La terapia di prima linea delle LAL-T oggi: c'è un futuro per l'immunoterapia?

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Disclosures of Cristina Papayannidis

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Pfizer					x	x	
Amgen						x	
Astellas					x		
Abbvie					x		
Menarini Stemline						x	
Servier					x		
Incyte					x		
Janssen						x	
Syndax						x	
Blueprint					x	x	
GSK						x	
Istituto Gentili					x	x	
Jazz Pharmaceuticals					x	x	

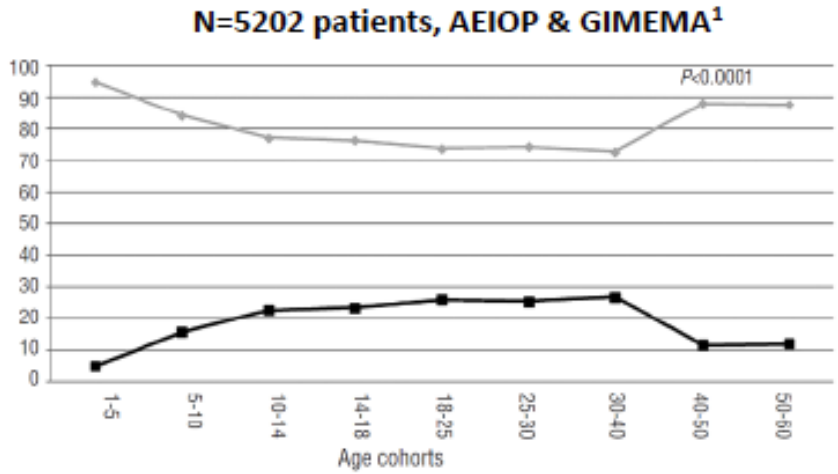
T-ALL in adult patients

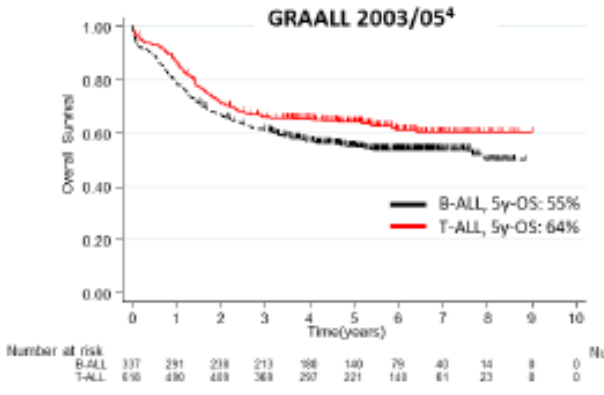
- T-ALL accounts for about 20% of all cases of ALL and is more common in AYA vs children or older adults

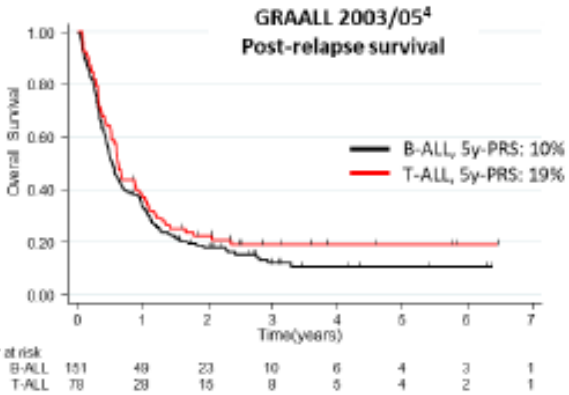
- When compared to B-ALL, clinical presentation of T-ALL more frequently includes:
-high WBC
-CNS involvement
-mediastinal mass

- In recent adult protocols, the outcome of T-ALL tends to be similar or even better than Ph neg B-ALL

- About 30-35% of T-ALL patients still relapse. The prognosis of these patients remains dismal, with less than 20% long term survivors







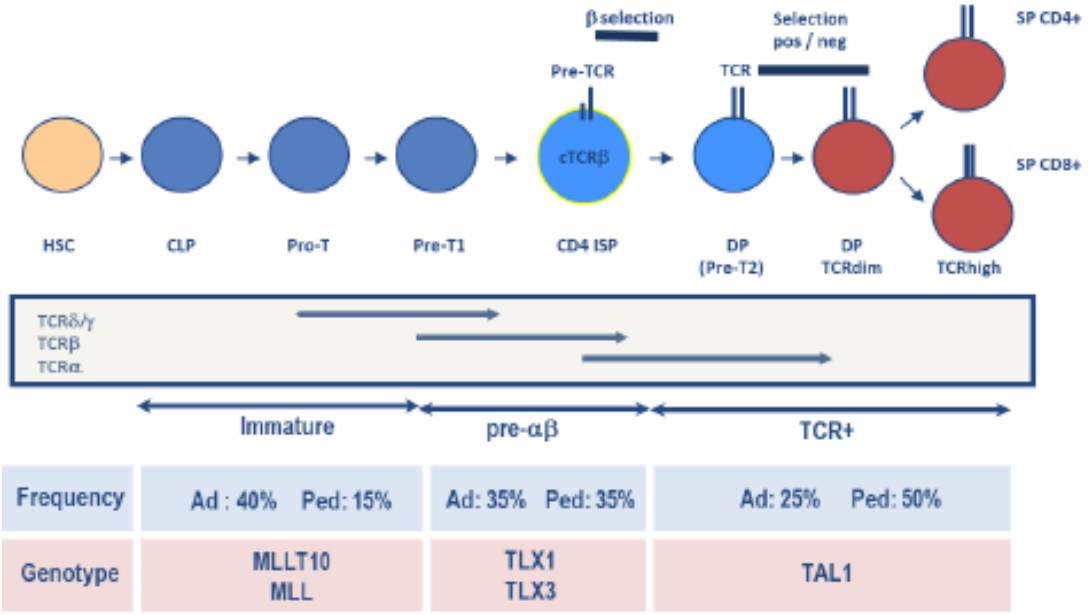
Chiaretti S et al, Haematologica 2013; Marks D et al, Blood 2009;
Desjonqueres A et al, Blood Cancer J 2016

Genomic landscape of T-ALL

- «**Founding events**» related to maturation arrest, mostly translocations involving transcription factors (TAL1, TLX1, TLX3, HOXA9/10…)

- «**Cooperating events**» not related to maturation arrest:

- NOTCH1 pathway
- IL7R/JAK1-3/STAT pathway
- PI3K/AKT/mTOR pathway
- Cell Cycle inhibitors (CDKN2A, CDKN2B…)
- Epigenetic regulators (DNMT3A, TET2, IDH1/2…)



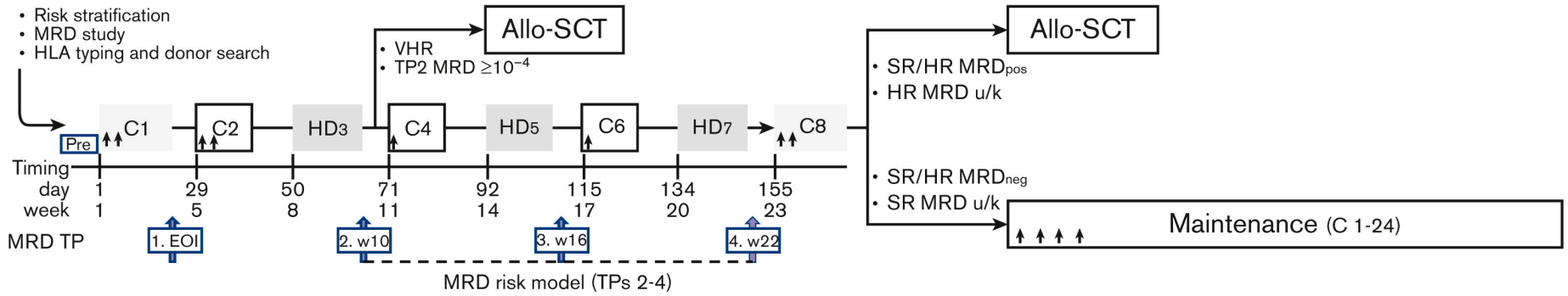
Bassan R et al, JCO 2018

Cytogenetics and molecular alterations in T-ALL

T-lineage ALL		
TAL and *LMO* rearrangements/del(1)(p32), t(1;14)(p32;q11), t(1;7)(p32;q34), t(7;9)(q34;q32), t(11;14)(p15;q1), t(11;14)(p13;q1), t(7;11)(q35;p13)	30%-40% Favorable and partly depending on additional lesions	*SIL-TAL1* rearrangement, TCR rearrangements with *TAL1*, *TAL2*, *LMO1*, and *LMO2*
HOXA aberrations/inv(7)(p15q34), t(7;7)(p15;q34), t(10;11)(p13;q14), t(v;11q23), del(9)(q34)	20%-25% Outcome depending on additional lesions	*TCR-HOXA* rearrangement, *MLLT10 and MLL* rearrangements with various partners, *SET-NUP214* rearrangement
TLX1-10q24 rearrangements/t(7;10)(q34;q24), t(10;14)(q24;q11)	20%-30% No impact on prognosis	*TCR-TLX11* rearrangement
ETP ALL	10%-15% Unfavorable/controversial	Deregulation of myeloid transcription factors, of members of RAS pathway and of epigenetic regulators
TLX3-5q35 rearrangement/t(5;14)(q35;q32)	10% No impact on prognosis	*TLX3-BCL11B* rearrangement
t(8;14)(q24;q11)	1% Unfavorable	*MYC* involvement
ABL1 rearrangements	~3% Potentially targetable by tyrosine kinase inhibitors	*NUP214, EML1; ETV6*
LYL/MEF2C rearrangement and immature cluster/t(7;19)(q34;p13), del(5)(q14)	3%-17% Unfavorable; improved by intensive treatment	*TCR* with *LYL1* *MEF2C* rearrangements

Gokbuget N et al, Blood 2024

GIMEMA 1913 trial



Treatment phase	Drugs	Dosing and administration	Days
Prephase	Prednisone Cyclophosphamide	20 mg/m² PO q12h 300 (200 if age >55) mg/m² IV over 30'	−5 to −1 −3 to −1
Course 1	Idarubicin Vincristine Dexamethasone Pegaspargase IT prophylaxis(↟)	12 (9 if age >55) mg/m² IV over 30' 1.4 mg/m² (max. 2 mg) IV push 5 mg/m² IV over 5' q12h 2000 (1000 if age >55) IU/m² IV over 120'	1,2 1,8,15,22 1-5, 15-19 10 1,15
Courses 2,4,6	Vincristine Idarubicin Cyclophosphamide Dexamethasone Cytarabine Pegaspargase 6-mercaptopurine IT prophylaxis (↟)	1.4 mg/m² (max. 2 mg) IV push 12 (9 if age >55) mg/m² IV over 30' 1000 mg/m² IV over 60' 5 mg/m² PO q12h 75 mg/m² SC 2000 (1000 if age >55) IU/m² IV over 120' 60 mg/m² PO q12h	1,8 (no course 2) 1 1 1-5 2-5 8 (no course 4) 1-10 1(and 15, course 2)
HD courses 3,7	Methotrexate Cytarabine	2500 (B), 5000 (T), 1500 (age >55) mg/m² IV over 24h; FAR 2000 mg/m² IV q12h	1 3,4

↟ Methotrexate 12.5 mg, Cytarabine 50 mg, Dexamethasone 4 mg (or Methylprednisolone 40 mg)

