

## Supplementary Online Content

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

**eTable 1.** Patient, Disease and Treatment Related Characteristics at Time of Allo-HCT1 (All Population on Intent-to Receive First Intervention)

<b>Variables</b>	<b>DLI (n=281) DLI only=230 DLI+allo-HCT2=51</b>	<b>Allo-HCT2 (n=137) Allo-HCT2 only=135 Allo-HCT2+DLI=2</b>	<b>p-value</b>
<b>Median age (range), years, at intervention</b>	48 (18-73) IQR=37-57	43 (18-67) IQR=32-52	<b>0.001</b>
Recipient gender Female Male	128 (46%) 153 (54%)	62 (45%) 75 (55%)	0.95
Donor gender Female Male Missing/unknown	88 (31%) 192 (69%) 1	42 (31%) 95 (69%) 0	0.87
Donor→recipient gender matching F→M Others Missing/unknown	44 (16%) 236 (84%) 1	26 (19%) 111 (81%)	0.40
AML <i>de novo</i> Secondary	245 (87%) 36 (13%)	114 (83%) 23 (17%)	0.27
Cytogenetic risk Good Intermediate Poor Unknown/failed	25 (9%) 153 (54%) 77 (27%) 26 (9%)	8 (6%) 88 (64%) 32 (23%) 9 (7%)	0.26

<b>Remission status at time of allo-HCT1</b> CR1 CR2 CR3	218 (78%) 56 (20%) 7 (2%)	119 (87%) 18 (13%) 0	<b>0.03</b>
<b>Median (range), year of allo-HCT1</b>	2007 (1992-2014)	2006 (1996-2014)	<b>0.03</b>
<b>Regimen used for allo-HCT1</b> MAC RIC Missing/unknown	154 (55%) 126 (45%) 1	92 (67%) 45 (33%) 0	<b>0.02</b>
Donor source MRD URD	149 (53%) 132 (47%)*	85 (62%) 52 (38%)**	0.08
Cell source BM PBSC	51 (18%) 230 (82%)	31 (23%) 106 (77%)	0.28
<b><i>In vivo</i> T-cell depletion</b> Yes No Missing/unknown	158 (57%)^ 120 (43%) 3	57 (43%)^^ 77 (57%) 3	<b>0.006</b>

Patient CMV serology			0.053
Positive	181 (65%)	74 (55%)	
Negative	97 (35%)	60 (45%)	
Missing/unknown	3	3	
Donor CMV serology			0.26
Positive	131 (48%)	72 (54%)	
Negative	143 (52%)	62 (46%)	
Missing/unknown	7	3	

***Bold denotes significant difference***

**Abbreviations:** DLI, donor lymphocyte infusion; allo-HCT2, second allogeneic hematopoietic cell transplant; IQR, interquartile range; F, female; M, male; CR1, first complete remission; CR2, second complete remission; CR3, third complete remission; allo-HCT1, first allogeneic hematopoietic cell transplant; MAC, myeloablative conditioning regimen; RIC, reduced intensity conditioning regimen; MRD, HLA-matched related donor; URD, unrelated donor; BM, bone marrow cells; PBSC, peripheral blood stem cells; CMV, cytomegalovirus

\*HLA-matched unrelated: 8/8 (n=4), 10/10 (n=65); HLA-mismatched unrelated: 7/8 (n=3), 9/10 (n=30), 8/10 (n=3), <7/82 (n=2), ≤ 5/6 (n=12), unknown/missing (n=13)

\*\* HLA-matched unrelated: 8/8 (n=2), 10/10 (n=29); HLA-mismatched unrelated: 9/10 (n=6), 8/10 (n=3), ≤ 5/6 (n=3), unknown/missing (n=9)

^antithymocyte globulin (n=132), alemtuzumab (n=26)

^^ antithymocyte globulin (n=50), alemtuzumab (n=7)

**eTable 2.** Causes Of Non-Relapse Deaths (DLI vs. Allo-HCT2)

<b>Causes of non-relapse deaths</b>	<b>DLI (n=52)</b>	<b>Allo-HCT2 (n=50)</b>
Infection	21	22
GVHD	17	18
Hepatic SOS/VOD	0	4
Hemorrhage	4	1
Cardiac	0	1
Idiopathic pulmonary syndrome	2	0
Secondary malignancies	3	1
Other transplant related	10*	4**

