

Quali sono i vantaggi delle DLI manipolate (mDLI)

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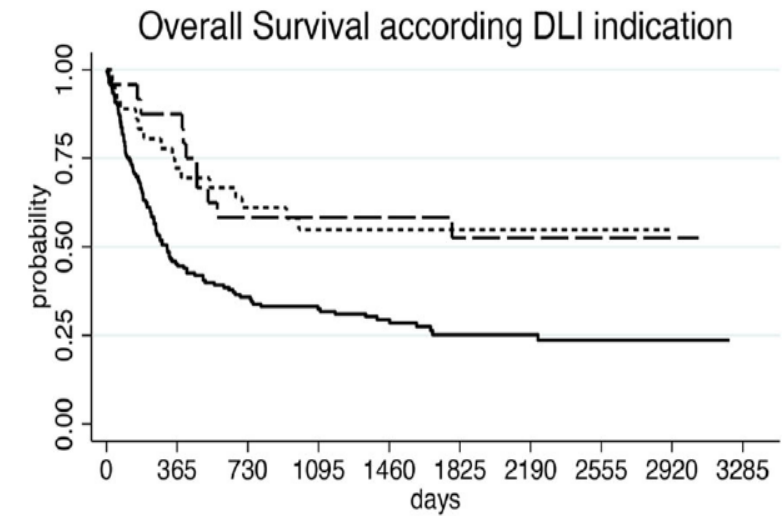
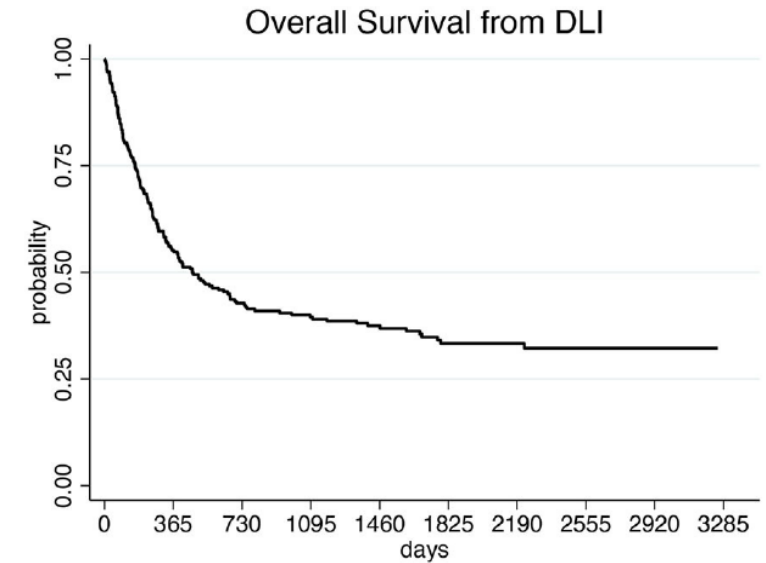
Background

	N pDLI	AML	ALL	MDS	Lymphoma/MM	Reason pDLI	Median time after allo-SCT	Median CD3 dose/kg	ORR	OS	aGVHD	cGVHD	NRM
Dey et al. [43]	16	0	0	0	15/1	MC	35 d	1×10^7	75%	44%@3y	44%	NR	12%
Dominietto et al. [44] ^a	17	NR	NR	0	0	MRD	NA	NT	NA	80%@3y	NR		12%
Lutz et al. [51] 2008 ^b	26	0	26	0	0	High risk/MC	60 d	3.7×10^7	NR	70%@3y	86%/50%		11%
Peggs et al. [60] 2011	22	0	0	0	22/0	MC	287 d	1×10^6	95%	NR	NR		NR
Beitinjaneh et al. [76] 2012	8	0	0	0	0/8	MRD	240 d	$0.5-5 \times 10^7$	50%	40%@5y	25%		NR
Yan et al. [47]	56	56	0	0	0	MRD	NR	1×10^8	NR	54@3y	31%	34%	14%
Krishnamurthy et al. [16] ^c	62	34	0	28	0	MC or falling C	176 d	5×10^5	65%	80%@5y			5%
Eefting et al. [52] 2014	14	0	25	0	0	High risk	185 d	$1.5-3 \times 10^6$	NR	68%@2y	28%	17%	20%
Solomon et al. [46] 2014	36	14	0	4	13	MC	60 d	$0.5-1 \times 10^7$	NR	57%@2y	17%	59%	14%
Tan et al. [45] ^d	16	8	8	0	0	MRD	NA	5.6×10^7	100%	93%@1y	31%	NR	6%

Background

	1stDLI
Total number of cases	252
Time between transplant and first DLI (days)	258 (55–3,784)
Time between DLIs	
DLI indication	
AL relapse	172/235 (73%)
Mixed chimerism	39/235 (17%)
Pre-emptive/prophylaxis	24/235 (10%)
Missing	17

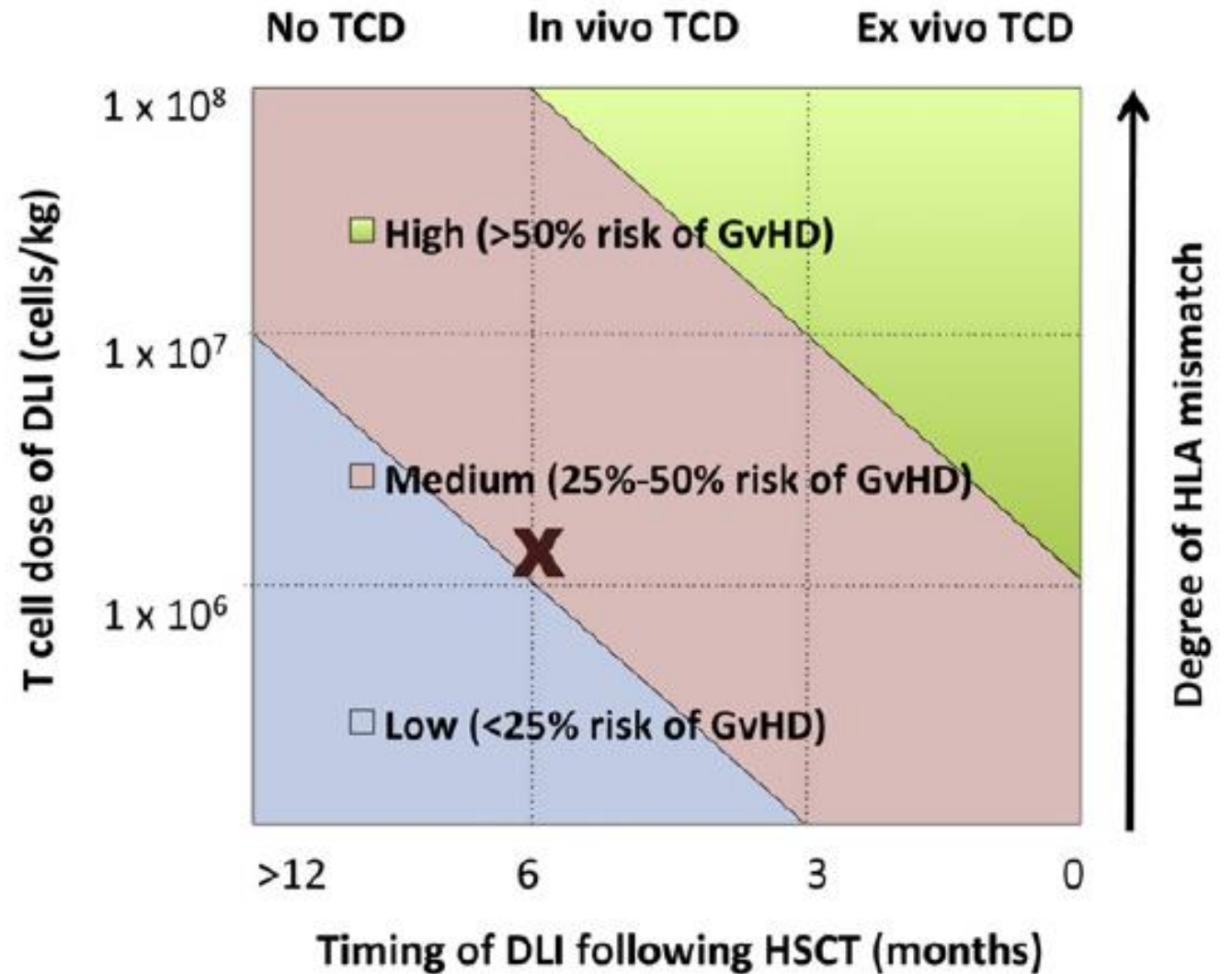
aGVHD= 13%
cGVHD= 14%
DLI-related NRM= 9%