Treatment phase	Drugs	Dosing and administration	Days
HD course 5	Methotrexate Pegaspargase 6-mercaptopurine	2500 (B), 5000 (T), 1500 (age >55) mg/m² IV over 24 h; FAR 2000 (1000 if age >55) IU/m² IV over 120' 25 mg/m² PO	1 3 8-18
Course 8	Vincristine Idarubicin Dexamethasone Cyclophosphamide Prednisone IT prophylaxis (↟)	1.4 mg/m² (max. 2 mg) IV push 10 (7.5 if age >55) mg/m² IV over 30' 5 mg/m² PO q12h 300 (200 if age >55) mg/m² IV over 30' 20 mg/m² PO q12h	1,8 1,8 1-5 1-3 8-12 1,15
Maintenance courses 1,3,5,7,9,11	Cyclophosphamide 6-mercaptopurine Methotrexate IT prophylaxis (↟)	100 mg/m² PO 75 mg/m² PO 15 mg/m² PO/IM	1-4 8-28 8,15,22 1 (courses 3,5)
courses 2,4,6,8,10,12	Vincristine Prednisone 6-mercaptopurine Methotrexate IT prophylaxis (↟)	1 mg/m² (max. 2 mg) IV push 20 mg/m² PO q12h 75 mg/m² PO 15 mg/m² PO/IM	1 1-5 8-28 8,15,22 1 (courses 2,4)
courses 13-24	6-mercaptopurine Methotrexate	75 mg/m² PO 15 mg/m² PO/IM	8-28 1,8,15,22

Bassan R et al,
Blood Adv 2023

GIMEMA 1913 trial

7.7.1 Very High Risk (VHR)

When any one (or more than one) of these features is (are) detectable:

- **B-precursor:**
  - WBC count >100 x10^9/L;
  - adverse cytogenetics/molecular biology such as t(4;11)/MLL rearrangement at 11q23, +8, -7, del6q, t(8;14), low hypodiploidy with 30-39 chromosomes, near triploidy with 60-78 chromosomes, complex with >5 unrelated anomalies.
- **T-precursor:**
  - WBC count >100 x10^9/L;
  - early/late non-cortical immunophenotype EGIL T-I/II/IV (CD1a-);
  - adverse cytogenetics/molecular biology (as above).

7.7.2 High Risk (HR)

When any one (or more than one if applicable) of these features is (are) detectable, in the absence of any VHR feature:

- **B-precursor:**
  - WBC count >30x10^9/L;
  - pro-B immunophenotype;
  - complete remission after cycle 2.
- **T-precursor:**
  - complete remission after cycle 2.

7.7.3 Standard Risk (SR)

When all of these features are detectable, in the absence of any VHR/HR feature:

- **B-precursor:**
  - WBC count <30x10^9/L.
- **T-precursor:**
  - WBC count <100x10^9/L;
  - cortical immunophenotype EGIL T-III (CD1a+).
- **LL**

Bassan R et al,
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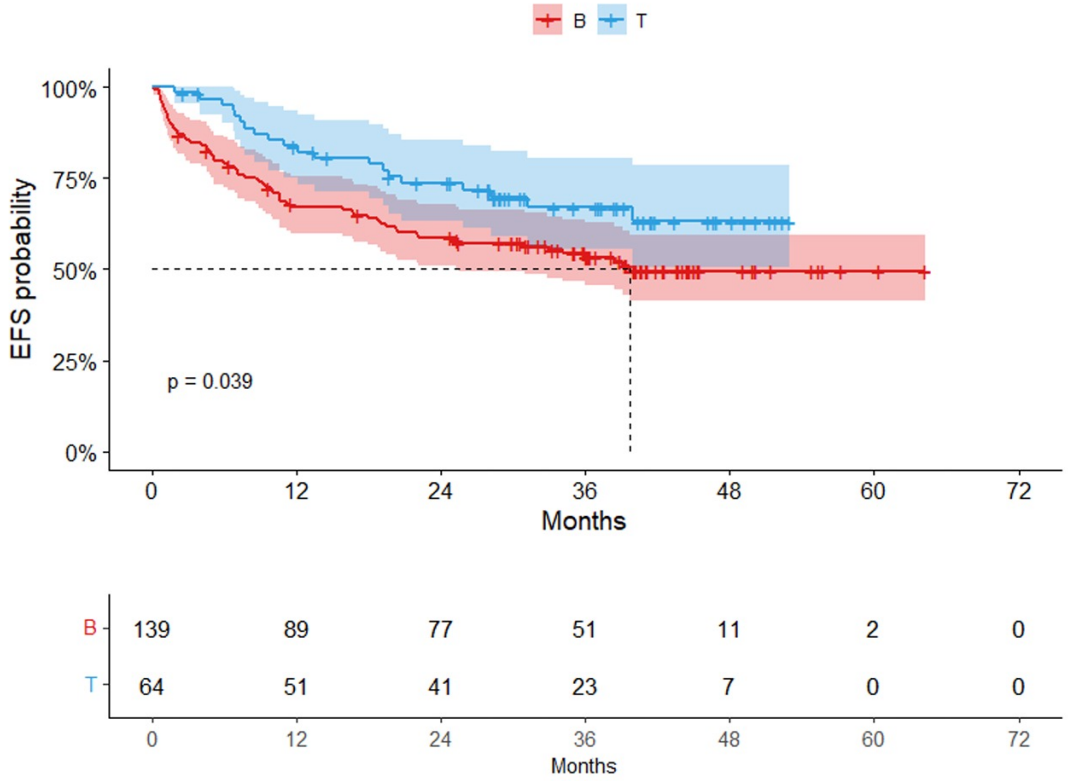


Characteristic	24 Months	36 Months
Lineage		
B	68% (60%, 77%)	61% (53%, 71%)
T	74% (63%, 86%)	67% (56%, 81%)

How can we improve these results?

Bassan R et al, Blood Adv 2023

T-ALL: relapse options

Early

1. Nelarabine combination
2. Other

- Goal to obtain mol CR
- SCT in mol CR if possible
- If no SCT: Cons./Maint.
- **For 'Other' : Toolkit of regimens**

Late

1. Repeated induction

- **Experimental 'targeted therapy'**
  - **Venetoclax + X**
  - **Dasatinib + X**
  - **CD38 antibodies + X**

Italian Campus ALL experience

TABLE 1 Patients' characteristics (118 cases)

Age (years) at diagnosis	
Mean ± SD	36.9 ± 13.4
Median (range)	36 (10-73)
Age (years) at nelarabine therapy	
Mean ± SD	38.1 ± 13.2
Median (range)	37 (18-74)
Diagnosis	
T-ALL	77/118 (65%)
T-LBL	41/118 (35%)
Phenotype	
Early / MatureT	86/118 (73%)
Thymic	32/118 (27%)
Previous lines of therapy	
1	53/118 (45%)
2	47/118 (40%)
≥3	18/118 (15%)
Disease status prior to nelarabine treatment	
Relapsed	67/118 (57%)
Refractory	51/118 (43%)
Time from diagnosis to nelarabine treatment	
Median - months (range)	11 (1-145)
Number of nelarabine cycles / patient	
Median (range)	2 (1-4)
Number of total nelarabine cycles	210

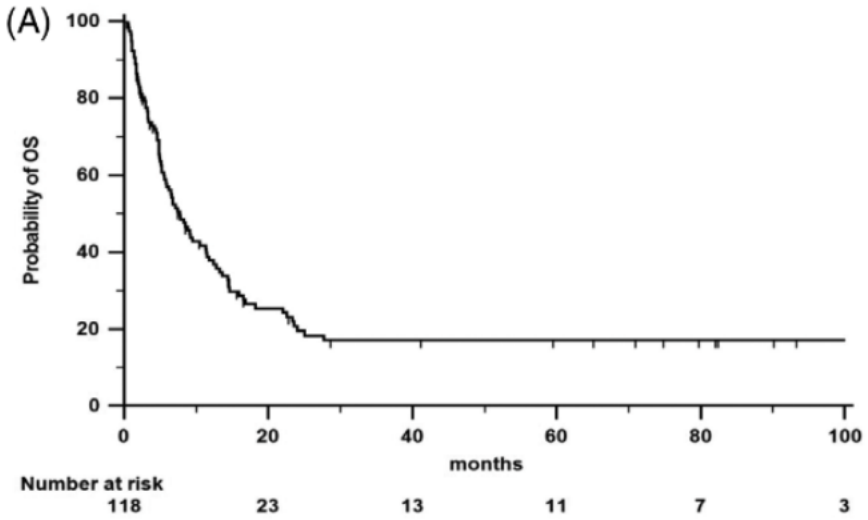
(A) Response to nelarabine	
Complete remission (CR)	43/118 (36%)
Partial remission (PR)	16/118 (14%)
No response (NR)	59/118 (50%)

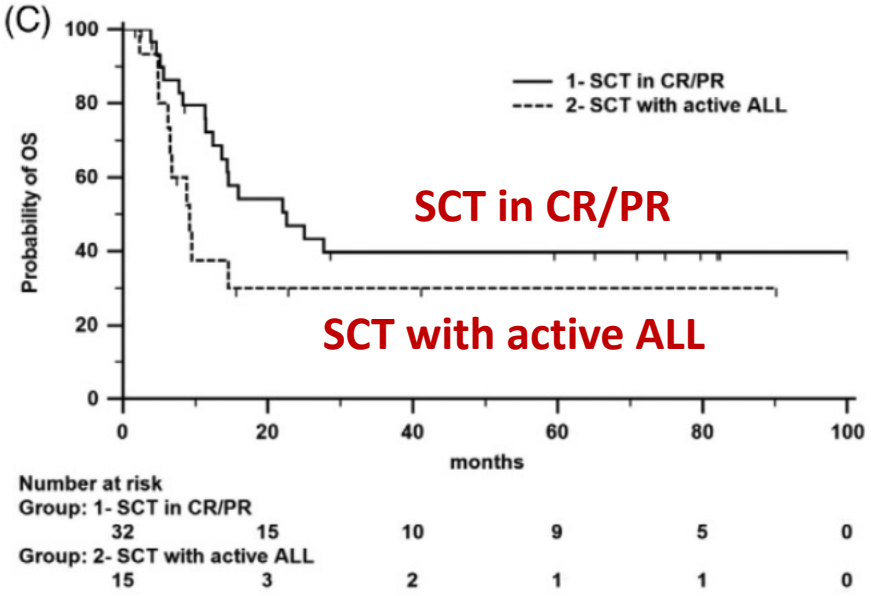
Factors affecting nelarabine response

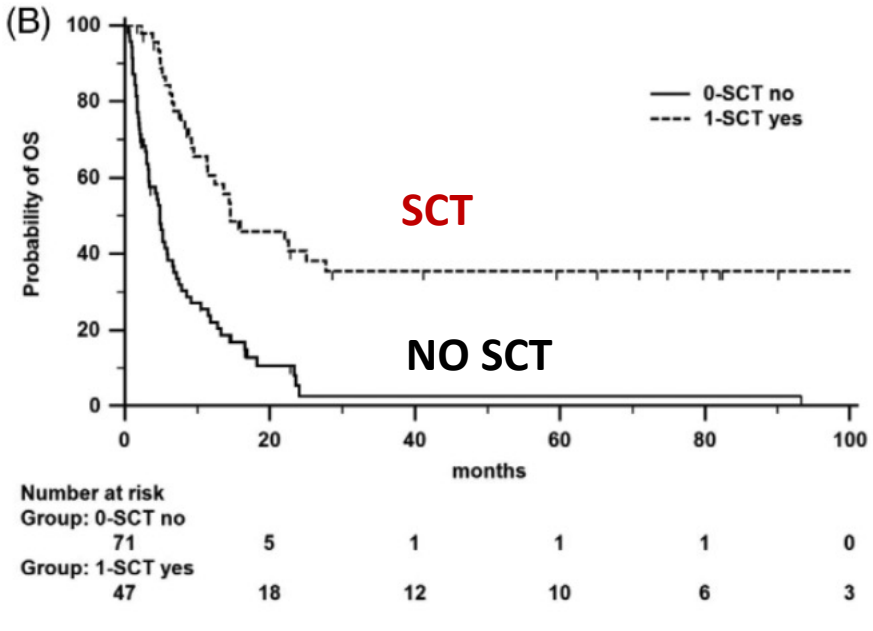
Factor	% ORR (CR + PR)	P*
Age		.71
18-40 y	20/63 (48)	
>40 y	29/55 (33)	
Diagnosis		.43
T-ALL	41/77 (53%)	
T-LBL	18/41 (44%)	
Phenotype		.83
Early T/Mature	17/32 (53)	
Thymic	42/86 (49)	
Previous lines of therapy		.19
1 line	31/54 (57)	
2 or more lines	28/64 (44)	
Disease status before nelarabine		.008
Relapsed	41/67 (61)	
Refractory	18/51 (35)	