**Abbreviations:** GVHD, graft-versus-host disease; SOS/VOD, sinusoidal obstructive syndrome/veno-occlusive disease

\*Euthanasia (n=1), terminal cachexia with secondary multiorgan failure (n=1), transplant-related but exact cause unknown (n=8)

\*\* Transplant-related but exact cause unknown (n=4)

**eTable 3.** Multivariate Analysis for NRM and OS (All Patients)

Variables	NRM (all patients)		OS (all patients)	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Allo-HCT2 vs. DLI	<b>4.06</b> <b>(2.32-7.08)</b>	<b>&lt;0.0001</b>	1.23 (0.95-1.60)	0.12
Age at intervention (per 10 years)	1.20 (0.96-1.51)	0.11	1.05 (0.95-1.15)	0.36
Poor risk cytogenetics vs. others	1.33 (0.73-2.42)	0.35	<b>1.42</b> <b>(1.10-1.84)</b>	<b>0.008</b>
Secondary vs. <i>de novo</i> AML	0.75 (0.34-1.63)	0.46	1.17 (0.85-1.61)	0.34
Year of allo-HCT1	1.01 (0.94-1.09)	0.78	0.99 (0.96-1.02)	0.48
CR1 at time of allo-HCT1	0.73 (0.37-1.42)	0.35	0.95 (0.70-1.28)	0.73
URD vs. MRD at allo-HCT1	1.00 (0.28-3.56)	1.0	0.80 (0.44-1.45)	0.46
RIC vs. MAC at allo-HCT1	0.94 (0.52-1.71)	0.84	1.25 (0.96-1.63)	0.09
Grade 2-4 vs. none aGVHD prior to DLI/allo-HCT2	<b>2.18</b> <b>(1.14-4.17)</b>	<b>0.02</b>	<b>1.62</b> <b>(1.15-2.29)</b>	<b>0.006</b>
cGVHD (all grades) vs. none prior to DLI/allo-HCT2	1.04 (0.59-1.83)	0.90	<b>0.71</b> <b>(0.53-0.95)</b>	<b>0.02</b>
Time from allo-HCT1 to relapse (months)	0.99 (0.98-1.00)	0.15	<b>0.99</b> <b>(0.98-0.99)</b>	<b>0.0003</b>
Time from relapse to DLI/allo-HCT2 (months)	0.98 (0.85-1.13)	0.81	0.97 (0.91-1.04)	0.42
Other donor vs. MRD	1.27 (0.37-4.37)	0.71	1.32 (0.74-2.36)	0.34
CR vs. no CR at DLI/allo-HCT2	0.91 (0.50-1.67)	0.76	<b>0.55</b> <b>(0.41-0.74)</b>	<b>&lt;0.0001</b>

**Bold denotes significant difference**

**Abbreviations:** NRM, non-relapse mortality; OS, overall survival; allo-HCT2, second allogeneic hematopoietic cell transplant; DLI, donor lymphocyte infusion; allo-HCT1, first allogeneic hematopoietic cell transplant; CR1, first complete remission; MRD, HLA-matched related donor; URD, unrelated donor; MAC, myeloablative conditioning regimen; RIC, reduced intensity conditioning regimen; aGVHD, acute graft-versus-host disease; cGVHD, chronic GVHD

