0)	3 (7.7)	0 (0)	
	NOS	2 (1.9)	1 (3.7)	0 (0)	1 (2.6)	
	Secondary AML	30 (28.6)	5 (18.5)	10 (25.6)	15 (38.5)	
Good risk subgroup	NPM1+/FLT3ITD-		16 (59.3)			ND
	NPM1+/FLT3ITDlow		2 (7.4)			
	Double CEBPA		2 (7.4)			
	inv(16)		4 (14.8)			
	t(8;21)		3 (11.1)			
MRC	Good	7 (6.8)	7 (25.9)	0 (0)	0 (0)	ND
	Intermediate	76 (73.8)	18 (66.7)	38 (97.4)	20 (54.1)	
	Poor	20 (19.4)	2 (7.4)	1 (2.6)	17 (45.9)	
	missing	2	0	0	2	

Supplementary Table 4 Clinical Outcomes of the Entire Study Population

Outcomes	1 year	2 years	4 years
CR1	54.8 (51.7-60.5)		
OS	58.7 (54.2-63)	40.7 (36.3-45.0)	30.2 (26-34.5)
LFS	41.6 (37.2-45.9)	27.8 (23.9-31.9)	21.7 (18.1-25.5)
RI*	45.8 (41.3-50.1)	58.3 (53.8-62.5)	63.3 (58.8-67.5)
NRM	12.7 (9.9-15.8)	13.9 (11-17.1)	15 (12-18.4)
NRM no HSCT**	11.6 (9-14.6)	12.4 (9.7-15.5)	13.6 (10.7-16.8)
HSCT	15.6 (12.6-19)	20.6 (17.1-24.3)	21.9 (18.3-25.7)

Median FU (95%CI): 4.3 (4.0-4.5)

*Persisting leukemia after initial treatment or relapse ; **HSCT as competing event

Supplementary Table 5 Univariate outcomes for the HSCT population

Variables	Modalities	2y OS (post TX)	2y PFS (post TX)	2y RI (post TX)	2y TRM (post TX)
Donor type	MSD	76.1 [54.4-88.5]	76.3 [54.6-88.6]	11.9 [2.9-27.8]	11.9 [2.9-27.8]
	Haploidentical	68.2 [44.6-83.4]	62.9 [39.2-79.5]	23.4 [8.1-43.2]	13.6 [3.3-31.4]
	MUD	68.7 [53.5-79.8]	64.8 [49.5-76.5]	24.8 [13.6-37.7]	10.5 [3.8-21.1]
	MMUD	38.1 [6.1-71.6]	42.9 [9.8-73.4]	28.6 [2.8-64.6]	28.6 [3-63.9]
	P value	0.21	0.21	0.49	0.62
ELN2017	Good	67.9 [45.7-82.5]	68.5 [46.6-82.9]	15.2 [4.6-31.5]	16.3 [4.9-33.7]
	Intermediate	75.9 [58.7-86.7]	76.4 [59.4-86.9]	13.2 [4.7-26.2]	10.4 [3.2-22.5]
	Poor	61.4 [44.4-74.7]	53.8 [37.2-67.9]	33.3 [19.1-48.3]	12.8 [4.6-25.4]
	P value	0.32	0.22	0.12	0.96
Secondary AML	No	69.6 [57.5-78.8]	68.5 [56.5-77.9]	16.4 [9-25.8]	15.1 [8-24.3]
	Yes	65.6 [45.4-79.9]	59 [39.1-74.3]	34.4 [17.7-51.8]	6.7 [1.1-19.5]
	P value	0.23	0.28	0.07	0.53
Disease status	CR1	70.2 [56.9-80]	65.2 [51.8-75.8]	24.9 [14.8-36.5]	9.8 [4-18.9]
	CR2+	63.3 [39.3-79.9]	64.8 [41.4-80.8]	21.2 [7.4-39.7]	14 [3.3-32.3]
	Active disease	68.4 [42.8-84.4]	68.4 [42.8-84.4]	10.5 [1.7-29.1]	21.1 [6.2-41.7]
	P value	0.828	0.927	0.653	0.48
Age at transplant	(16.6,45)	87.8 [70.6-95.2]	87.9 [70.9-95.3]	6.1 [1-17.9]	6.1 [1-17.9]
	(45,61)	59.3 [41.1-73.5]	56.5 [38.5-71.1]	23.1 [10.7-38.3]	20.4 [8.8-35.3]
	(61,73.4)	58.4 [39.8-73.1]	53.3 [35.1-68.5]	35.2 [19.4-51.5]	11.4 [3.5-24.6]
	P value	**0.005**	**0.004**	**0.02**	0.25
Myeloablative regimen	No	62.5 [49.9-72.8]	58.6 [46.1-69.2]	28.5 [18.4-39.4]	12.9 [6.3-22]
	Yes	81.1 [62.7-91.1]	81.2 [62.9-91.1]	6.2 [1.1-18.4]	12.5 [3.9-26.5]
	P value	**0.03**	**0.02**	**0.009**	0.88