Candoni A et al, AJH 2020

Italian Campus ALL experience







Candoni A et al, AJH 2020

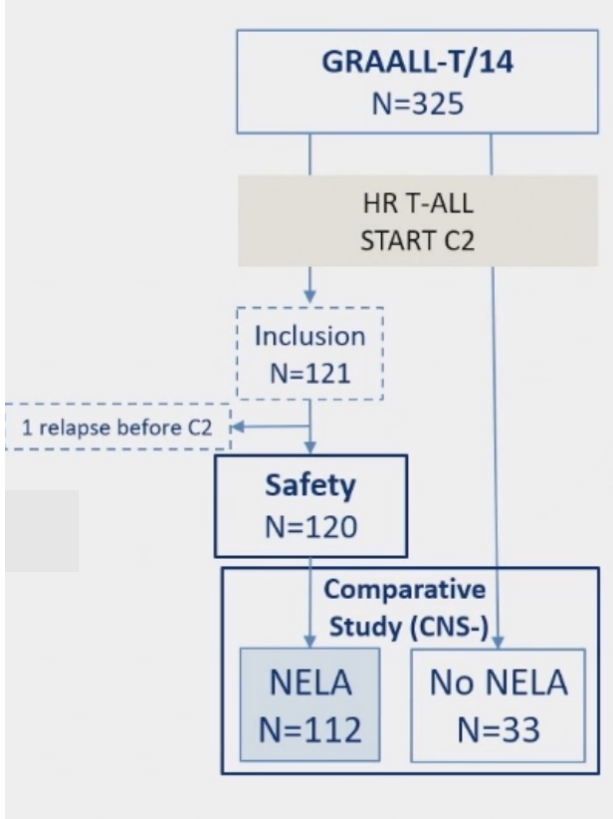
Italian Campus ALL experience

(B) Toxicity and grade	Number of cases (%)
Hematologic toxicity (CTCAE grade III-IV)	59/118 (50%)
Neutropenia (Grade III-IV)	53/118 (45%)
Thrombocytopenia (Grade III-IV)	50/118 (42%)
Extra-hematologic toxicity (any grade)	38/118 (32%)
Grade I-II	14/118 (12%)
Grade III	15/118 (13%)
Grade IV	9/118 (8%)
Type of extra-hematologic toxicity (any grade)	
Neurologic toxicity	16/118 (14%)
Infections	13/118 (11%)
Others	9/118 (8%)
Neurologic toxicity grade III-IV	9/118 (8%)
Adverse events-related deaths	3/118 (3%)

Candoni et al Campus ALL Study (2020)	Gökbuget et al Phase II Study (2011) [6]
118 cases	126 cases
T-ALL 65% / T-LBL 35% REF 43% / REL 57%	T-ALL 85% / T-LBL 15% REF 74% / REL 36%
Median age	Median age
37 (18–74)	33 (18-81)
Total N° of nelarabine cycles: 210	Total N° of nelarabine cycles: 201
RESPONSE	RESPONSE
CR 36%	CR 36%
PR 14%	PR 10%
NR 50%	NR 52%
NE 0%	NE 2%
Transplantation rate 40%	Transplantation rate 29%
TRM 13%	TRM 11%
1-year OS 38%	1-year OS 24%
3-year OS in SCT 40%	3-year OS in SCT 31%

Candoni A et al, AJH 2020

Frontline Consolidation with Nelarabine for Adults with High-Risk T-Cell Acute Lymphoblastic Leukemia. Results of the Graall-2014/T Atriall Phase 2 Study



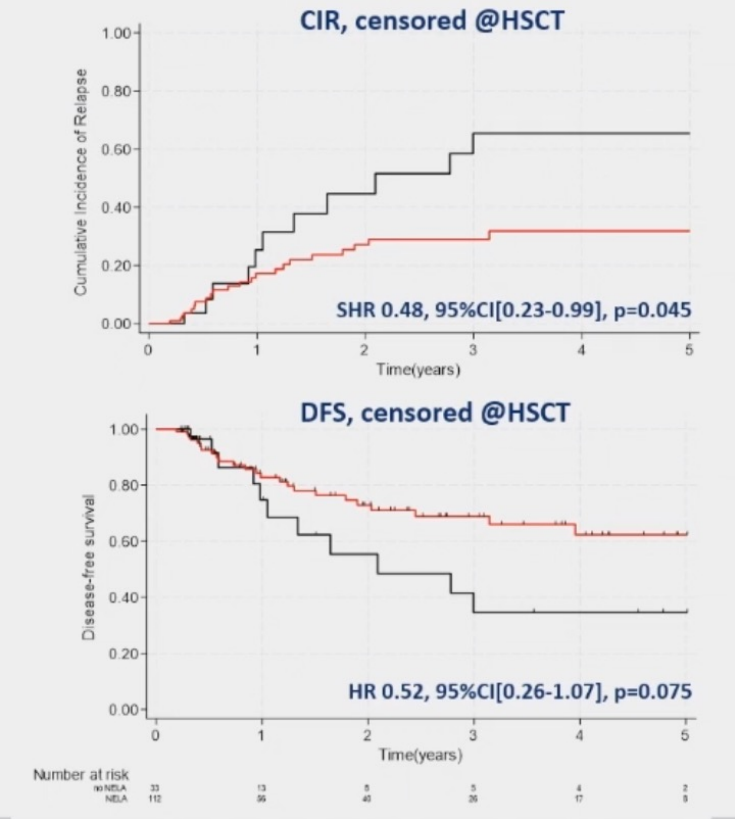
	NELA (ATRIALL) n=112	No NELA N=33	p
MRD response (after conso 2)			
$MRD3_{neg}$, N(%)	75/96 (78)	15/26 (58)	0.05
$MRD3_{neg}$ if MRD1 ≥ 10^{-4} , N(%)	36/55 (65)	5/16 (31)	0.02
Allo-HSCT rate	38/112 (34)	15/33 (45)	0.30
Median follow-up	3.0	5.8	<0.001
3y-CIR (95%CI)	27% (20-37)	47% (31-67)	0.14
3y-CIR, censored at HSCT (95%CI)	29% (20-41)	65% (43-85)	0.045
3y-DFS (95%CI)	67% (56-75)	49% (30-66)	0.32
3y-DFS, censored at HSCT (95%CI)	69% (56-79)	35% (13-57)	0.075
3y-OS (95%CI)	72% (62-80)	76% (56-88)	0.80
3y-OS, censored at HSCT (95%CI)	74% (61-83)	69% (41-86)	0.97

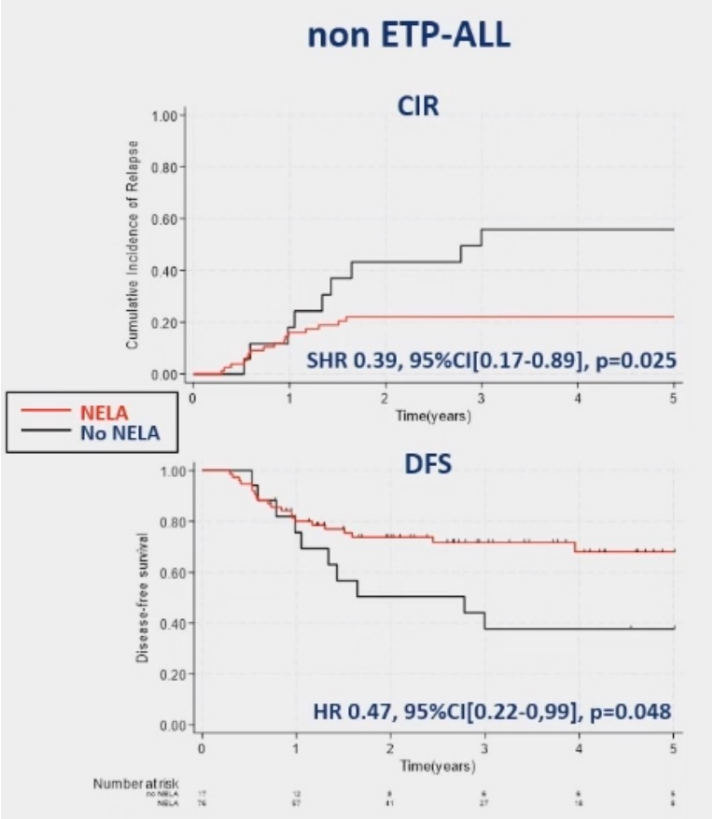
After Nelarabine:

- Significant improvement of MRD response
- No significant reduction in CIR or improvement of DFS
- Significant reduction in CIR censored @HSCT

Boissel N et al, ASH 2023 Abstract 962

Frontline Consolidation with Nelarabine for Adults with High-Risk T-Cell Acute Lymphoblastic Leukemia. Results of the Graall-2014/T Atriall Phase 2 Study





- Patients inelegible to HSCT or with a non-ETP phenotype seem to benefit from Nelarabine in terms of relapse risk reduction and DFS
- The role of Nelarabine in T-LBL was not investigated

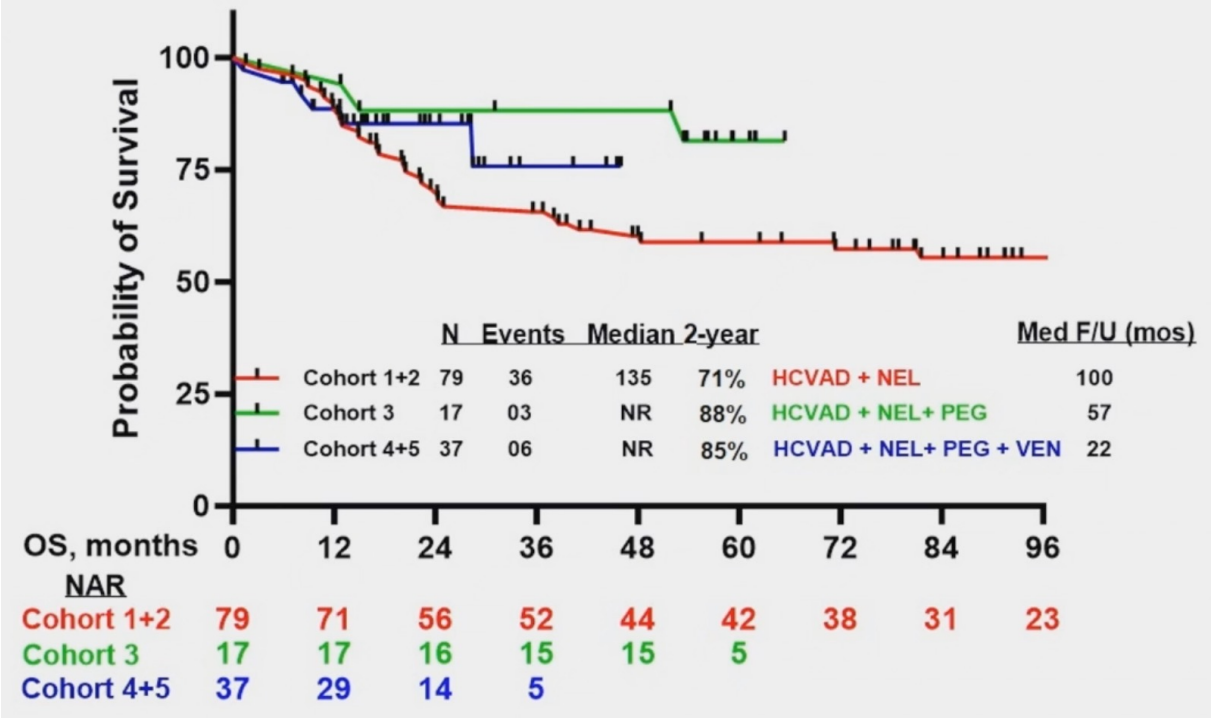
Boissel N et al, ASH 2023, Abstract 962

Nelarabine, Pegylated Asparginase and Venetoclax Incorporated to HCVAD Chemotherapy in the Frontline Treatment of Adult Patients with T-ALL/T-LBL