**eTable 4.** Multivariate Analysis for RI, LFS, NRM and OS (Only Patients in CR)

Variables	RI		LFS		NRM		OS	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Allo-HCT2 vs. DLI	1.21 (0.63-2.31)	0.56	1.52 (0.88-2.63)	0.14	2.93 (0.96-8.88)	0.06	1.55 (0.89-2.71)	0.12
Age at intervention (per 10 years)	0.90 (0.73-1.12)	0.35	0.92 (0.77-1.11)	0.39	0.99 (0.66-1.46)	0.94	0.95 (0.77-1.16)	0.59
Year of allo-HCT1	1.01 (0.93-1.09)	0.80	1.04 (0.97-1.11)	0.25	1.12 (0.97-1.29)	0.12	1.05 (0.98-1.13)	0.18
Grade 2-4 vs. none aGVHD prior to DLI/allo-HCT2	1.36 (0.59-3.14)	0.47	1.82 (0.95-3.48)	0.07	<b>3.75</b> <b>(1.23-11.41)</b>	<b>0.02</b>	<b>2.42</b> <b>(1.22-4.77)</b>	<b>0.01</b>
cGVHD (all grades) vs. none prior to DLI/allo-HCT2	0.91 (0.46-1.80)	0.79	0.97 (0.55-1.70)	0.90	1.18 (0.42-3.36)	0.76	0.97 (0.53-1.77)	0.93
Time from allo-HCT1 to relapse (months)	1.00 (0.98-1.01)	0.56	1.00 (0.99-1.01)	0.85	1.01 (0.98-1.03)	0.71	1.00 (0.99-1.01)	0.98
Time from relapse to DLI/allo-HCT2 (months)	0.99 (0.86-1.13)	0.84	0.95 (0.84-1.07)	0.36	0.88 (0.69-1.11)	0.28	0.91 (0.80-1.03)	0.13
Status at intervention CR3 vs. CR2	1.67 (0.79-3.54)	0.18	1.62 (0.84-3.13)	0.15	1.38 (0.34-5.56)	0.65	1.23 (0.63-2.40)	0.55
Poor risk cytogenetics vs. others	1.10 (0.52-2.32)	0.81	1.42 (0.77-2.60)	0.26	2.40 (0.76-7.54)	0.13	1.64 (0.85-3.18)	0.14
Other donor vs. MRD	1.02 (0.54-1.91)	0.96	1.40 (0.83-2.36)	0.21	<b>3.51</b> <b>(1.26-9.80)</b>	<b>0.02</b>	<b>1.84</b> <b>(1.07-3.17)</b>	<b>0.03</b>

**Bold denotes significant difference**

**Abbreviations:** RI, relapse incidence; LFS, leukemia-free survival; NRM, non-relapse mortality; OS, overall survival; allo-HCT2, second allogeneic hematopoietic cell transplant; DLI, donor lymphocyte infusion; allo-HCT1, first allogeneic hematopoietic cell transplant; aGVHD, acute graft-versus-host disease; cGVHD, chronic GVHD; CR2, second complete remission; CR3, third complete remission; MRD, HLA-matched related donor

**eTable 5.** Patient-, Disease-, and Treatment-Related Characteristics of Patients Who Received Only Allo-HCT2 or DLI

<b>Variables</b>	<b>DLI (n=230)</b>	<b>Allo-HCT2 (n=135)</b>	<b>p-value</b>
<b>Median age (range), years, at intervention</b>	<b>50 (19-75) IQR=40-60</b>	<b>43 (18-67) IQR=32-52</b>	<b>&lt;0.0001</b>
Recipient gender			0.77
Female	102 (44%)	62 (46%)	
Male	128 (56%)	73 (54%)	
Donor gender			0.12
Female	74 (33%)	51 (38%)	
Male	153 (67%)	82 (62%)	
Missing/unknown	3	2	
<b>Same original donor</b>			<b>&lt;0.0001</b>
<b>Yes</b>	<b>224 (100%)</b>	<b>72 (60%)</b>	
<b>No</b>	<b>-</b>	<b>49 (41%)</b>	
<b>Missing/unknown</b>	<b>6*</b>	<b>14</b>	
<b>Remission status at intervention</b>			<b>&lt;0.0001</b>
<b>CR2</b>	<b>33 (14%)</b>	<b>46 (34%)</b>	
<b>CR3</b>	<b>14 (6%)</b>	<b>7 (5%)</b>	
<b>Relapsed 1</b>	<b>143 (62%)</b>	<b>71 (53%)</b>	
<b>Relapsed 2</b>	<b>40 (17%)</b>	<b>11 (8%)</b>	
Donor source			0.16
MRD	122 (54%)	75 (56%)	
URD	105 (46%)	58 (43%)	
Haploidentical	0	2 (1%)	
Missing/unknown	3	0	



Cell source BM PBSC BM+PBSC Missing/unknown	9 (4%) 217 (96%) 0 4	6 (4%) 128 (95%) 1 (1%) 0	0.42
<b>Median time (range) from allo-HCT1 to relapse, days</b>	<b>193 (20-3872) IQR=114-482</b>	<b>342 (30-4569) IQR=132-699</b>	<b>0.005</b>
<b>Median time from allo-HCT1 relapse to intervention, days</b>	<b>32 (0-305) IQR=17-69</b>	<b>68 (6-311) IQR=39-119</b>	<b>&lt;0.0001</b>
<b>Grade 2-4 aGVHD prior to intervention</b> Yes No Missing/unknown	<b>18 (8%) 212 (92%) 3</b>	<b>24 (18%) 108 (82%) 3</b>	<b>0.003</b>
cGVHD (any grade) prior to intervention Yes No Missing/unknown	46 (21%) 170 (79%) 14	32 (25%) 96 (75%) 7	0.43
Cytotoxic therapy including hypomethylating agents prior to DLI Yes No Missing/unknown	146 (66%) 76 (34%) 8	-	-