Supplementary Table 6. Candidate Patient Review: Donor and AML phenotype for those without HSCT.

Variable	Modalities	Good (N=24)	Intermediate (N=6)	Poor (N=7)
PTRV Yes, reason for non HSCT indication	Good risk	20 (83.3)	2 (33.3)**	0 (0)
	Comorbidities	3 (12.5)	4 (66.7)	6 (85.7)
	Age	1 (4.2)*	0 (0)	0 (0)
	No HLA typing	0 (0)	0 (0)	1 (14.3)§
Donor available	Identical sibling	3 (13.6)	1 (16.7)**	0 (0)
	Haplo	6 (27.3)	2 (33.3)	2 (33.3)
	Matched unrelated	1 (4.5)	0 (0)	3 (50)
	Mismatched unrelated	5 (22.7)	1 (16.7)***	0 (0)
	Unknown donor type	1 (4.5)	0 (0)	0 (0)
	No donor available	6 (27.3)	2 (33.3)	1 (16.7)
	missing	2	0	1§
AML type	de novo	23 (95.8)	6 (100)	2 (28.6)
	secondary AML	1 (4.2)	0 (0)	5 (71.4)
Time between diagnosis and PTRV	Around AML diagnosis (+/- 120d)	24 (100)	5 (83.3)	6 (85.7)
	After CR1 post 2nd line treatment	0 (0)	1 (16.7)	0 (0)
	During the previous diagnosis	0 (0)	0 (0)	1 (14.3)
Remission	No CR	0 (0)	0 (0)	2 (28.6)
	CR1	24 (100)	4 (66.7)	4 (57.1)
	NRM	0 (0)	2 (33.3)	1 (14.3)