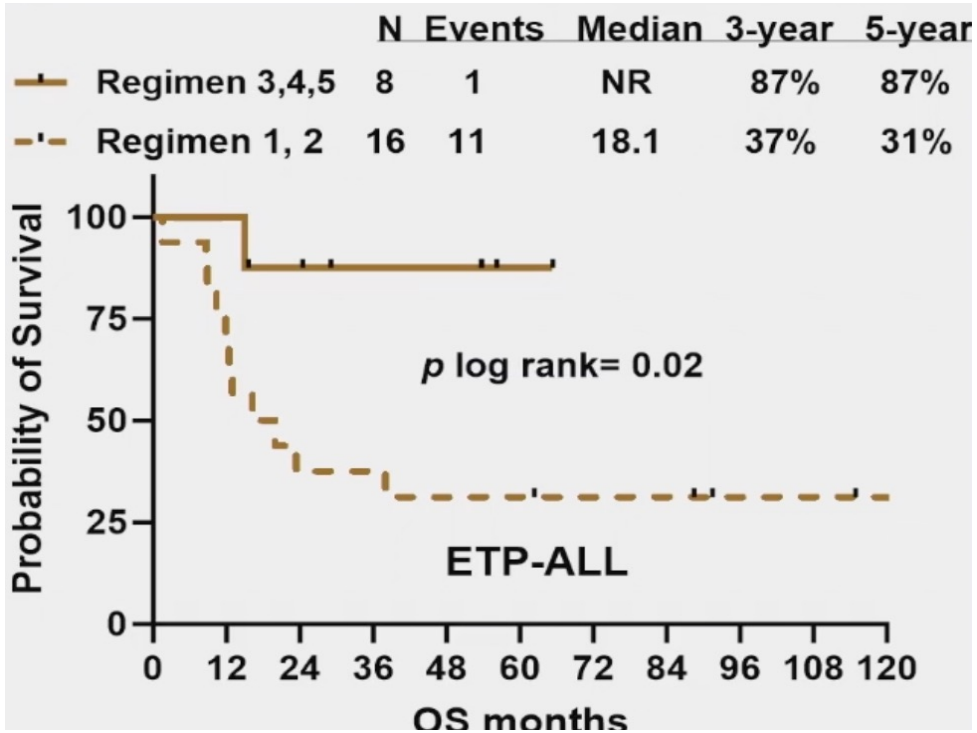
Regimens	N	Year	Hyper-CVAD	Nelarabine (NEL)	Pegasparaginase (PegAsp)	Venetoclax (Ven)	ORR
1	30	2007-2011	Hyper-CVAD 1,3,5,7 MTX/Ara-C 2,4,6,8	After C8 for 2 cycles Cycles 6-7 of maintenance	-	-	96%
2	49	2011-2017		After C4 (4N) and C5 (5N) Cycles 6-7 of maintenance	-	-	98%
3	17	2017-2019			PegAsp with NEL in Cycles 4N and 5N PegAsp with NEL in Cycles 6-7 of maintenance	-	100%
4	16	2019-2021				Days 1-7 of all Induction/ consolidation cycles	100%
5	21	2021-2023				Days 1-7 of C1; Days 1-3 for C2-C8* only for ETP-ALL / MRD+	89%

Jain N et al, ASH 2023, Abstract 963

Nelarabine, Pegylated Asparginase and Venetoclax Incorporated to HCVAD Chemotherapy in the Frontline Treatment of Adult Patients with T-ALL/T-LBL



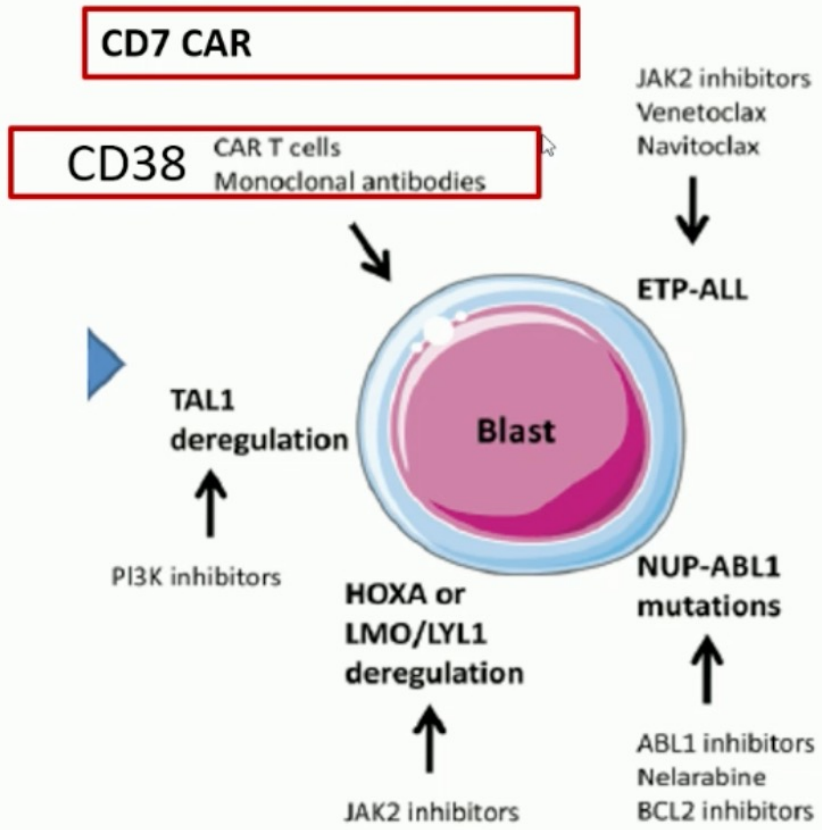
ETP-ALL



- Prolonged thrombocytopenia more common in Ven containing arms

Jain N et al, ASH 2023, Abstract 963

Experimental approaches in T-ALL



Drugs / Pathways

BCL2-Inhibition (e.g. Venetoclax)
JAK Inhibition (e.g. Ruxolitinib, Tofacitinib)
MTOR-Inhibition (e.g.Temsirolimus, Everolimus)
Demethylation (e.g. Azacytidin)
B-RAF inhibition (e.g. Trametinib)
RAF inhibition (e.g. Dabrafenib)
FLT3 inhibition (e.g. Sorafenib, Gilteritinib)
IDH1-Inhibition
CD33 inhibition
CD30 inhibition
SRC/ABL inhibition (e.g. Dasatinib)
(NOTCH1, GSI inhibitors)
CD38

Thomas et al, Exp Opinion Invest Drugs 2023

Daratumumab in T-ALL:Campus ALL experience

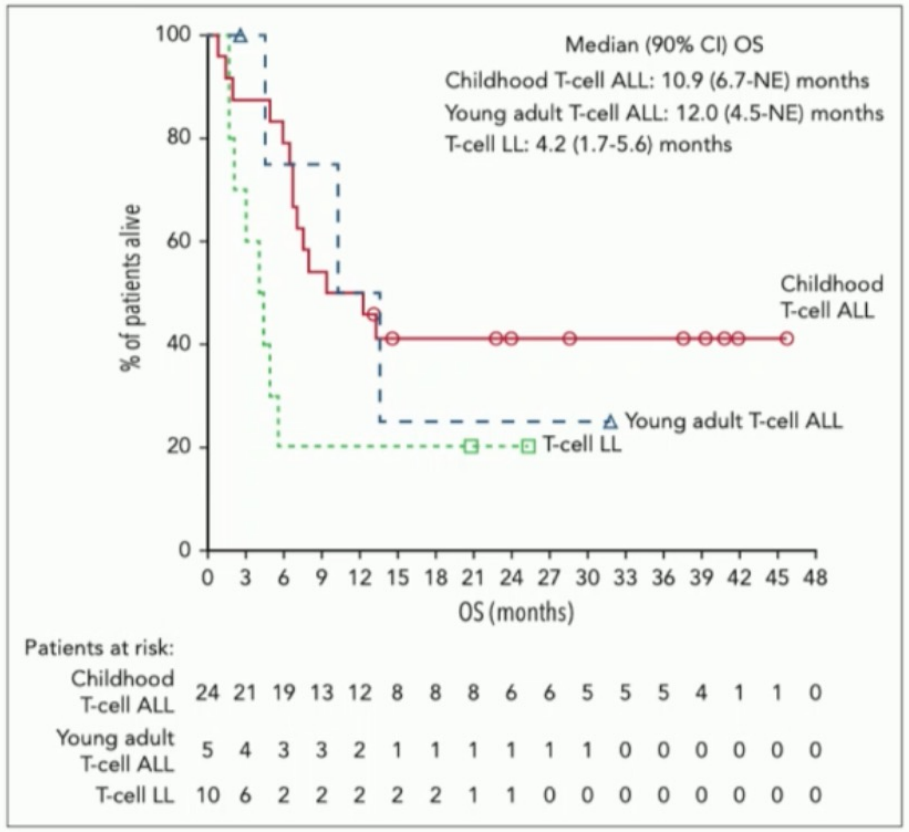
Variable	N. or median	% or range
Male sex	17	85
Type of ALL	18	80
T	13	65
ETP	4	20
B	4	20
MPAL	1	5
Type of LBL	2	10
T	1	5
B	1	5
Firstline treatment		
LAL-1913	11	55
Hyper-CVAD	3	15
AIEOP-BFM	4	20
Others (EWALL, BFM)	2	10
Allo-HCT before daratumumab	9	45
Lines of treatment before daratumumab	3	1 - 4
Age at daratumumab start, years	35	8 - 73
Below 18 years	3	15
Disease status at daratumumab start		
Isolated BM relapse	8	40
Extramedullary and BM	8	40
Extramedullary and MRD positivity	2	10
Extramedullary only	1	5
CR, MRD-positive	1	5
Disease characteristics at daratumumab start		
White blood cells, $x10^9$/L	3.34	0.1 - 39
Platelets, $x10^9$/L	34	1 - 233
Peripheral blood blasts, %	14	0 - 98
Bone marrow blasts, %	45	0 - 100
ECOG at daratumumab start	2	0 - 4
Concomitant chemotherapy	9	45
Time from diagnosis to daratumumab, months	13	7 - 28

Outcome	N. or median	% or range
Response to daratumumab		
Responders	4	20
CR, MRD-negative	2	10
CR, MRD-positive	1	5
PR	1	5
Non-responders	16	80
Stable disease	2	10
Progressive disease	12	60
Not evaluable	2	10
Allo-HCT post-daratumumab	4	20
in CR/PR	2	10
Treatment duration, weeks	2	2-120
Discontinued treatment	19	95

Cerrano M et al, Haematologica 2022

Daratumumab in pediatric relapsed/refractory ALL or Lymphoblastic Lymphoma: the DELPHINUS study

	T-cell ALL	T-LBL
Evaluable	29	10
Age	2-25	5-22
Extramed	17-40%	100%
CR	**52%**	**40%**
CRi/PR*	31%	10%
MRD neg (any)	**41%**	**50%**
SCT rate	**72%**	**30%**



Bhatia et al, Blood 2024

Clinical Trial > Ann Hematol. 2024 Aug;103(8):2993-3004.
doi: 10.1007/s00277-024-05775-z. Epub 2024 Apr 25.