Regimen used for allo-HCT2 MAC RIC Missing/unknown	-	48 (37%) 83 (63%) 4	-
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***Bold denotes significant difference***

**Abbreviations:** DLI, donor lymphocyte infusion; allo-HCT2, second allogeneic hematopoietic cell transplant; IQR, interquartile range; CR2, second complete remission; CR3, third complete remission; MRD, HLA-matched related donor; URD, unrelated donor; BM, bone marrow cells; PBSC, peripheral blood stem cells; allo-HCT1, first allogeneic hematopoietic cell transplant; aGVHD, acute graft-versus-host disease; cGVHD, chronic GVHD; MAC, myeloablative conditioning regimen; RIC, reduced intensity conditioning regimen

\*Although information missing, these are presumably from same donor

**eTable 6.** Treatment Outcomes for Patients Who Received Only Allo-HCT2 or DLI

Outcomes	DLI	Allo-HCT2	P-value
<b>Response</b>			<b>&lt;0.0001</b>
CR (before and after) intervention	<b>47 (20%)</b>	<b>53 (39%)</b>	
CR (after) intervention	<b>62 (27%)</b>	<b>52 (39%)</b>	
No response	<b>119 (52%)</b>	<b>21 (16%)</b>	
Not available*	<b>2 (1%)</b>	<b>9 (7%)</b>	
OS (all patients)			0.51
2-year	24% (95%CI=19-30%)	26% (95%CI=18-33%)	
5-year	14% (95%CI=9-19%)	18% (95%CI=11-25%)	
<b>NRM (all patients)</b>			<b>&lt;0.0001</b>
2-year	<b>9% (95%CI=6-13%)</b>	<b>27% (95%CI=20-35%)</b>	
5-year	<b>10% (95%CI=6-14%)</b>	<b>29% (95%CI=21-37%)</b>	
<b>Grade 2-4 aGVHD after intervention (all patients)</b>			<b>0.003</b>
2-year	<b>22% (95%CI=17-27%)</b>	<b>37% (95%CI=29-46%)</b>	
5-year	<b>22% (95%CI=17-27%)</b>	<b>37% (95%CI=29-46%)</b>	
Causes of death (all patients)			-
Relapse	151 (77%)	62 (55%)	
Non-relapse	44 (23%)	51 (45%)	

**Bold denotes significant difference**

**Abbreviations:** DLI, donor lymphocyte infusion; allo-HCT2, second allogeneic hematopoietic cell transplant; CR, complete remission; OS, overall survival; NRM, non-relapse mortality; aGVHD, acute graft-versus-host disease

**eTable 7.** Causes of Non-Relapse Deaths (DLI vs. Allo-HCT2) for Patients Who Received Only Allo-HCT2 or DLI

<b>Causes of non-relapse deaths</b>	<b>DLI (n=44)</b>	<b>Allo-HCT2 (n=51)</b>
Infection	14	22
GVHD	16	18
Hepatic SOS/VOD	0	4
Hemorrhage	2	1
Cardiac	0	1
Idiopathic pulmonary syndrome	1	0
Secondary malignancies	3	1
Other transplant related	8	4