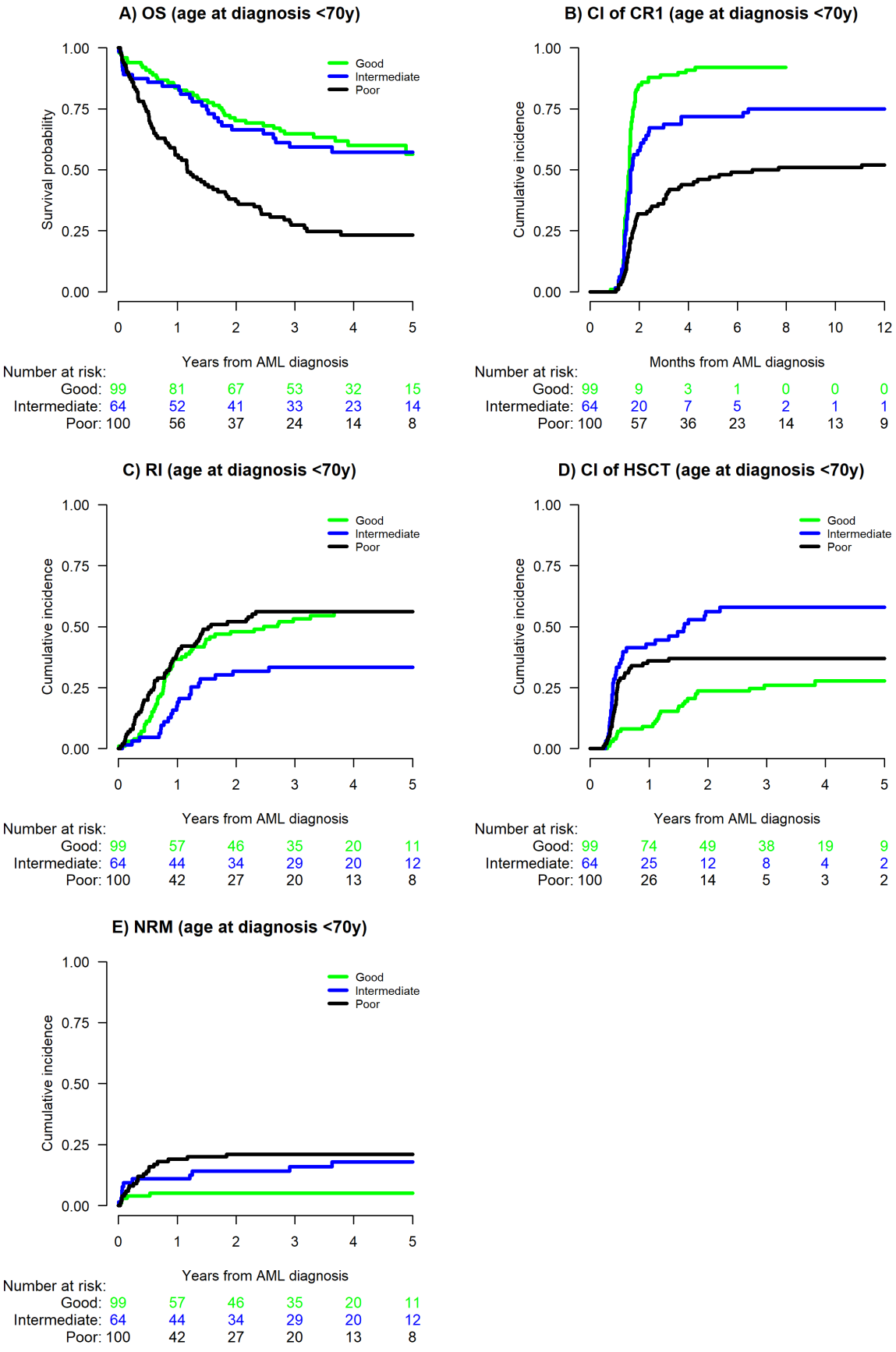
*: 66y at diagnosis, no donor available

**Normal K, NPM1-, FLT3ITD-, CEBPA bi allelic -,

***Normal K, pas de NGS, NPM1+ (PCR), FLT3ITD ratio 0.55

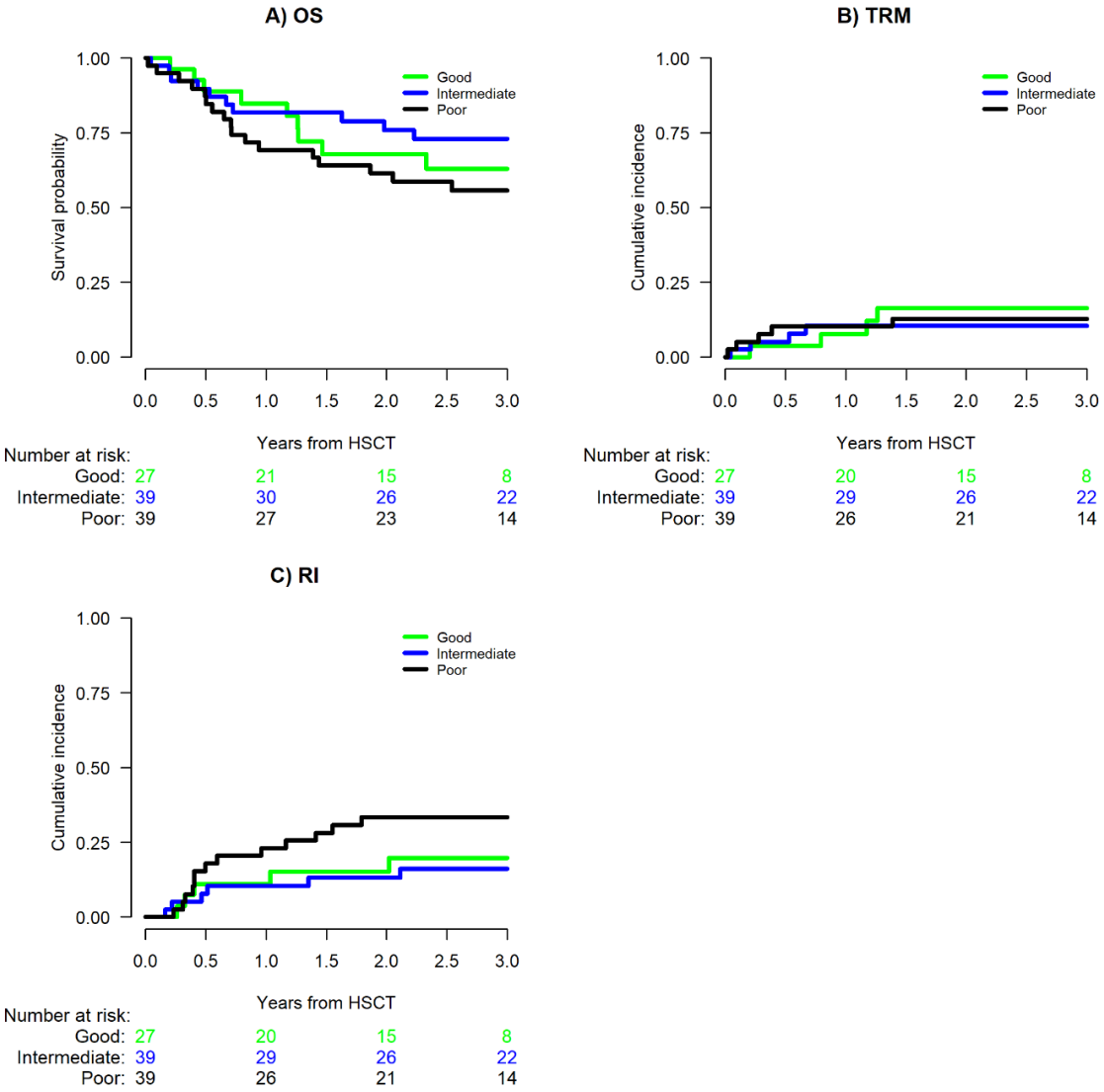
§ No HLA typing

Supplementary figure 1; Patients younger than 70: Outcomes by ELN classification from diagnosis. A: Overall survival (OS), B: Cumulative incidence (CI) of first complete remission (CR1). C: CI of relapse (RI). D: CI of transplantation (HSCT). E: CI of non-relapse mortality (NRM) according to ELN 2017