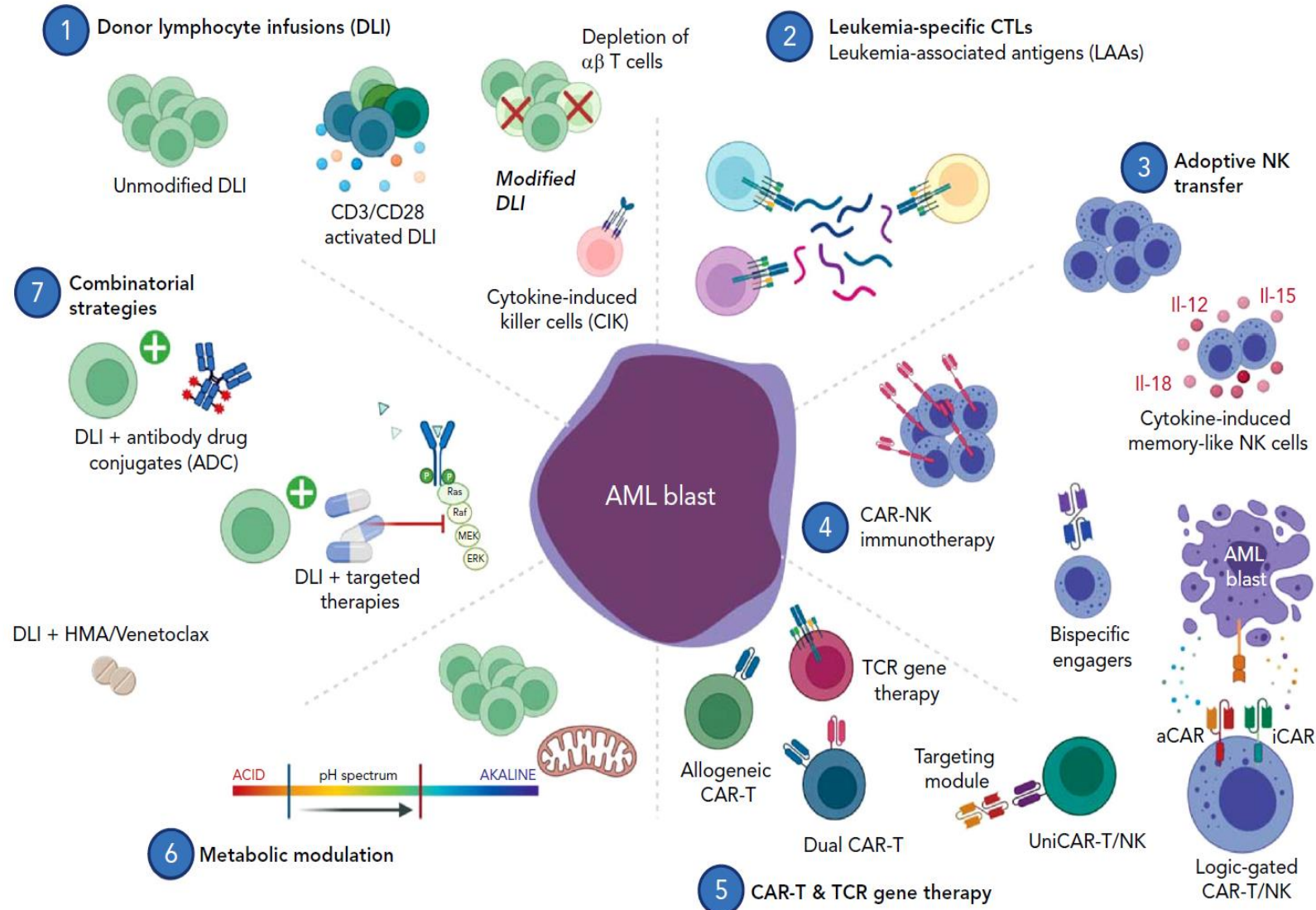
Background

Less GVHD/NRM more GVL

- ☐ Intensity of CTX regimen
- ☐ In vivo TCD
- ☐ DLI composition
- ☐ Degree mis-match
- ☐ Disease and its burden
- ☐ Intensity IS post-Allo
- ☐ Level of donor chimerism