**Abbreviations:** GVHD, graft-versus-host disease; SOS/VOD, sinusoidal obstructive syndrome/veno-occlusive disease

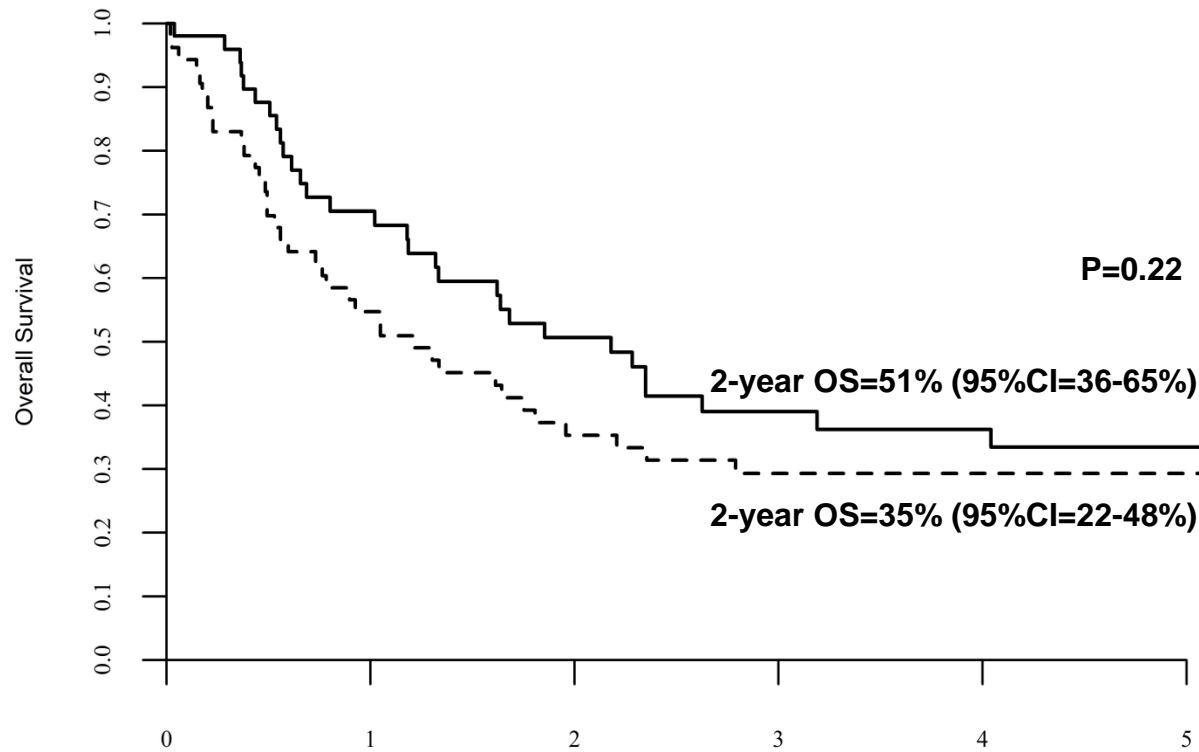
**eTable 8.** Multivariate Analysis for NRM and OS (All Patients) Who Received Only Allo-HCT2 or DLI

Variables	NRM (all patients)		OS (all patients)	
	HR (95%CI)	p-value	HR (95%CI)	p-value
Allo-HCT2 vs. DLI	<b>4.06</b> (2.27-7.26)	<b>&lt;0.0001</b>	1.11 (0.84-1.45)	0.47
Age at intervention (per 10 years)	1.18 (0.94-1.49)	0.15	1.05 (0.95-1.16)	0.39
Poor risk cytogenetics vs. others at time of allo-HCT1	1.53 (0.82-2.83)	0.18	<b>1.43</b> (1.08-1.89)	<b>0.01</b>
Secondary vs. <i>de novo</i> AML	0.71 (0.31-1.60)	0.40	1.18 (0.85-1.65)	0.33
Year of allo-HCT1	1.01 (0.94-1.09)	0.76	0.98 (0.95-1.02)	0.30
CR1 at time of allo-HCT1	0.69 (0.35-1.38)	0.29	0.94 (0.68-1.29)	0.68
URD vs. MRD at allo-HCT1	0.77 (0.22-2.81)	0.70	0.68 (0.37-1.27)	0.22
RIC vs. MAC at allo-HCT1	0.86 (0.46-1.58)	0.62	1.13 (0.86-1.50)	0.38
Grade 2-4 vs. none aGVHD prior to DLI/allo-HCT2	<b>2.21</b> (1.14-4.30)	<b>0.02</b>	<b>1.57</b> (1.09-2.26)	<b>0.02</b>
cGVHD (all grades) vs. none prior to DLI/allo-HCT2	1.01 (0.56-1.82)	0.98	<b>0.68</b> (0.50-0.93)	<b>0.02</b>
Time from allo-HCT1 to relapse (months)	0.99 (0.98-1.01)	0.25	<b>0.98</b> (0.98-0.99)	<b>&lt;0.0001</b>
Time from relapse to DLI/allo-HCT2 (months)	0.92 (0.78-1.08)	0.31	0.96 (0.90-1.03)	0.32
Other donor vs. MRD at DLI/allo-HCT2	1.60 (0.45-5.63)	0.47	1.53 (0.84-2.80)	0.17
CR vs. no CR at DLI/allo-HCT2	0.90 (0.48-1.69)	0.75	<b>0.56</b> (0.42-0.76)	<b>0.0002</b>