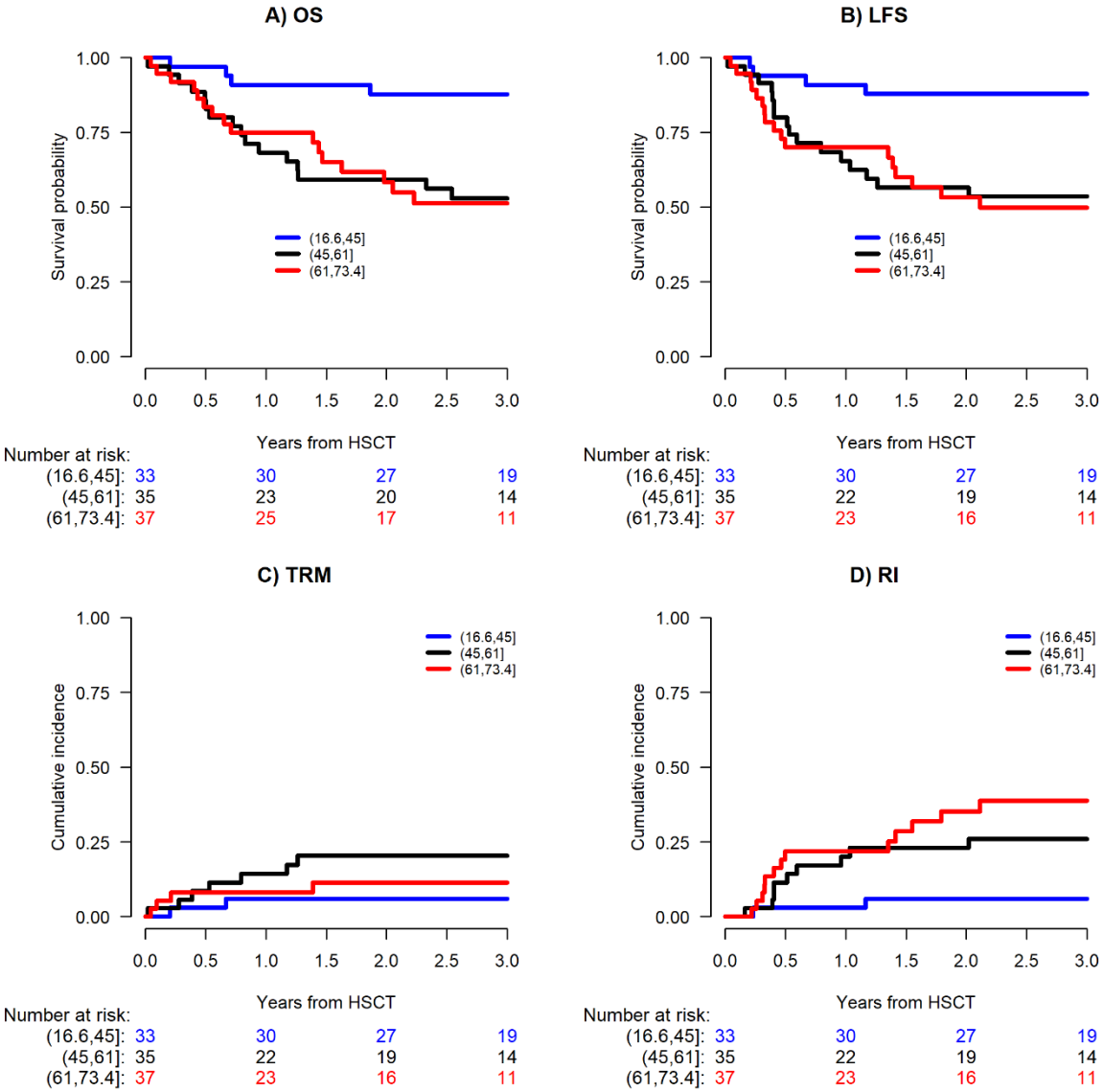
Supplementary Figure 2 Outcomes after transplantation by ELN 2017 classification

A: Overall survival (OS) B: Cumulative incidence (CI) of first transplant related mortality (TRM). C: CI of relapse (RI).