Background



Background

Enhanced GVL

- DLI CD8 depleted
- DLI Treg-depleted
- **DLI mobilized GCSF**
- **CIK**
-

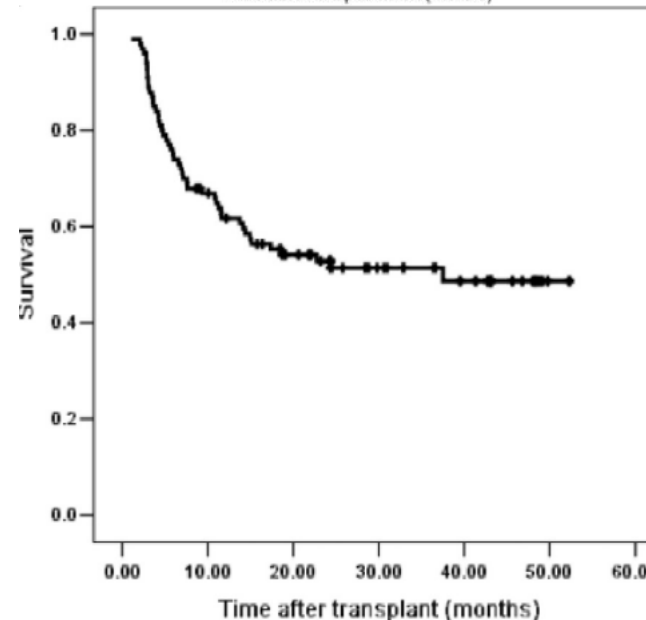
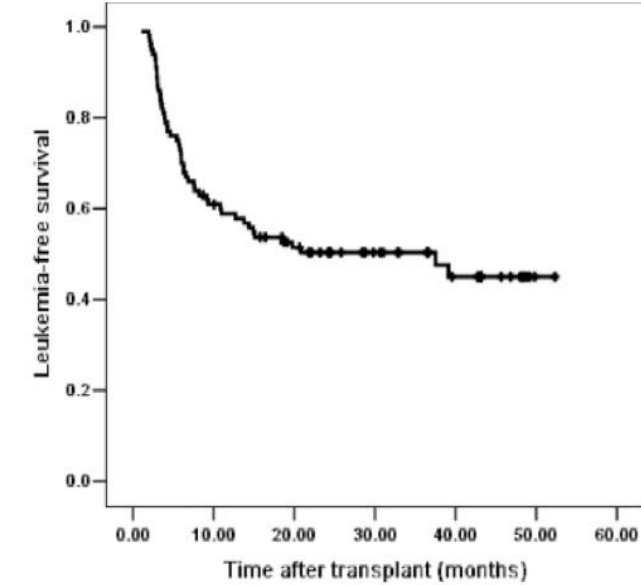
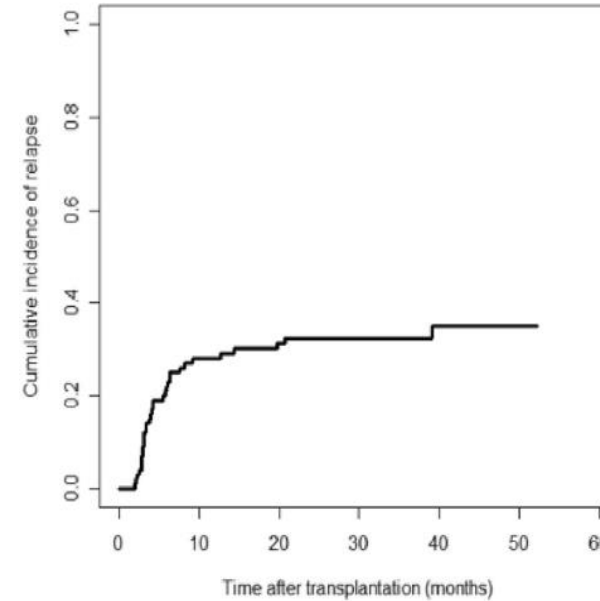
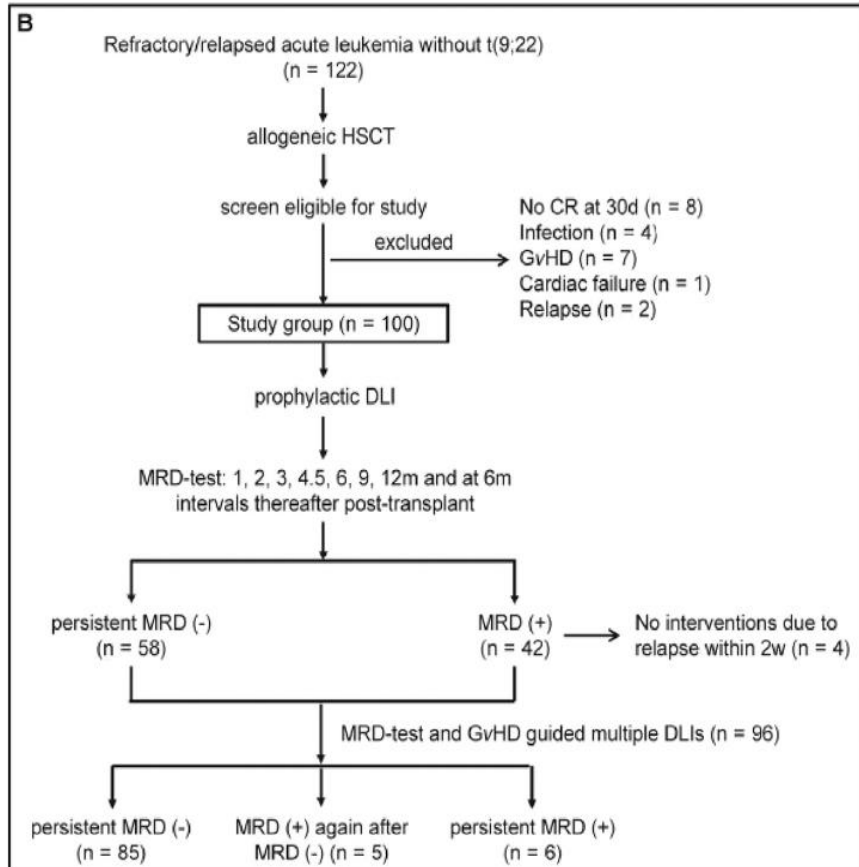
Decreased GVHD

- **DLI CD45RA+ depleted**
- DLI $\alpha\beta$ depleted
- DLI Treg depleted
-

DLI mobilized by GCSF

- Why to use GCSF to harvest DLI (gDLI)?
 - T cell hyporesponsiveness and polarization of T-cell from Th1 to Th2
 - Increase natural killer T cell–dependent CD8+ cytotoxicity

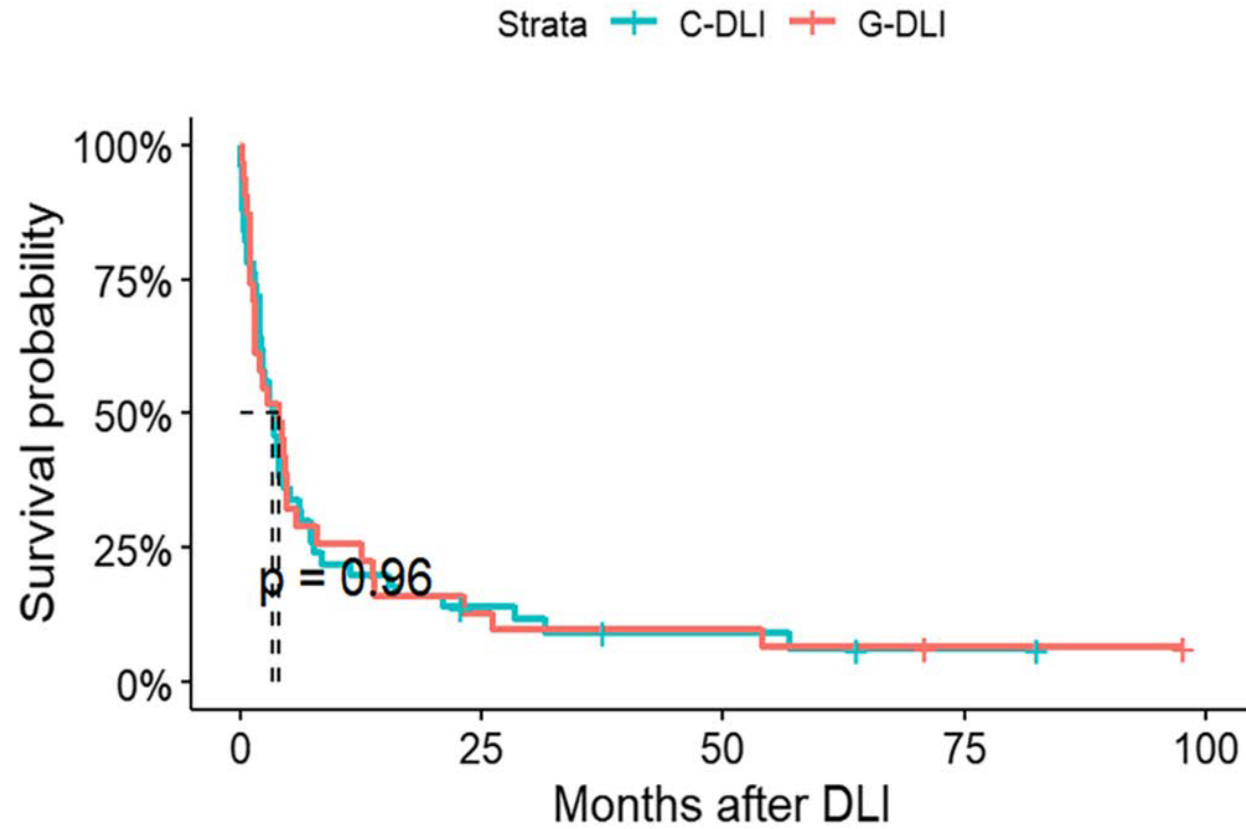
DLI mobilized by GCSF



GVHD and TRM	CI
Grade 2-4 aGVHD	29%
Grade 3-4 aGVHD	9%
cGVHD	66%
Severe cGVHD	9%
TRM@3y	17%