Daratumumab and venetoclax combined with CAGE for late R/R T-ALL/LBL patients: Single-arm, open-label, phase I study

Hui Shi [1], Fan Yang [1], Miaomiao Cao [1], Teng Xu [1], Peihao Zheng [1], Yuelu Guo [1], Guoai Su [1], Shaomei Feng [1], Ruiting Li [1], Rui Liu [1], Haidi Liu [1], Lixia Ma [1], Xiaoyan Ke [2] [3], Kai Hu [4]

Schedule: Dara + Ven with aclarubicin, cytarabine, granulocyte colony-stimulating factor, and etoposide (CAGE)

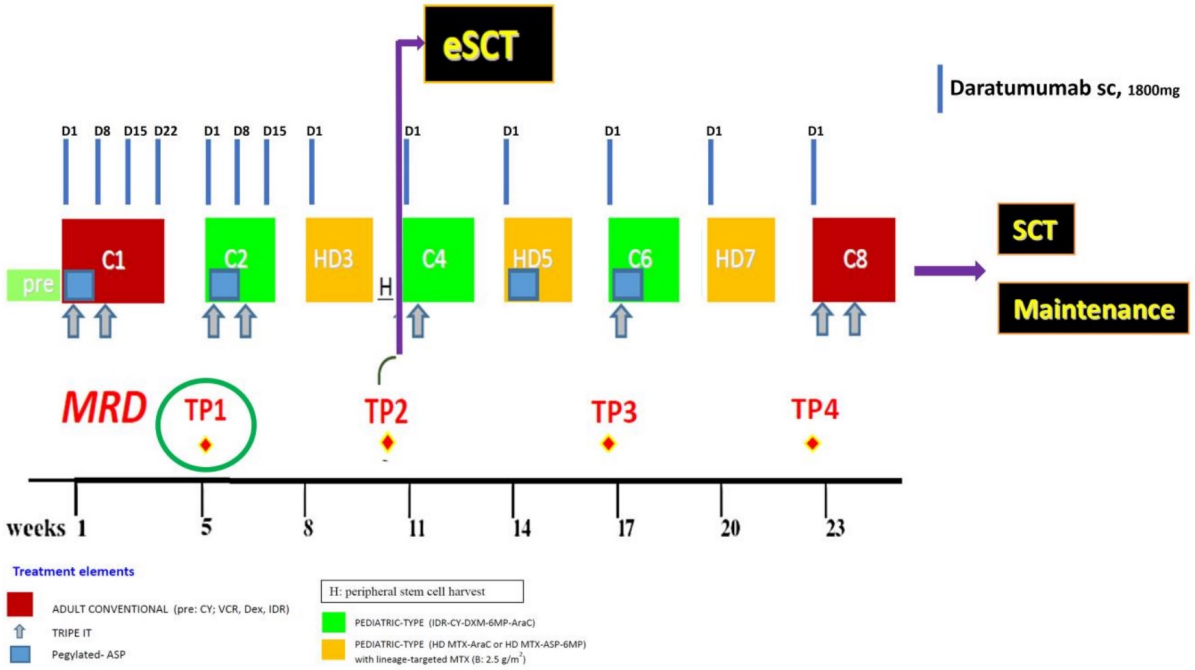
N=21 R/R T-ALL / T-LBL
ORR 57.1%
CR 47.6%
Higher remission rate in ETP vs non-ETP (100% vs 44.4%, p=0.044)

Daratumumab in Adults with Very High-Risk T-Lineage Acute Lymphoblastic Leukemia (ALL) Treated According to the ALL National Treatment Program (DARATALL-VHR)

GIMEMA ALL3024

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche.

EU CT number 2024-511627-34-00
CT.gov identifier NCT06253637



Not yet recruiting

Testing the Addition of Daratumumab to Chemotherapy for Treating Patients With Newly-Diagnosed T-Cell Lymphoblastic Leukemia (T-ALL) and T-Cell Lymphoblastic Lymphoma (T-LL)

ClinicalTrials.gov ID NCT07072585

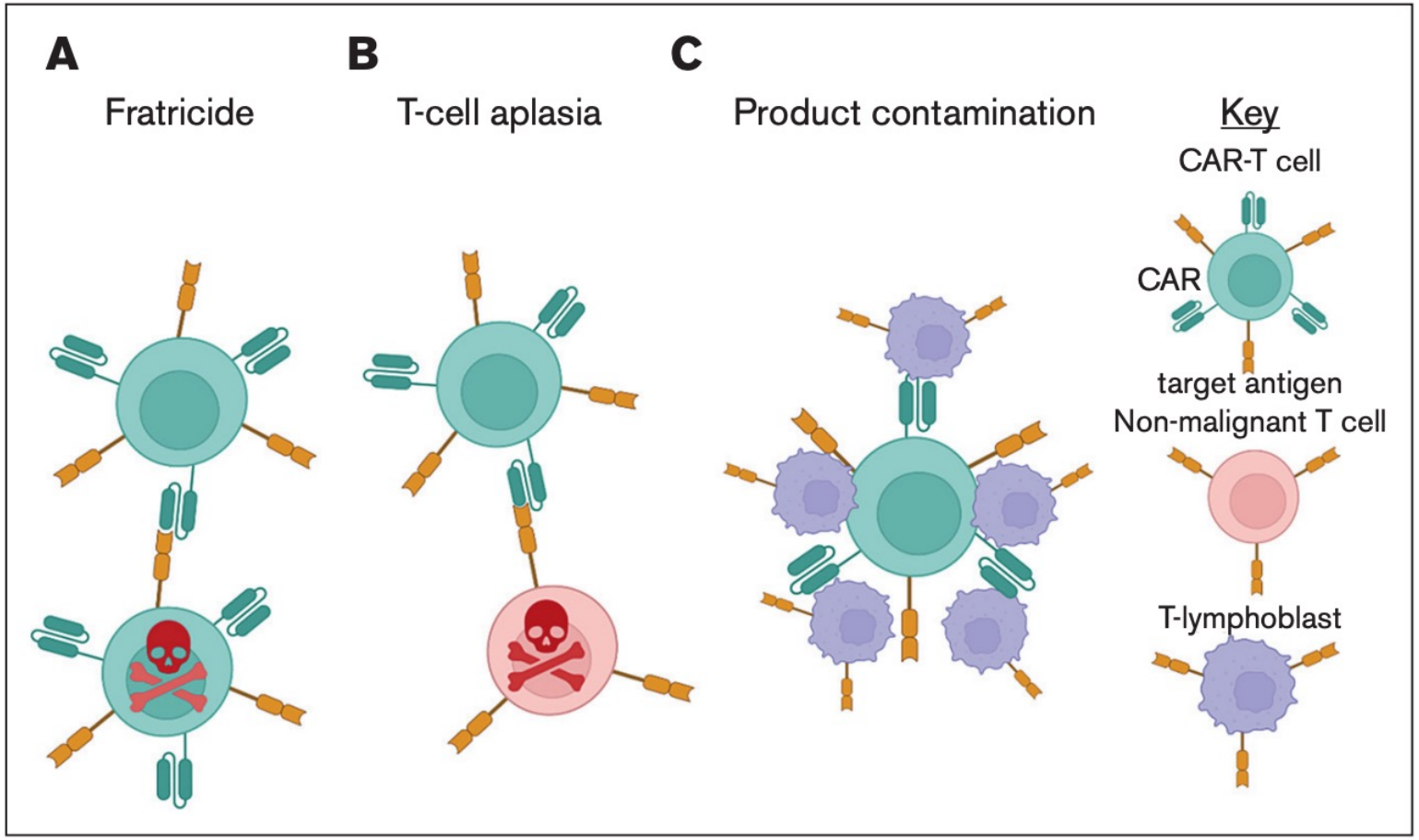
Sponsor Children's Oncology Group

Information provided by Children's Oncology Group (Responsible Party)

Last Update Posted 2025-09-25

www.clinicaltrials.gov

CAR-T in T-ALL: major challanges



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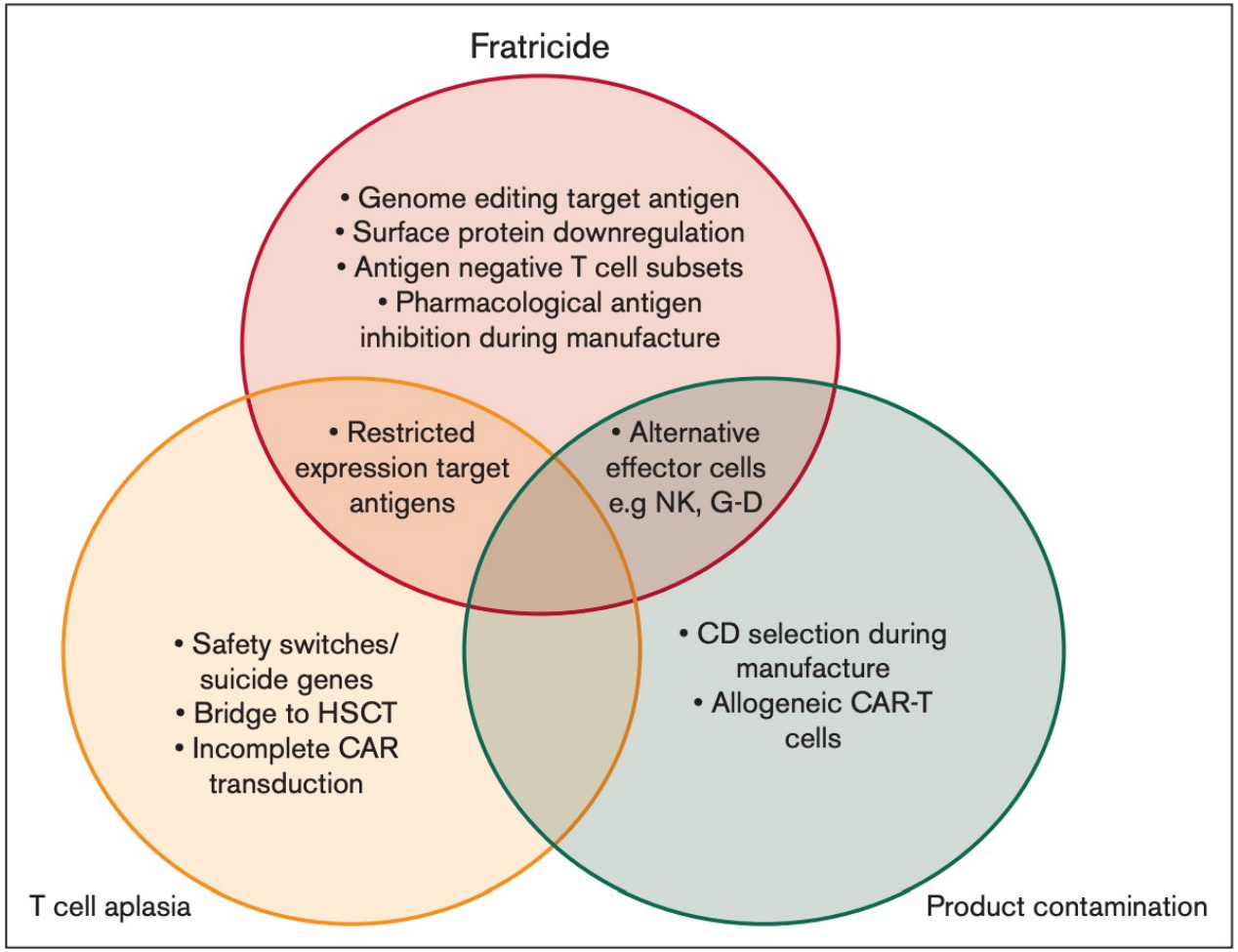
How can we overcome these limits?