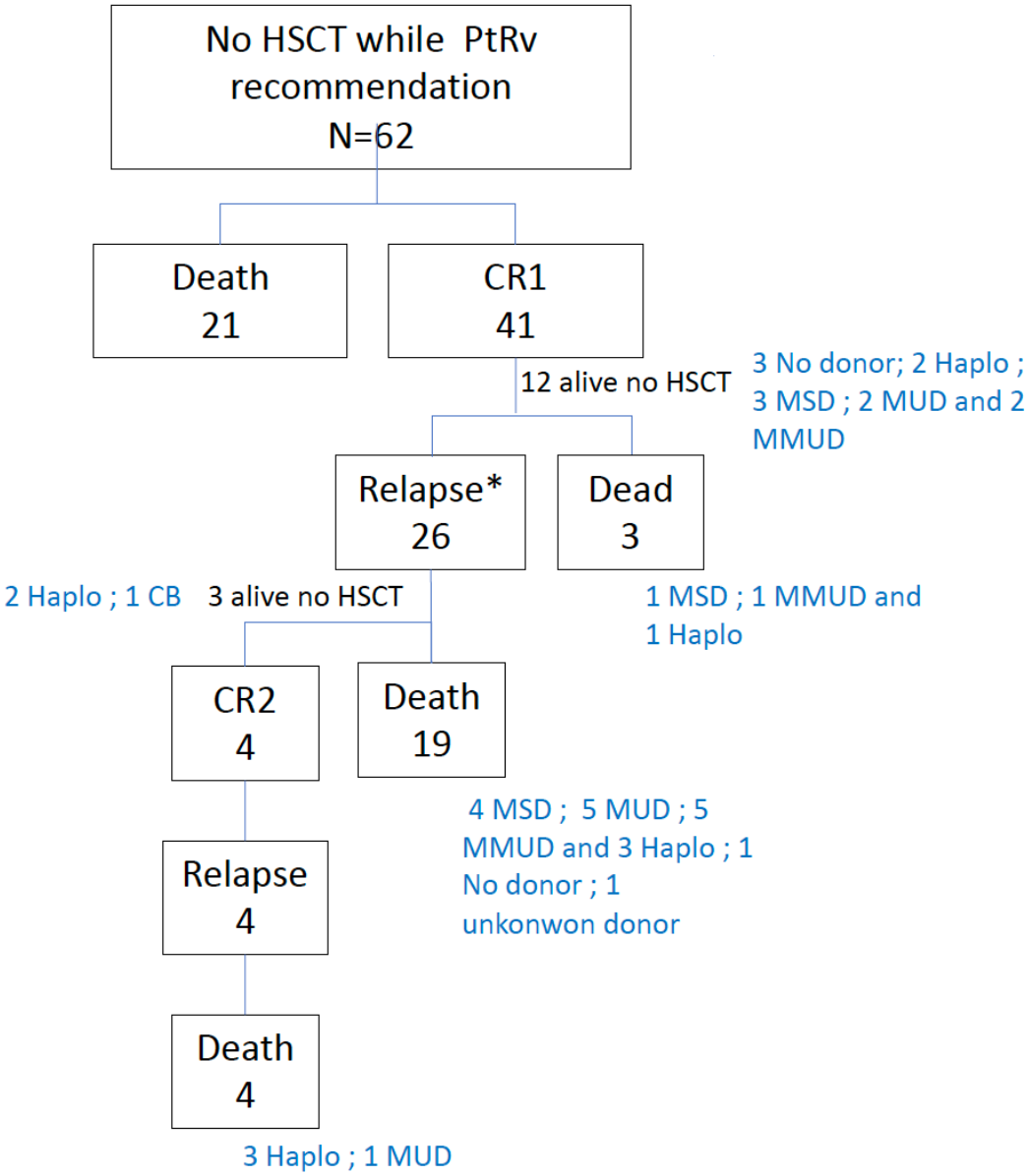


Supplementary Figure 3 Outcomes after transplantation (all transplanted patients)

A: Overall survival (OS) by age tertile: B Progression free survival by age. Cumulative incidence (CI) of first transplant related mortality (TRM) by age. C: CI of relapse (RI) by age.