DLI mobilized by GCSF

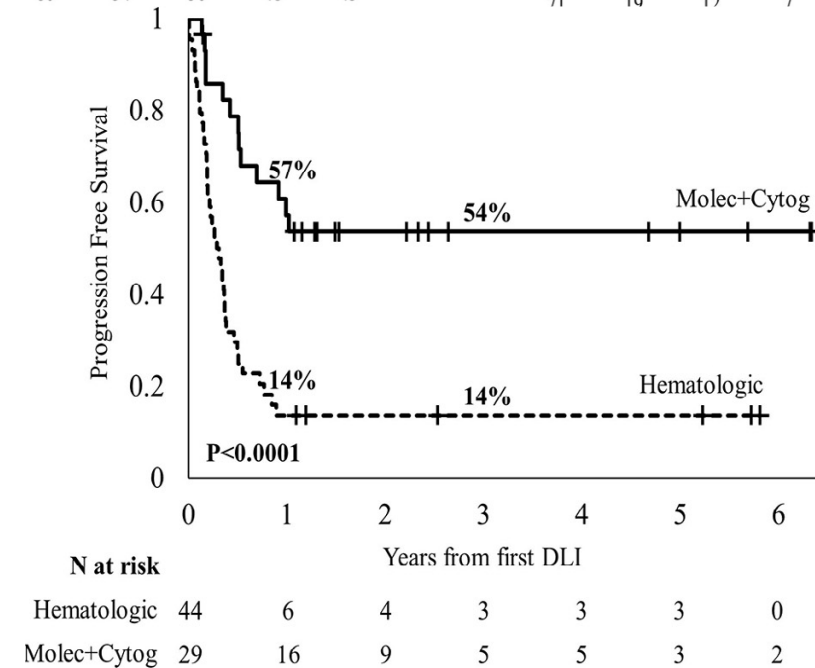
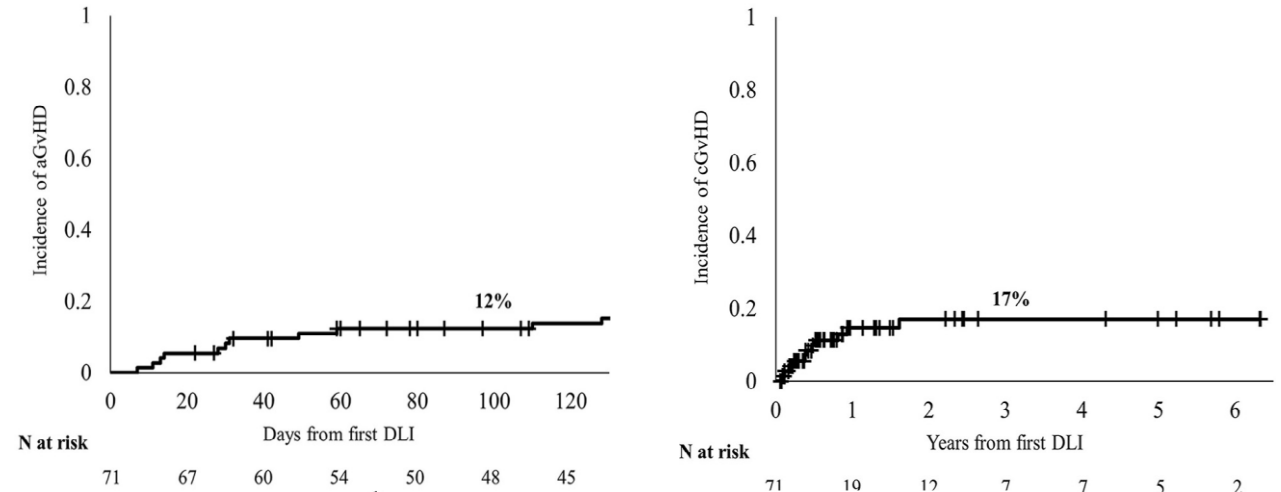
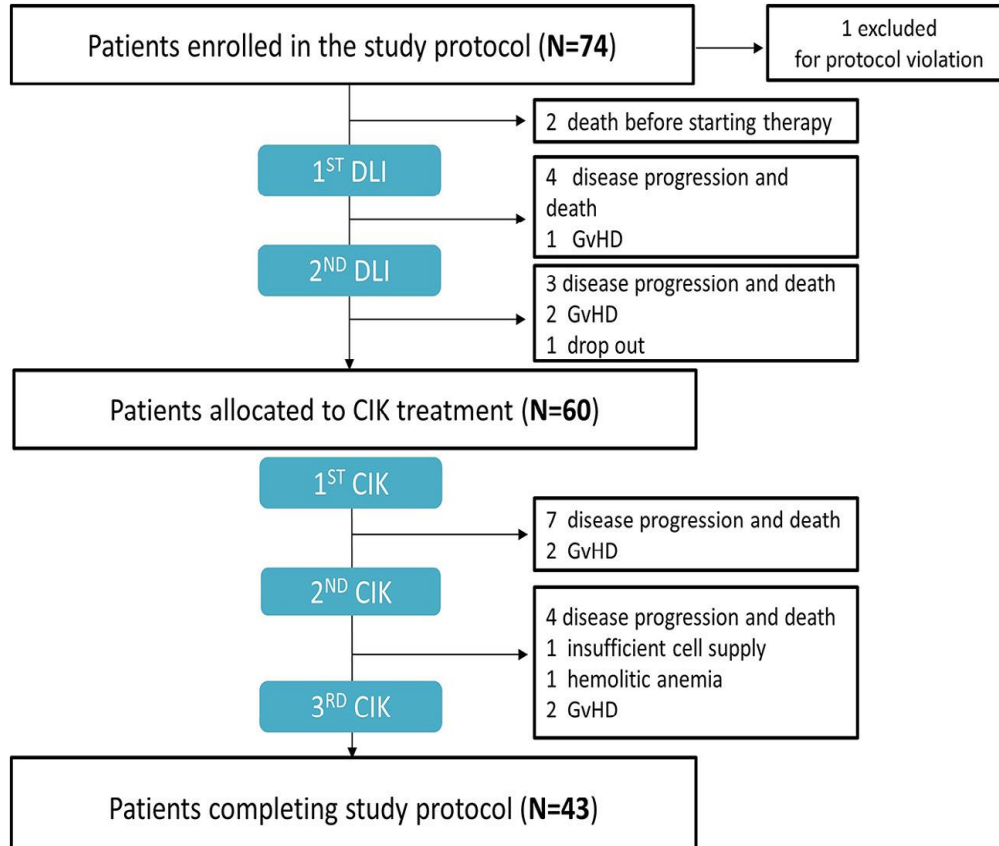
Therapeutic
cDLI vs gDLI
N= 81