Maciocia N et al, Blood Adv 2025

CAR-T in T-ALL

Cell source	Target	Fratricide prevention	Patients enrolled	Patients who received infusion	CR rate a day 30	Toxicity					Survival		Reference
						CRS	ICANS	ICAHT	Infection	GVHD	Median follow-up	PFS	OS	
Auto	CD7	Natural selection	65 (35 T-ALL, 25 T-LBL)	60	94%	Gd 1-2 (80.0%), Gd 3-4 (11.7%)	Gd 1 (3.3%), Gd 4 (1.7%)	Gd ≥3 (61.7%)	36.7% (any Gd), Gd 3 (16%)	3/11 (27%) mild	368.5 d	2 y 53.7%	2 y 63.5%	21
	CD7	PEBL	30	27	85%	Gd 1-2 (71%), Gd 3-4 (8%)	Gd 1 (7%)	Gd ≥3 (100%)	Gd 2 (8%)	Gd 2 (4%)	12 mo	1 y 22%	1 y 79%	24
	CD7	PEBL	8 (1 T-ALL, 1 MPL, 6 T-LBL)	8	75%	Gd 1-2 (87.5%), Gd 4 (12.5%)	Nil	Any Gd (100%)	Gd 5 (12.5%)	Nil	N/A	N/A	N/A	23
	CD7	PEBL	20*	17	94%	Gd 1-2 (77%)	Gd 1 (12%)	Gd ≥2 (100%)	Gd 1-2 (18%), Gd 3 (29%)	N/A	15 mo	N/A	N/A	24
Allo	CD7	PEBL	20	20	85%	Gd 1-2 (90%), Gd ≥3 (10%)	Gd 1-2 (15%)	Gd ≥3 (100%)	Gd 3-4 (5%), Gd 5 (20%)	Gd 1-2 (60%)	27 mo	2 y 36.8%	2 y 42.3%	26
	CD7	CRISPR/ Cas9 CD7 KO	28	26	52%	88.5% (any Gd), Gd ≥3 (19%)	Gd 1 (7.7%)	Neutropenia (19.2%)	Gd 3-4 (19.2%)	Gd 2 (3.8%)	N/A	N/A	N/A	27
	CD7	CRISPR/ Cas9 CD7 KO	12 (7 T-ALL, 4 T-LBL, 1 AML)	12	64%	Gd 1-2 (83%)	Nil	Gd 4 neutropenia (100%)	Gd 5 (8%)	Nil	10.5 mo	N/A	N/A	30
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Allo	CD70	CRISPR/ Cas9 CD70 KO	18 (TCL)	18	22%	Gd 1-2 (56%)	Gd 1-2 (17%)	N/A	Gd 1-2 (28%), Gd ≥3 (22%)	Nil	N/A	N/A	N/A	35

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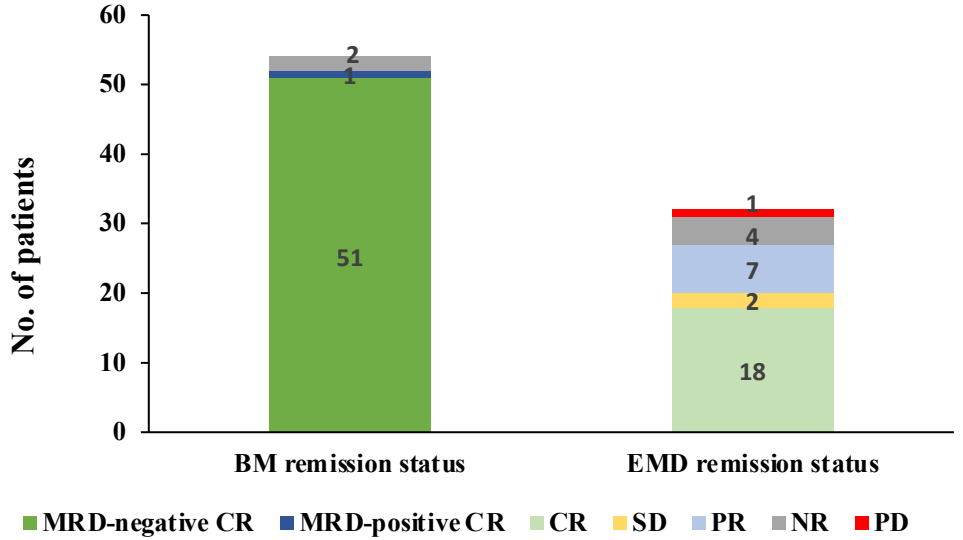
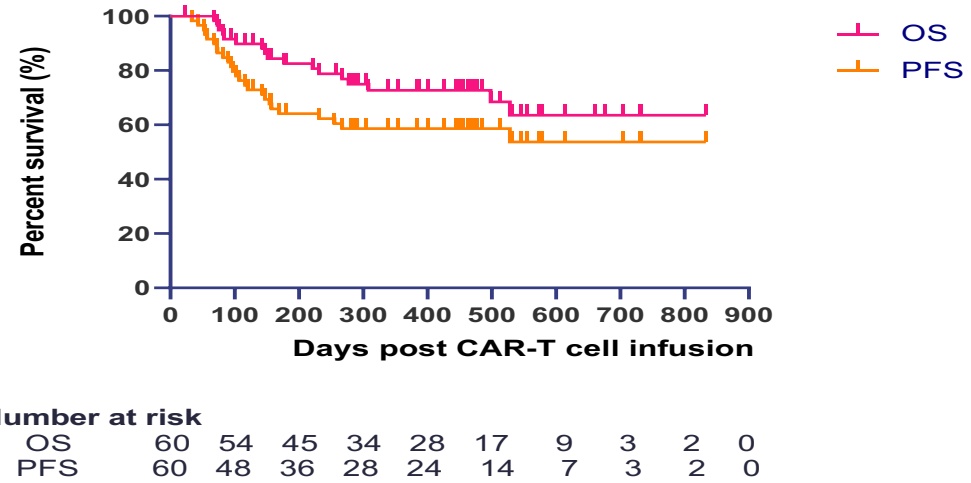
Auto CD7 CAR-T in T-ALL

- 60 pts with R-R T-ALL (n=35) and T-LBL (n=25); median age 19 yrs (2-47)
- Rx single dose 5 x 10^5/Kg to 2 x 10^6/Kg
- Median prior lines of Rx 5 (2-15)
- Median F/U 1 yr
- **D28 MRD-negative CR 94%;**
  - 32 pts with EMD 56% CR and 22% PR
- 6 pts G3 CRS and 1 had G4 CRS
- 1 pt G4 ICAN
- **2-yr OS 63%;** EFS 54%





Zhang . AJH. 2023

CAR-T in T-ALL

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Allogeneic CD5-specific CAR-T therapy for relapsed/refractory T-ALL: a phase 1 trial

Received: 20 December 2023

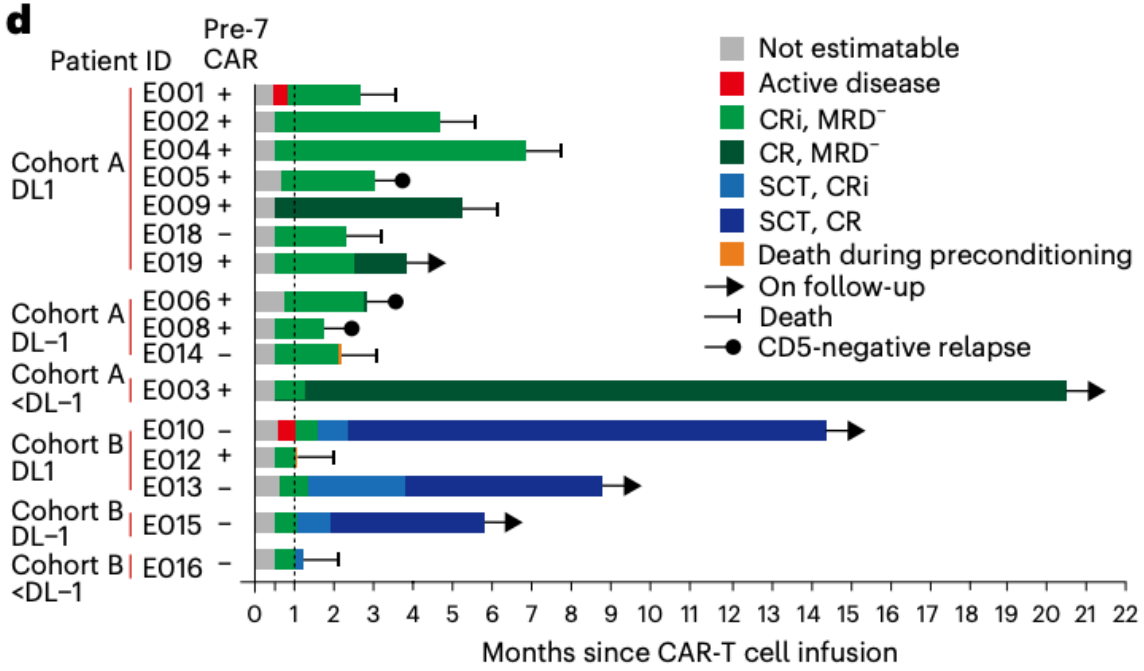
Accepted: 30 August 2024

Published online: 1 October 2024

Check for updates

Jing Pan[1,13] ✉, Yue Tan[2,3,13], Lingling Shan[2,3,13], Samuel Seery[4], Biping Deng[5], Zhuojun Ling[1], Jinlong Xu[1], Jiajia Duan[1], Zelin Wang[1], Kai Wang[1], Xinjian Yu[6], Qinlong Zheng[6], Xiuwen Xu[6], Guang Hu[7], Taochao Tan[7], Ying Yuan[8], Zhenglong Tian[9], Fangrong Yan[10], Yajing Han[2,3], Jiecheng Zhang[11] & Xiaoming Feng[2,3,12] ✉

N=19
CD5-edited cells
Lent 4-1BBz
CR rate 100%
4/12 allo SCT
High rates of infecition



Pan J et al, Nat Med 2024

CAR-T in T-ALL

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Maciocia N et al, Blood Adv 2025

Donor-Derived CD7 Chimeric Antigen Receptor T Cells for T-Cell Acute Lymphoblastic Leukemia: First-in-Human, Phase I Trial

Jing Pan, MD[1]; Yue Tan, BS[2]; Guoling Wang, BS[2]; Biping Deng, MS[3]; Zhuojun Ling, MD[4]; Weiliang Song, MD[4]; Samuel Seery, PhD[5,6]; Yanlei Zhang, MS[7]; Shuixiu Peng, MS[7]; Jinlong Xu, MD[4]; Jiajia Duan, MD[4]; Zelin Wang, MD[4]; Xinjian Yu, MD[8]; Qinlong Zheng, MD[8]; Xiuwen Xu, MD[8]; Ying Yuan, PhD[9]; Fangrong Yan, PhD[10]; Zhenglong Tian, PhD[11]; Kaiting Tang, BS[4]; Jiecheng Zhang, BS[12]; Alex H. Chang, PhD[7,13]; and Xiaoming Feng, PhD[2,14]

- 20 patients (children and adults)
- Donor-derived CAR-T (new or future allo donor)
- Lenti-41bbz

- CD7 ER retention strategy

Characteristic	All (N = 20)
Median age, years (range)	11 (2-43)
Male, No. (%)	15 (75)
Previous therapy	
Median lines of therapy (range)	3 (2-4)
Radiotherapy, No. (%)	4 (20)
Allogeneic SCT, No. (%)	12 (60)
DLI, No. (%)	9 (45)
Primary refractory disease, No. (%)	1 (5)
≥ grade 3 cytopenia,[a] No. (%)	16 (80)
Baseline disease burden[b]	
Bone marrow blasts, %	
> 25	6 (30)
5-25	5 (25)
0.01-5	7 (35)
< 0.01	2 (10)
Median marrow blasts (range)	6.17 (0-87.99)
EMD, No. (%)	
CNSL	4 (20)
Diffused	4 (20)