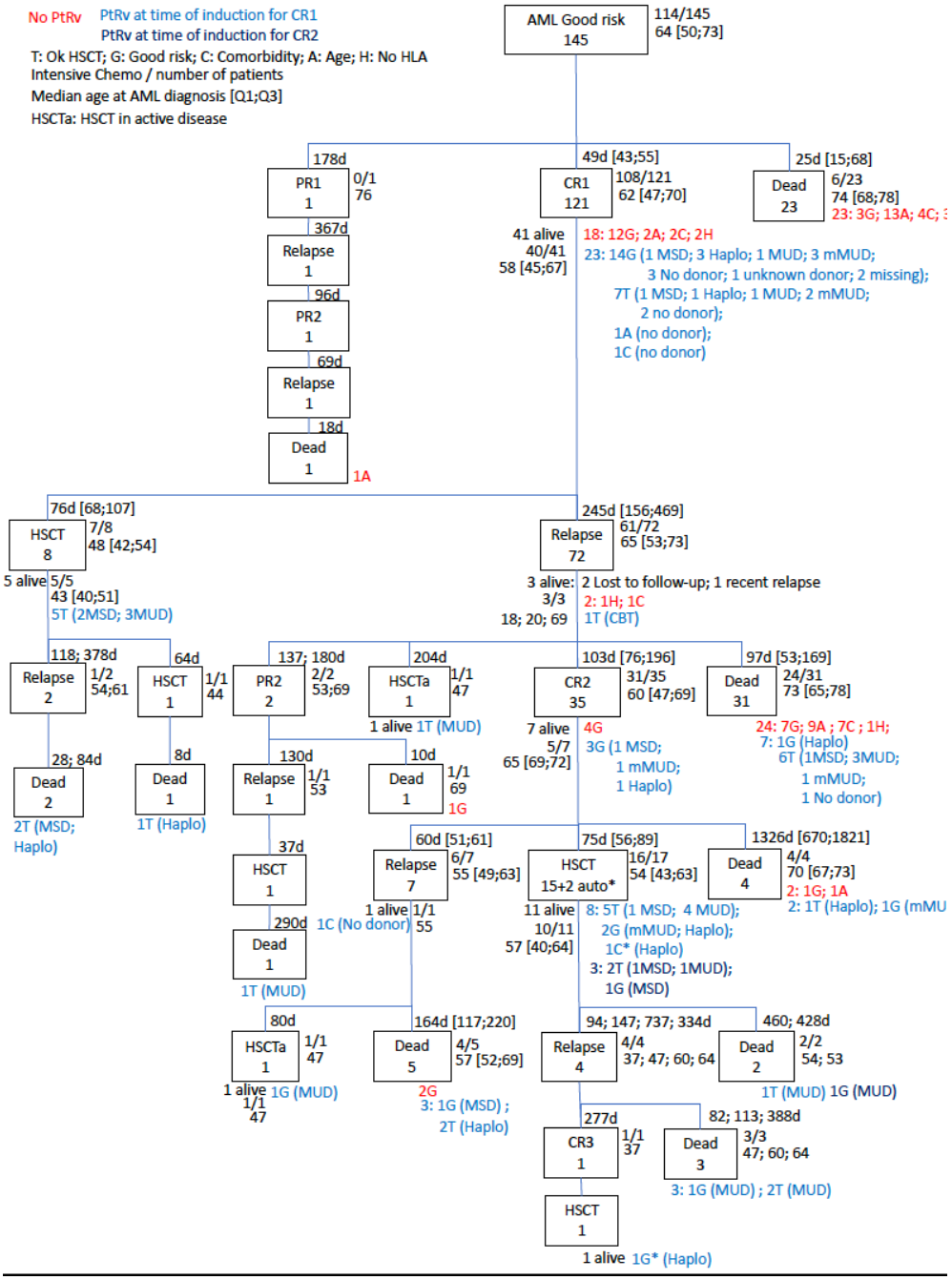


Supplementary Figure 4. 62 patients with HSCT recommendation in PtRv but did not underwent HSCT.