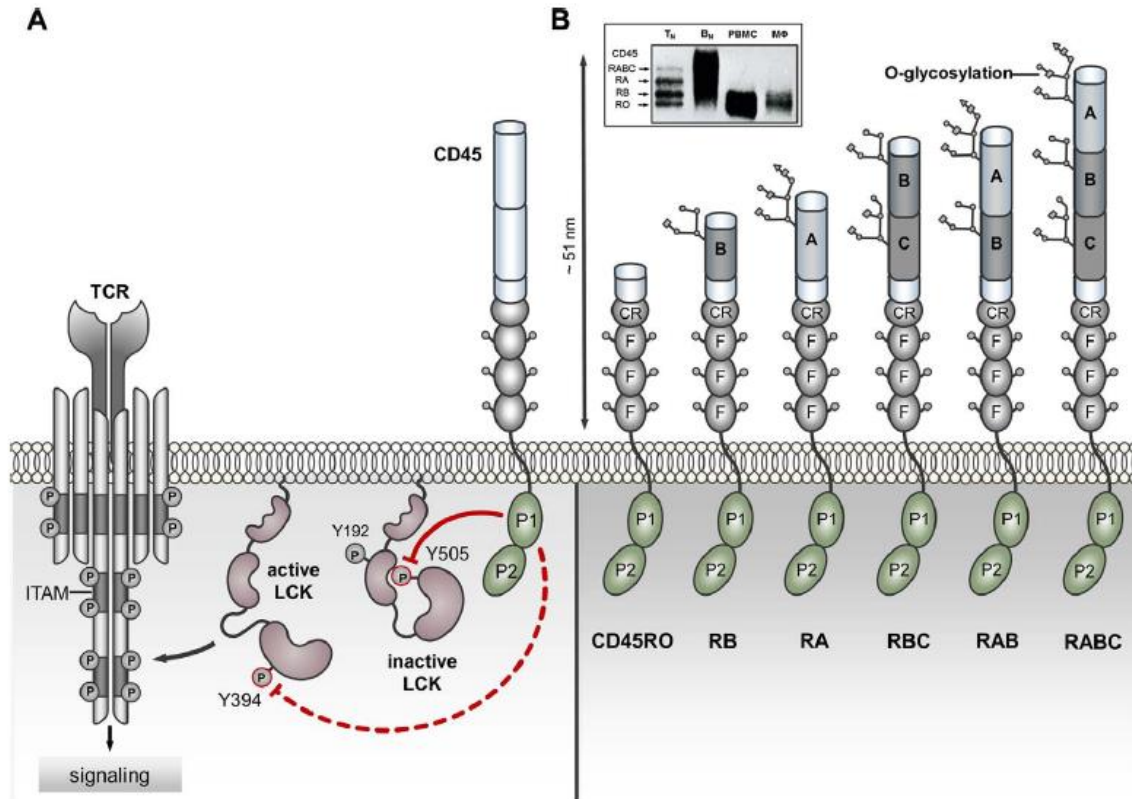
CIK

Study	Study design	Patients (N)	Disease (N of pts)	Setting	CIK source	Cell dose/ N infusion	Additional treatment	Response	GvHD	Outcome
Introna et al. Haematologica 2007 (140)	Single- center, open-label phase I study	11	AML (4) HD (3) CML (1) ALL (1) MDS (2)	Treatment	MRD MUD	Median dose 12.4×10 ⁶ cells/kg (range 7.2-87.4) (median infusions 2 range, 1-7)	None	1 SD 1 PR 3 CR	4 aGvHD (grade I-II) 2 cGvHD	Alive 5/11
Introna et al. BBMT 2010 (139)	Compassionate use study	5	AML (4) ALL (1)	Treatment	UCB	A median of 1.5×10 ⁶ cells/kg (range: 1-8×10 ⁶ cells/kg (median infusions 1 range, 1-4)	CT	1 CR	1 aGvHD (grade III)	Alive 0/5
Laport et al. BBMT 2011 (142)	Single center open-label phase I study	18	NHL (n=5) AML (n=3) MM (n=3) CLL (n=2) ALL (n=2) MDS (n=2) HD (n=1)	Treatment	MRD	Escalation doses: 1×10 ⁷ CD3 ⁺ cells/kg 5×10 ⁷ CD3 ⁺ cells/kg 1×10 ⁸ CD3 ⁺ cells/kg (single infusion)	None	2 CR 8 disease related deaths	2 aGvHD (grade II) 1 limited cGvHD	Alive 10/18
Linn et al. BBMT 2012 (143)	Phase I/II clinical study	24 (16 infused)	AML (8) ALL (3) CML (1) HD (3) NHL (1)	Treatment	MRD (15) MUD (8) UCB (1)	from 10 to 200×10 ⁶ cells/kg (1-12 infusions)	None	5 ORR	3 aGvHD	2-years Alive in CR 2/16
Rettinger et al. BMT 2013 (147)	single- center study	2	AML	Treatment	Haplo (2)	15-170 x10 ⁶ cells/kg (from 7 to 9 infusions)	None	2 PR	None	2/2 dead
Rettinger et al. Haematologica 2016 (146)	Retrospective multicenter study	13	AML (5) ALL (7) CML (1)	Treatment	MRD (1) MUD (6) Haplo (6)	From 5 to 100 x10 ⁶ cells/kg (from 1 to 6 infusions)	None	10 CR 1 PR 2 NR	6 aGvHD (3 grade I and 3 grade III) 3 cGvHD	OS 69%
Luo et al. Leukemia Research 2016 (138)	single- center, open-label phase I study	15	AML (4) ALL (2) CML (3) MM (2) NHL (4)	Treatment	MRD (8) Haplo (7)	From 1×10 ⁶ to 8×10 ⁷ cells/kg (from 1 to 10 infusions)	HCT	15 ORR	2 aGvHD 1 grade I and I grade III	6 Alive
Introna et al. BBMT 2017 (141)	Multicenter, open-label phase IIA, study	74	AML (41) ALL (19) HD (3) MM (4) NHL (2) MDS(2) MPN (2)	Treatment	MRD (37) MUD (31) Haplo (5)	1×10 ⁶ cells/kg 5×10 ⁶ cells/kg 10×10 ⁶ cells/kg (3 infusions)	DLI	19 CR (26%) 3 PR (4%) 8 SD (11%)	12 aGvHD (16%), 7 of grade I-II 5 grade III-IV 11 cGvHD (15%)	3-year PFS 29% OS 40%
Pfeffermann et al. Cytotherapy 2018 (148)	Compassionate use study	1	PTLD	Treatment	MUD	10×10 ⁶ CIK cells/kg; 9.57×10 ³ EBV- specific CIK cells/kg	IL-15 and EBV peptide pool	1 CR	None	2-years alive in CR 1
Merkel BBMT 2019 (145)	Retrospective, single-center, study	36 (32 pediatric)	AML (15) ALL (18) CML (1) NHL (2)	Treatment (8) Pre-emptive (17) Prophylaxis (11)	MRD (3) MUD (10) MMUD (23)	MRD/MUD median 10×10 ⁶ /Kg (0.7-200) MMUD median 5×10 ⁶ /Kg (0.1-9.4) (median infusions 2, range 1-9)	None	53% CR (68% CR pre-emptive +prophylactic)	9 aGvHD (25%) 8 grade I-II 1 grade III 2 limited cGvHD (6%)	0/8 alive (treatment) 6-months OS 77% (81% prophylaxis, 75% pre-emptive)
Narayan et al. BBMT 2019 (144)	Single- center, open-label phase II study	44 (31 infused)	AML (n=12) MDS (n=27) MPN (5)	Prophylaxis	MRD MUD MMUD	Escalation doses: 1×10 ⁷ cells/kg 3×10 ⁷ cells/kg 1×10 ⁸ cells/kg (single infusion)	None	/	1-year aGvHD 25.1%	2-year NRM 6.8% EFS 27.3% OS 50.6%