Pan J et al, JCO 2021

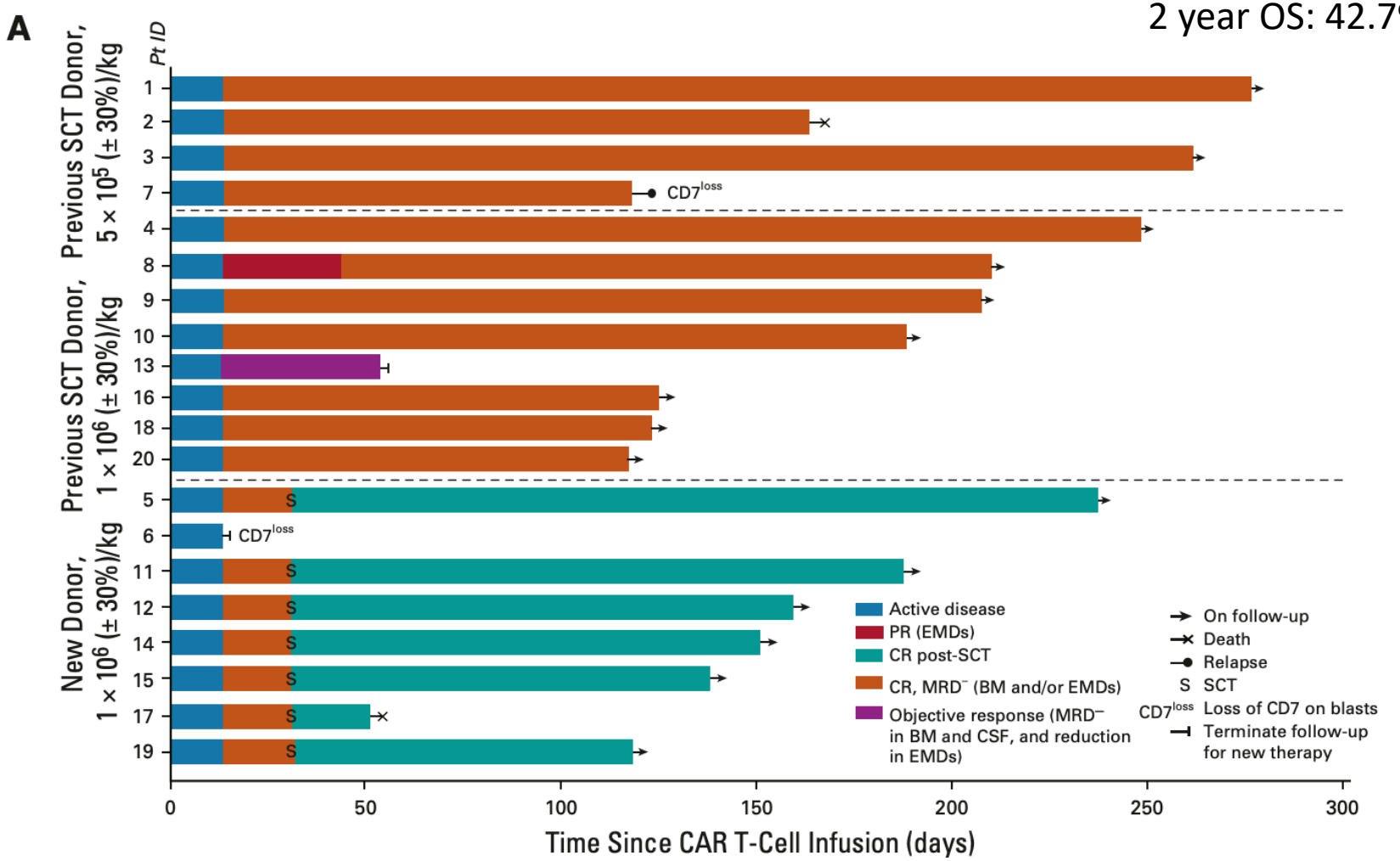
Safety

AE	Grade 1	Grade 2	Grade 3	Grade 4
CRS				
Total score	10 (50)	8 (40)	1 (5)	1 (5)
Fever	20 (100)	0	0	0
Hypoxia	0	8 (40)	1 (5)	1 (5)
Hypotension	0	0	2 (10)	0
ICANS				
Total score	3 (15)	0	0	0
ICE score	3 (15)	0	0	0
Depressed consciousness	0	0	0	0
Seizure	0	0	0	0
Motor weakness	0	0	0	0
Elevated ICP or cerebral edema	0	0	0	0

Pan J et al, JCO 2021

Response

Median follow up 27 months
2 year OS: 42.7%



Pan J et al, JCO 2021

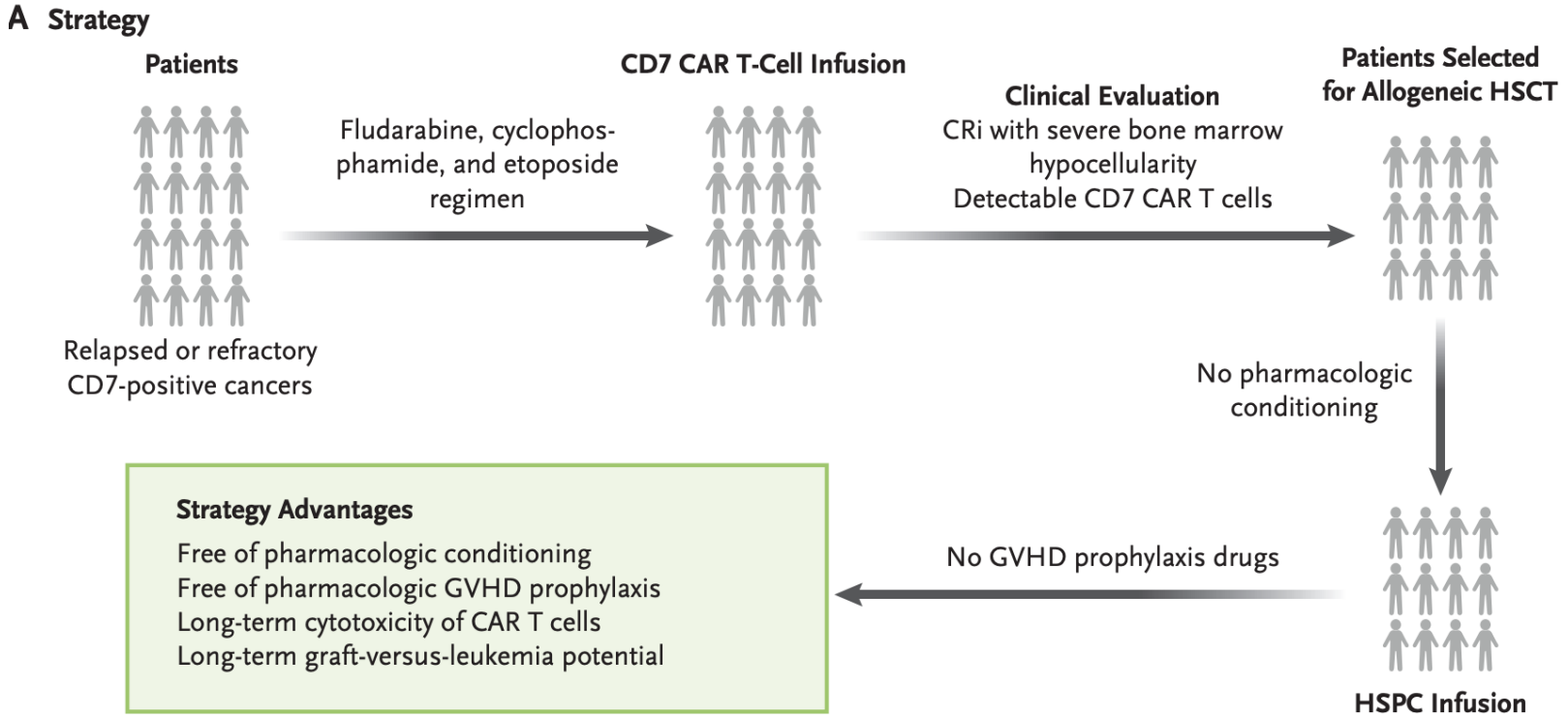
ORIGINAL ARTICLE

Sequential CD7 CAR T-Cell Therapy and Allogeneic HSCT without GVHD Prophylaxis

Yongxian Hu, M.D., Ph.D., Mingming Zhang, M.D., Ph.D., Tingting Yang, M.D., Zhuomao Mo, Ph.D., Guoqing Wei, M.D., Ph.D., Ruirui Jing, Ph.D., Houli Zhao, M.D., Ph.D., Rongrong Chen, M.D., Cheng Zu, M.D., Tianning Gu, M.D., Pingnan Xiao, M.D., Ph.D., Ruimin Hong, M.D., Jingjing Feng, M.D., Ph.D., Shan Fu, M.D., Ph.D., Delin Kong, Ph.D., Huijun Xu, B.S., Jiazhen Cui, M.S., Simao Huang, M.S., Bin Liang, M.D., Xiaolin Yuan, M.D., Qu Cui, M.D., Ph.D., Hongshan Guo, Ph.D., Yunxian Yu, Ph.D., Youqin Feng, M.D., Chunxiang Jin, M.D., Jiangtao Ren, Ph.D., Alex H. Chang, Ph.D., Dongrui Wang, Ph.D., and He Huang, M.D., Ph.D.

NEJM 2025

Study Design



Hu Y et al, NEJM 2025

Patients' characteristics

Table 1. Baseline Characteristics and Clinical Outcomes.*

Characteristic	Value (N=10)
Median age (range) — yr	56.5 (13.7–72.5)
Sex — no. (%)	
Female	6 (60)
Male	4 (40)
Primary disease — no. (%)	
Acute myeloid leukemia	7 (70)
T-cell acute lymphoblastic leukemia	2 (20)
T-cell lymphoblastic leukemia	1 (10)
Median no. of previous therapies (range)	9.5 (4–15)
Median percentage of blasts in bone marrow (range)	36.0 (2–87)
Median CD7 expression on blast cells (range) — %	93 (80.7–97.7)
Extramedullary involvement — no. (%)	2 (20)