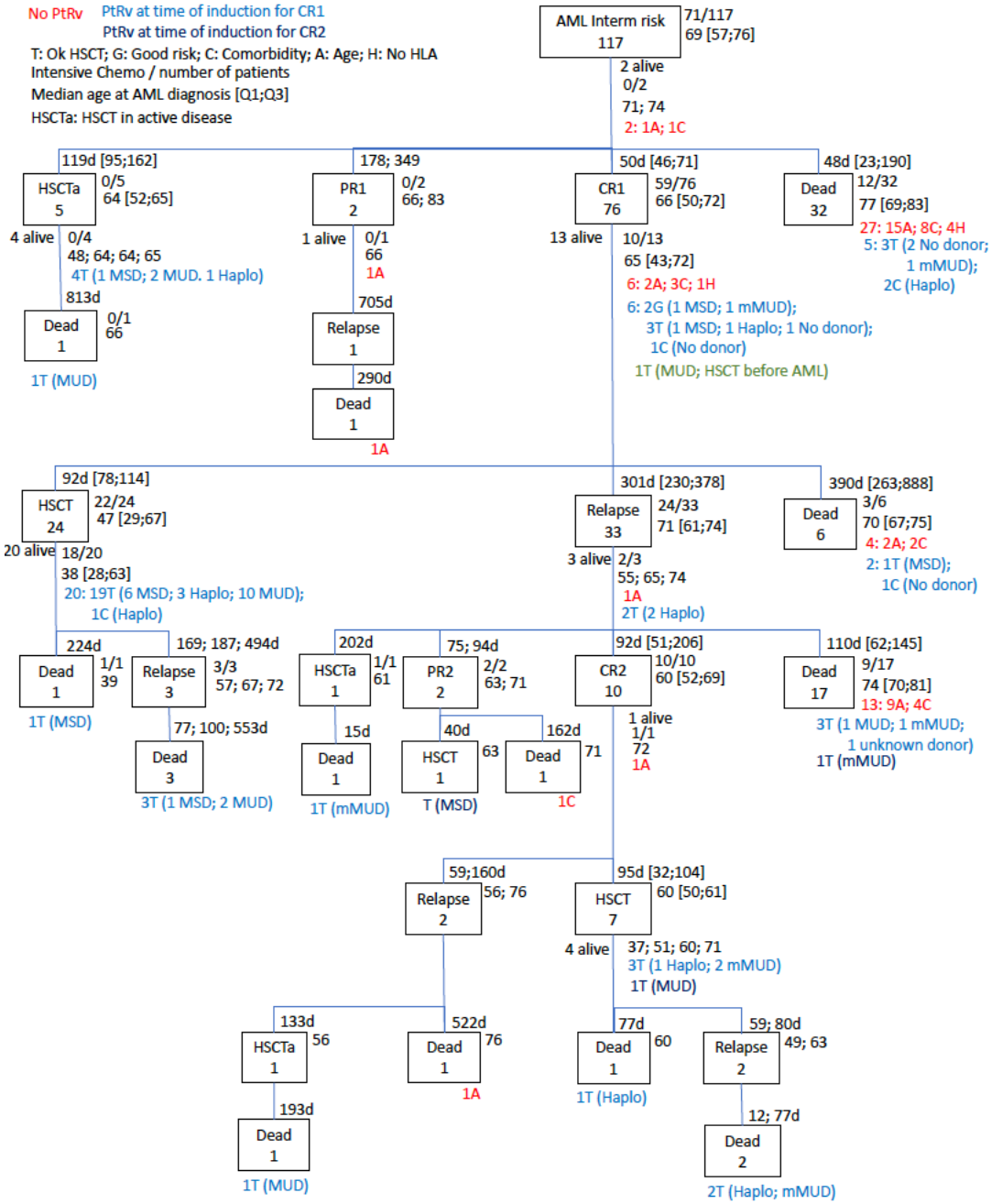


*2 PtRv post relapse 1

Supplementary Figure 5. Consort Diagram of Outcomes and Therapy by ELN Good Risk group



Supplementary Figure 6. Consort Diagram of Outcomes and Therapy by ELN Intermediate Risk group



Supplementary Figure 7. Consort Diagram of Outcomes and Therapy by ELN Poor Risk group