CIK



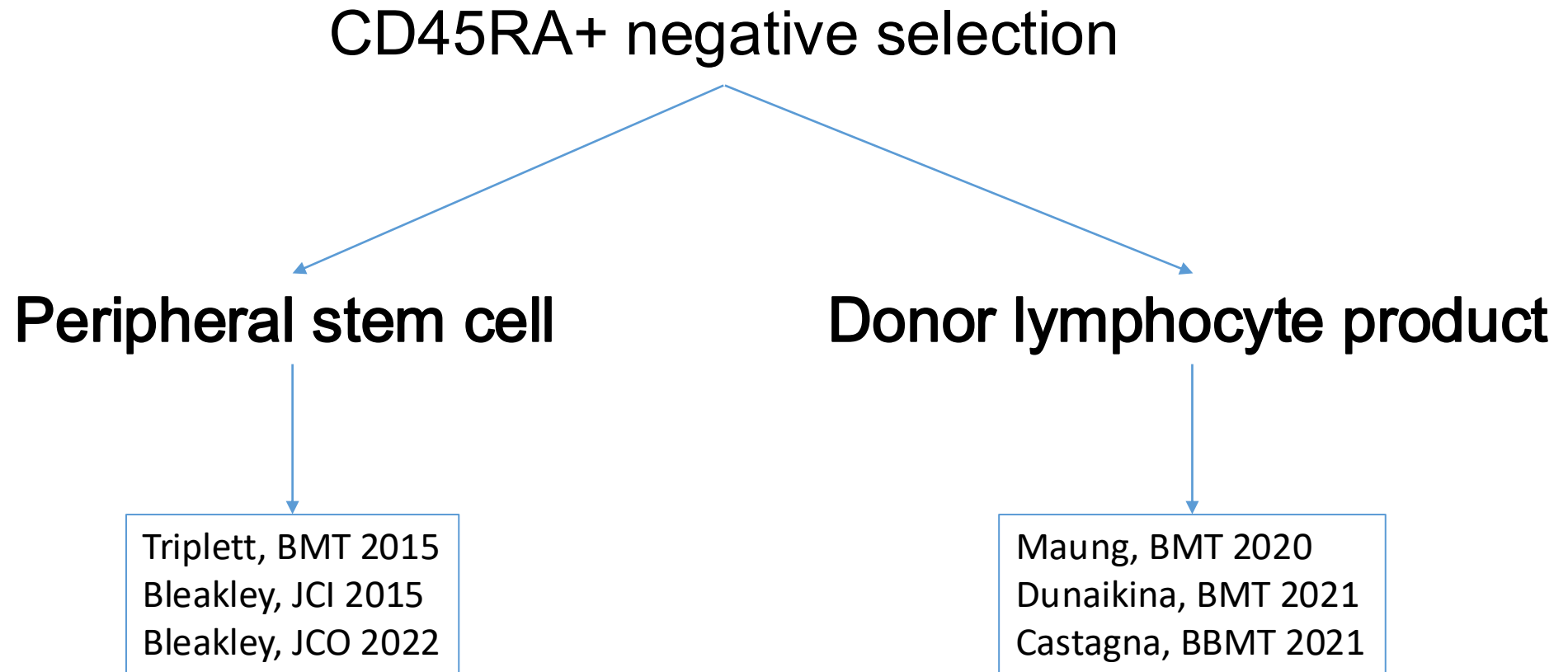
DLI: CD45RA+ negative selection



- It is expressed on the surface of all cells
- Many isoforms based on splicing exon 4, 5, 6: RA, RB, RC, RO
- CD45 is a phosphatase acting on SRC kinase such as Lck
- It regulates BCR and TCR
- **Memory T** cell expressed CD45RO
- **Naïve T** cells expressed CD45RA

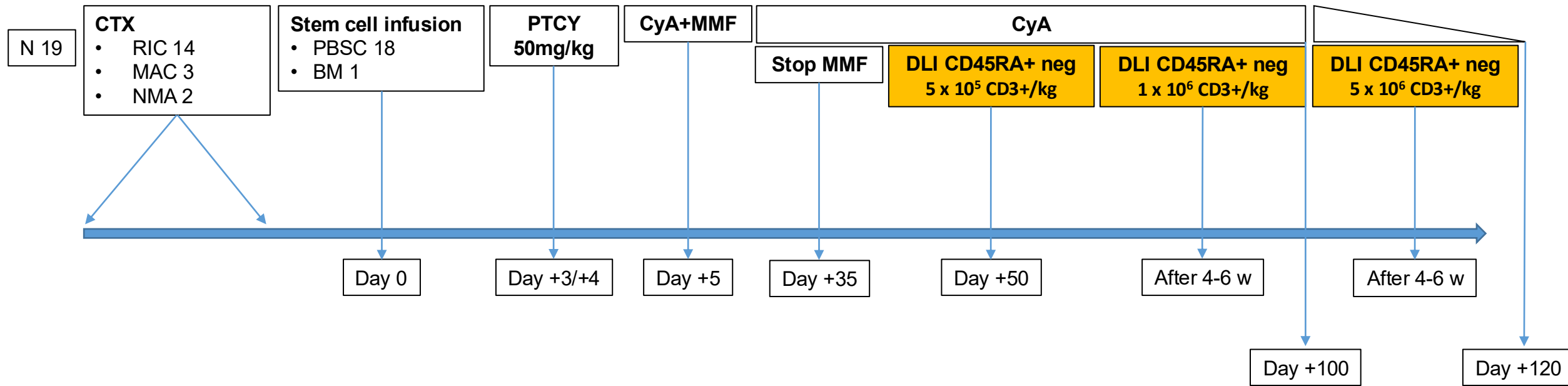
Naïve CD45RA+ T cells induced more severe GVHD compared to T_{CM} and T_M

DLI: CD45RA+ negative selection



Feasibility and Efficacy of CD45RA+ Depleted Donor Lymphocytes Infusion After Haploidentical Transplantation With Post-Transplantation Cyclophosphamide in Patients With Hematological Malignancies

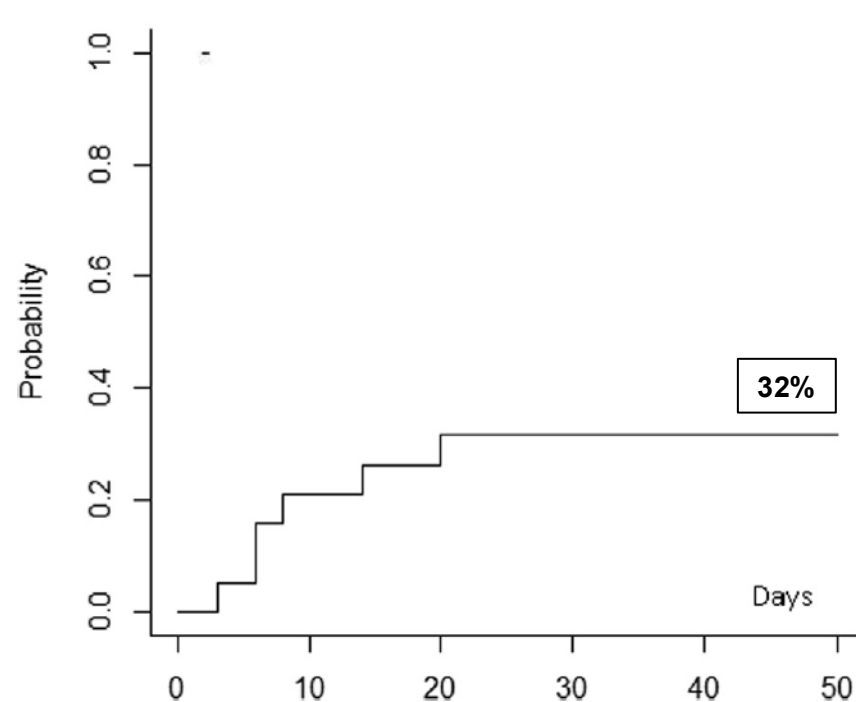
Luca Castagna^{1,*}, Viviana Valli¹, Inna Timofeeva¹, Rossana Capizzuto¹, Stefania Bramanti¹, Jacopo Mariotti¹, Chiara De Philippis¹, Barbara Sarina¹, Daniele Mannina¹, Laura Giordano⁵, Federica De Paoli², Jasper J.P. van Beek², Elisa Zaghi³, Michela Calvi^{3,4}, Clara Di Vito^{3,4}, Domenico Mavilio^{3,4}, Roberto Crocchiolo^{1,‡,†}, Enrico Lugli^{2,†}