**Bold denotes significant difference**

**Abbreviations:** NRM, non-relapse mortality; OS, overall survival; allo-HCT2, second allogeneic hematopoietic cell transplant; DLI, donor lymphocyte infusion; allo-HCT1, first allogeneic hematopoietic cell transplant; CR1, first complete remission; MRD, HLA-matched related donor; URD, unrelated donor; MAC, myeloablative conditioning regimen; RIC, reduced intensity conditioning regimen; aGVHD, acute graft-versus-host disease; cGVHD, chronic GVHD

**eFigure 1. OS (Allo-HCT2 vs. DLI), Patients in CR at Time of Intervention**

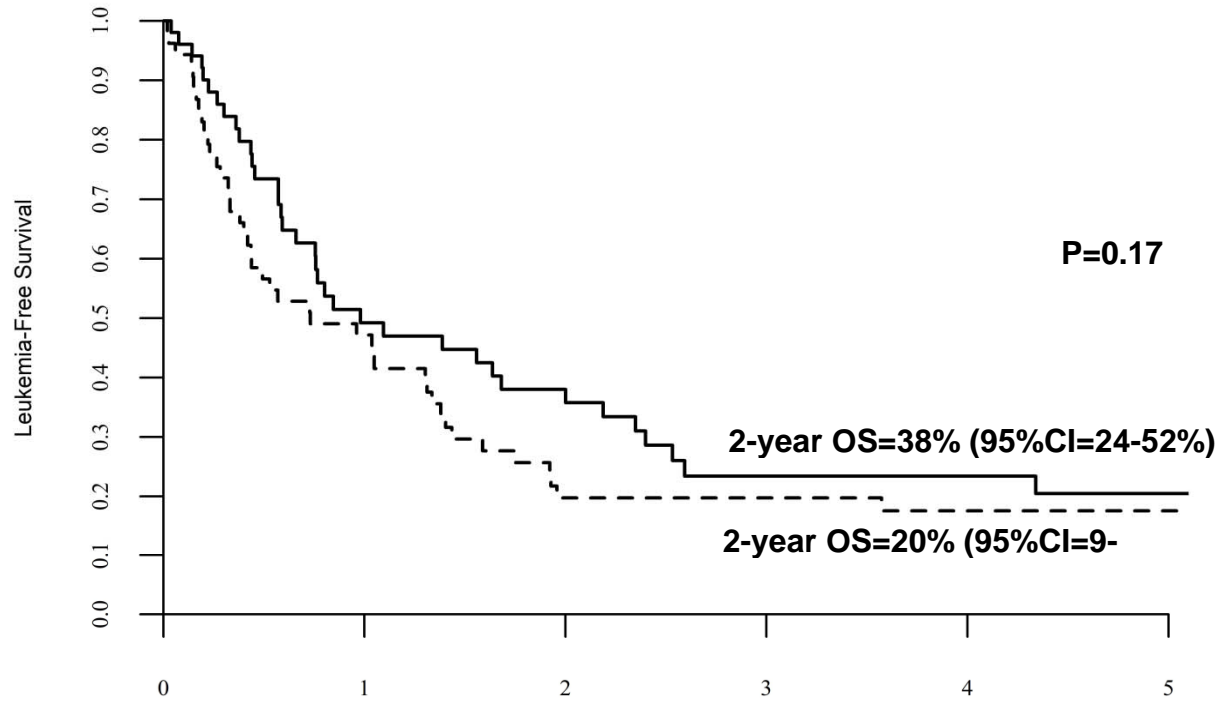


Time from transplant (years)

number of at-risk patients

— DLI	51	32	23	14	13	11
- - - Allo-HCT2	53	29	18	14	14	11

**eFigure 2.** LFS (Allo-HCT2 vs. DLI), Patients in CR at Time of Intervention



	number of at-risk patients						
	0	1	2	3	4	5	
— DLI	51	22	17	8	8	7	
- - - Allo-HCT2	53	25	10	9	8	7	