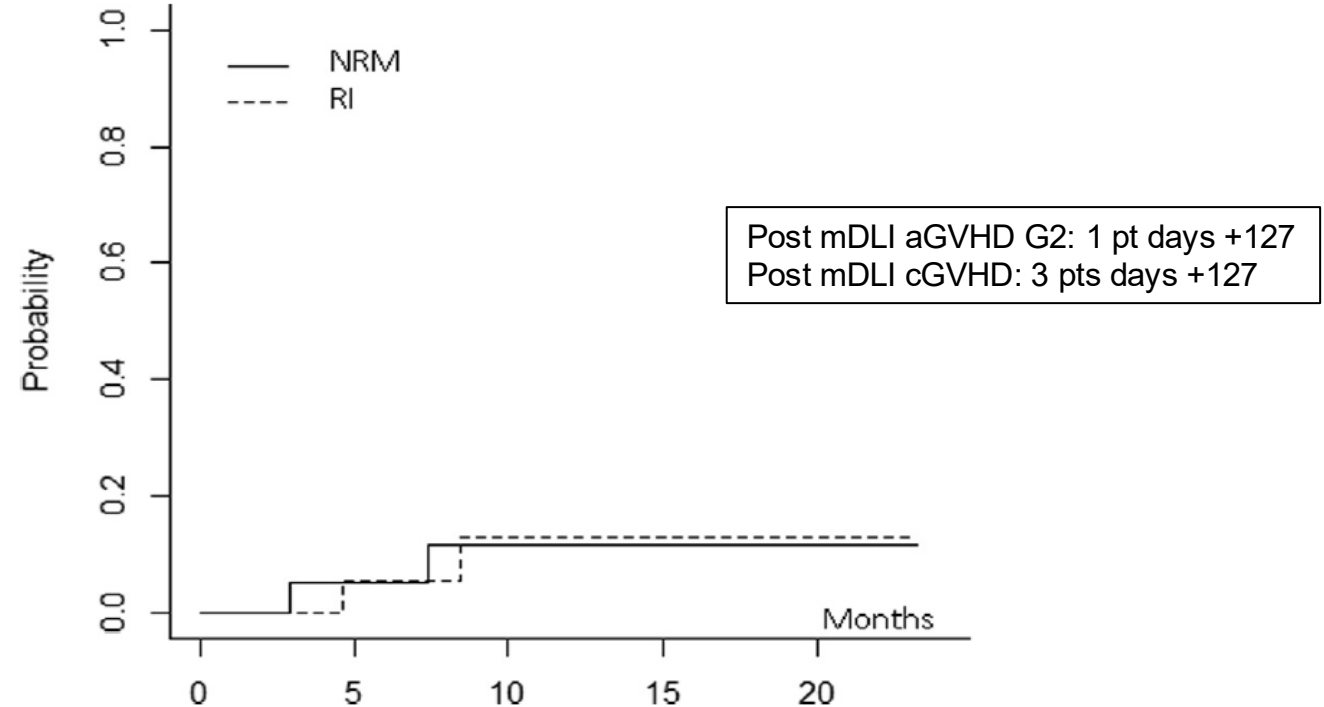
Median time to 1 mDLI infusione: 55 days (46-63)

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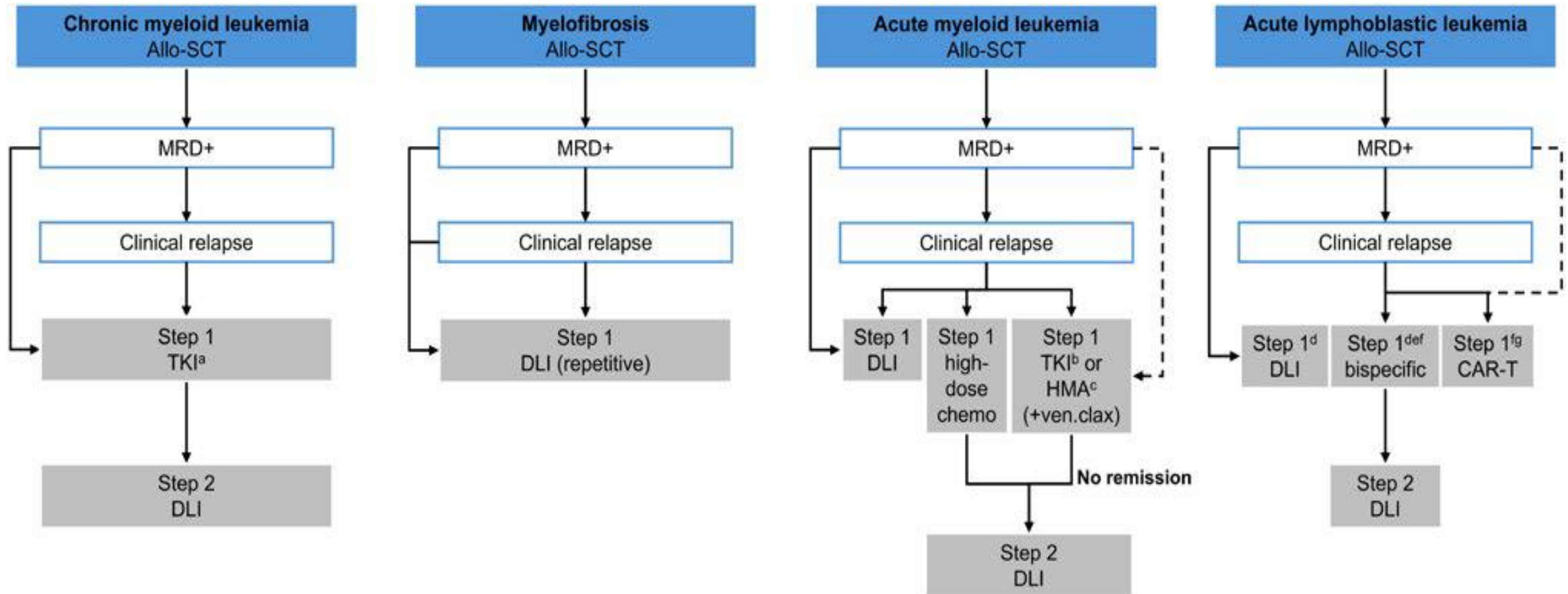


In our previous study, the CI viral infection (land mark analysis) was **53%**
Crocchiolo, Transplant Infect Disease 2015



Before CD45RA+ negative DLI infusion
42% had **HHV6** reactivation
No reactivation was observed after infusion

How to integrate DLI in the treatment landscape



Immunomodulation post ALLO in high risk patients

Patient population

- AML/ALL **MRD+ CR1/CR2**
- AML **ELN high-risk** (TP53, ASXL1, RUNX1, monosomal)
- MDS/MPN active disease
- Lymphomas in **PR**

2022-2025

Protocol

Early CyA tapering
+
Prophylactic DLI x 3

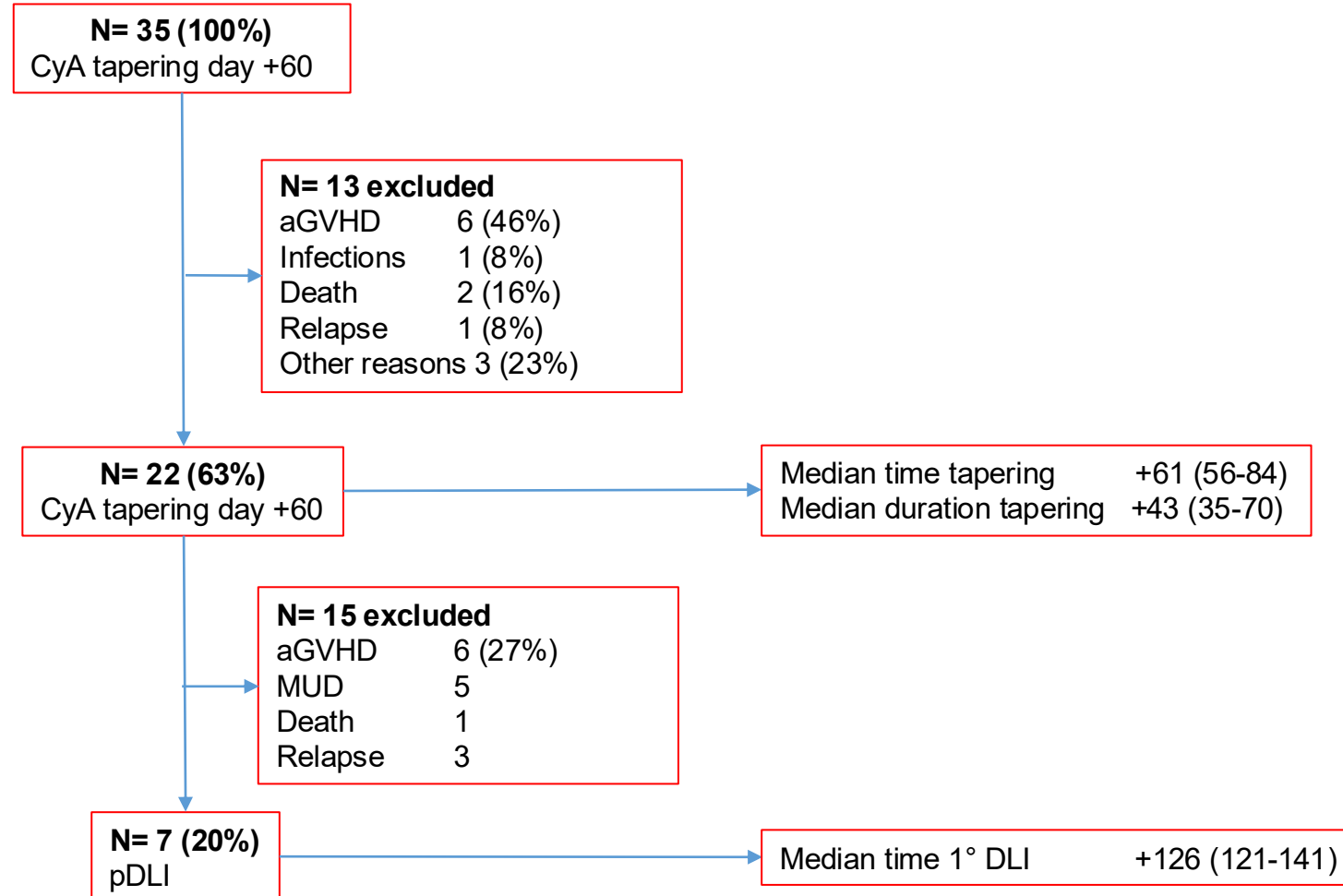
Timing

From day +60 to +90/100
+
From day +120

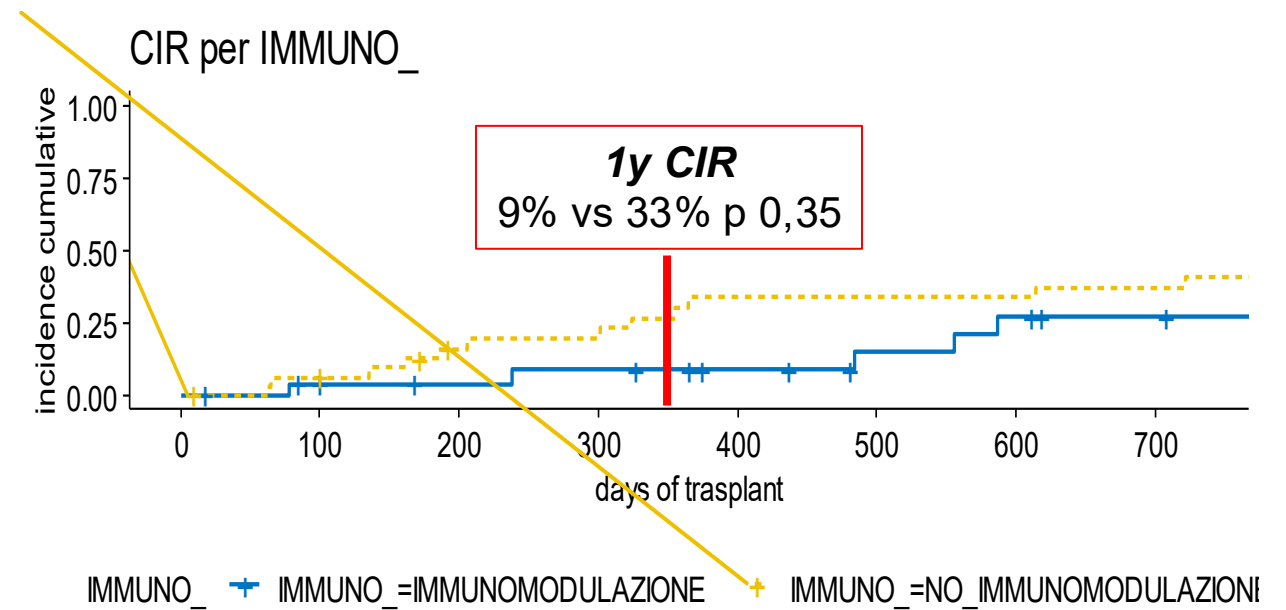
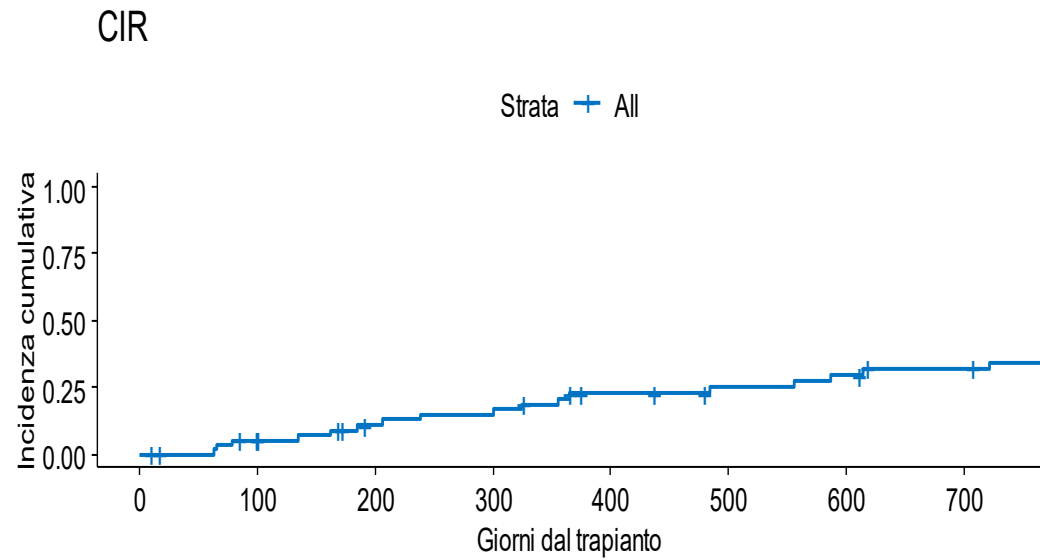
DLI in an immunomodulation program

	All patients N=68	Cohort A N=35 (immunomodulation) 2022-2025	Cohort B N=33 No (immunomodulation) 2017-2021	pvalue
Median age	55y (19-71)	60y (19-71)	53y (25-69)	0,0028
Disease				0,2021
AML	40 (59%)	17 (49%)	23 (70%)	
ALL	9 (13%)	6 (17%)	3 (9%)	
NHL	5 (7%)	2 (6%)	3 (9%)	
MDS/MPN	14 (21%)	10 (29%)	4 (12%)	
Donor				0,0233
HAPLO	25 (37%)	17 (49%)	8 (25%)	
MRD	22 (33%)	7 (20%)	15 (47%)	
MUD	15 (22%)	1 (3%)	4 (13%)	
mMUD	5 (8%)	10 (29%)	5 (16%)	
TCI				0,0007
High	18 (27%)	3 (9%)	15 (46%)	
Int	31 (46%)	17 (49%)	14 (42%)	
Low	19 (28%)	15 (43%)	4 (12%)	
GVHD prophylaxis				
ATG-based	33 (49%)	24 (69%)	9 (27%)	
PTCY-based	21	11 (31%)	10 (33%)	
Csa+MTX	13	/	13 (39%)	
Altro	1	/	1 (3%)	

Immunomodulation post ALLO in high risk patients



Immunomodulation post ALLO in high risk patients



Conclusions

- DLI are effective as prophylactic/preemptive or therapeutic strategy
- DLI manipulation, with different degree of complexity, usually allows to optimize GVL/GVH ratio
- DLI must integrate in the global treatment of patients at high risk or relapsed after ALLO.