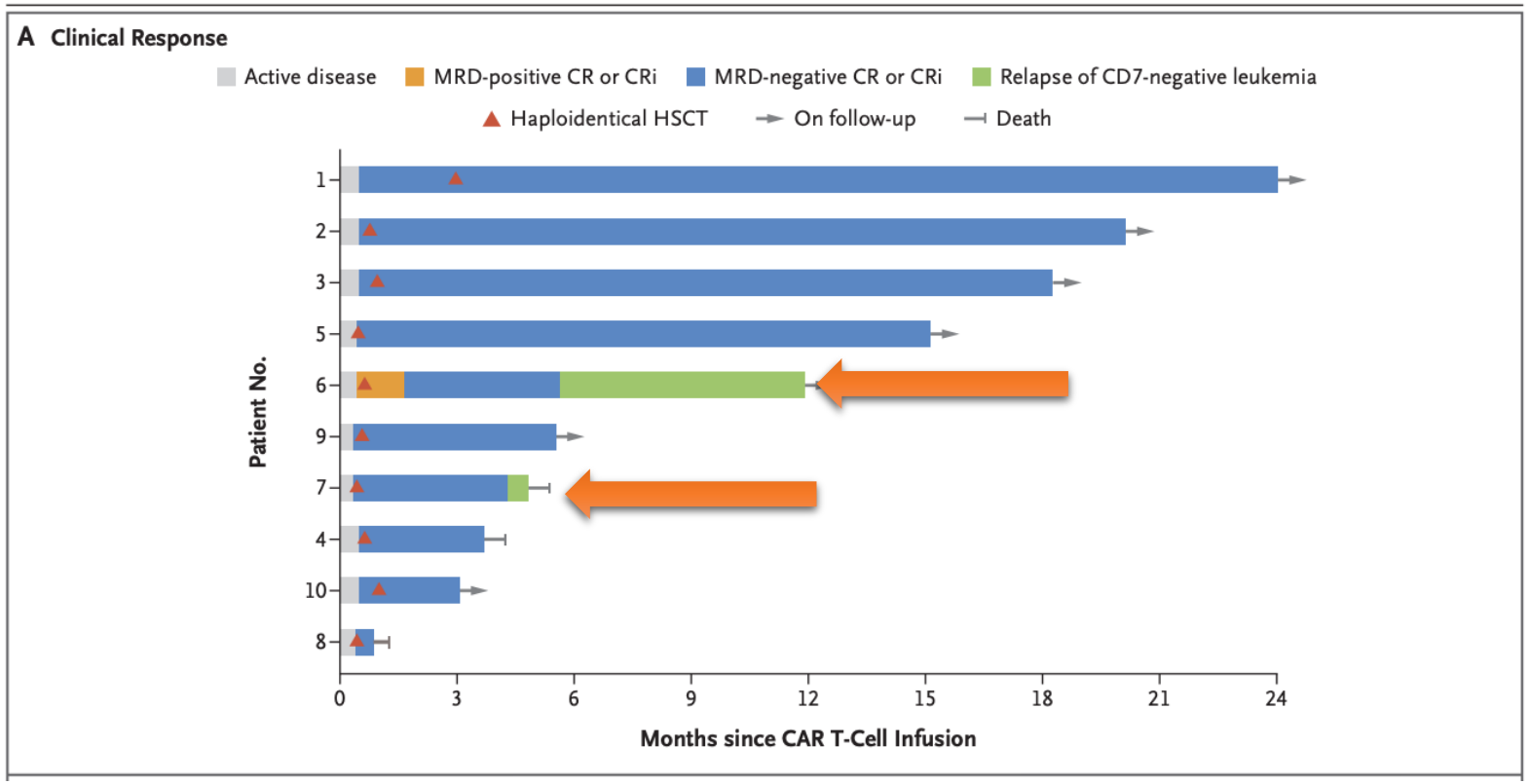
Hu Y et al, NEJM 2025

Patients' characteristics

Clinical efficacy after CAR-T cell therapy — no. (%)‡	
MRD-negative complete remission with incomplete hematologic recovery	9 (90)
MRD-positive complete remission with incomplete hematologic recovery	1 (10)
Median interval from CAR T-cell infusion to HSPC infusion (range) — days	19 (15–89)
Donor relationship — no. (%)	
Children	8 (80)
Brother	2 (20)
Median donor age (range) — yr	33.9 (17.2–42.4)
HLA match of HSCT graft — no. (%)	
5 of 10 alleles matched	7 (70)
6 of 10 alleles matched	3 (30)
Donor–recipient ABO match — no. (%)	
Matched	6 (60)
Mismatched	4 (40)
Donor sex — no. (%)	
Female	1 (10)
Male	9 (90)

Hu Y et al, NEJM 2025

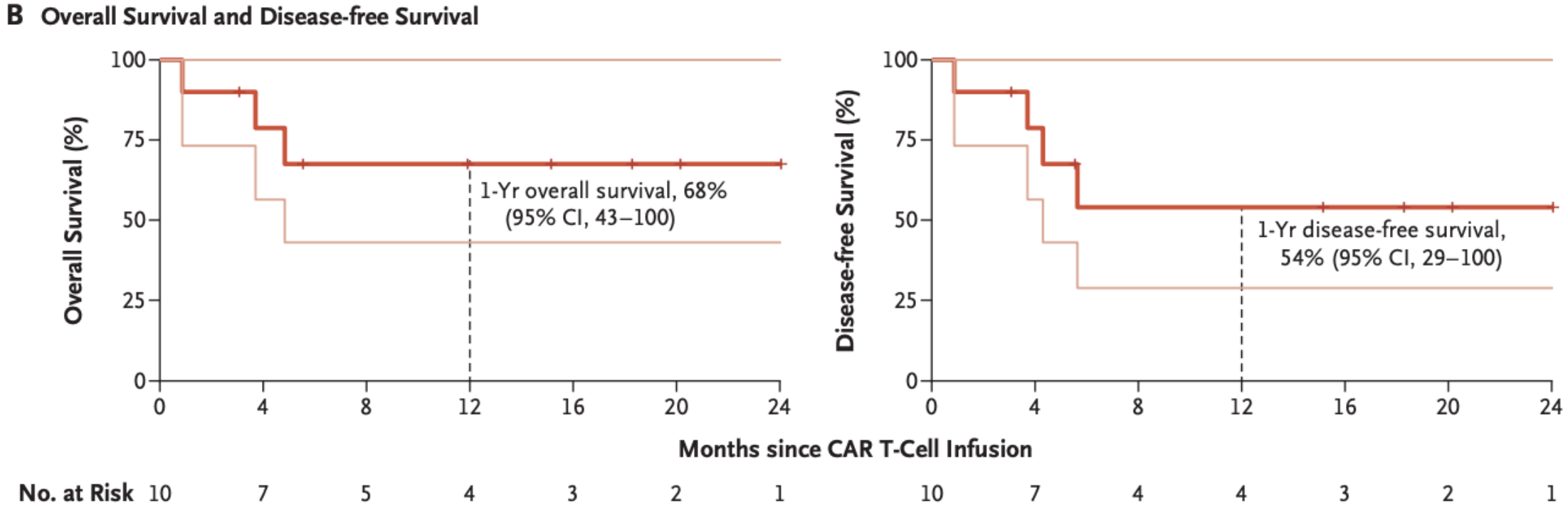
Outcome



Hu Y et al, NEJM 2025

Survival

Median follow up: 15.1 months



Hu Y et al, NEJM 2025

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Allo	CD5	CRISPR/ Cas9 CD5 KO	19 (T-ALL)	16	94%	Gd 1-2 (75%)	Gd 1-2 (25%)	Gd ≥3 (100%)	Gd 3 (12%), Gd 5 (25%)	Gd 1 (69%)	14.3 mo	N/A	NR (cohort B), 4.6 mo (cohort A)	33
Auto	TRBC1	None	12 (TCL)	12	50%	Any Gd (50%)	Nil	Gd 3-4 neutropenia (80%)	None Gd ≥3	N/A	N/A	N/A	N/A	34
Allo	CD70	CRISPR/ Cas9 CD70 KO	18 (TCL)	18	22%	Gd 1-2 (56%)	Gd 1-2 (17%)	N/A	Gd 1-2 (28%), Gd ≥3 (22%)	Nil	N/A	N/A	N/A	35

Maciocia N et al, Blood Adv 2025

ASH 2025

Abstract Number : abs25-11804

Abstract Title : WU-CART-007, a CD7-directed allogeneic CAR-T cell therapy for R/R T-cell acute lymphoblastic leukemia/lymphoma: Phase 1/2 correlative data and long-term follow-up update

Category: 700s - Transplantation and Adoptive Cell Therapies

Review Category: 704. Cellular Immunotherapies: Early Phase Clinical Trials and Toxicities

Authors

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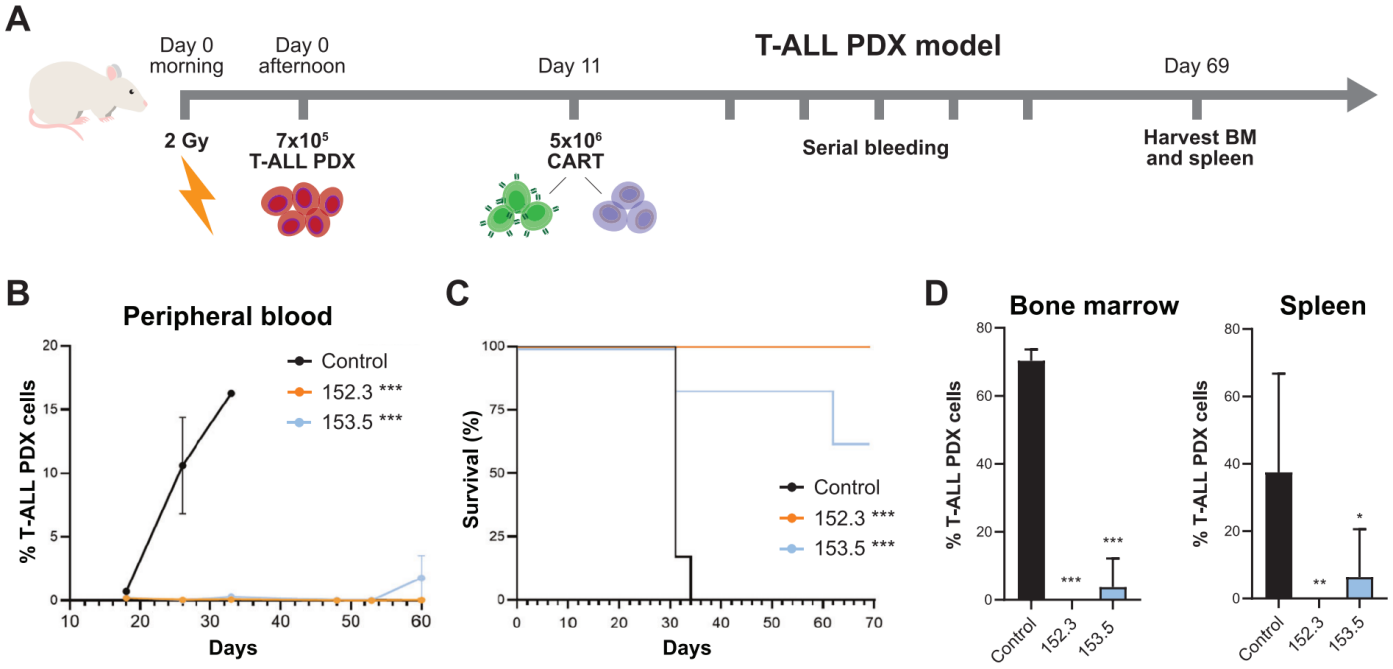
New target: CD84



CD84 (SLAMF5) is a homophilic cell surface glycoprotein in the SLAMF family, with two extracellular immunoglobulin-like domains: a membrane-distal V-set and a membrane-proximal C2-set.

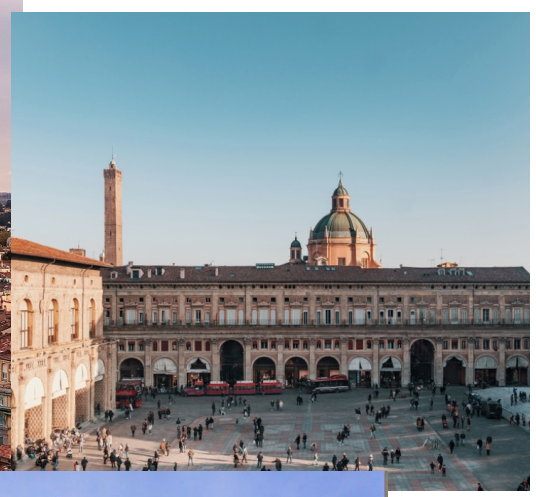
It is widely expressed on immune cells, especially monocytes, memory B and T lymphocytes, and platelets, where it plays a role in monocyte activation, T-B cell interactions, and B-cell tolerance at the germinal center checkpoint

Perez Amil L et al, Leukemia 2025

Take home messages

- ✓ Outcome of T-ALL patients if treated with a pediatric inspired approach has been improved.
- ✓ Options at relapse are still limited, mainly represented by chemotherapy.
- ✓ CAR-T cells are currently in clinical development in R/R T-ALL setting
- ✓ CD7- and CD5-targeting CAR-T have shown impressive response rates with some durable remissions, especially when consolidated with allo-HSCT. These data provide evidence that CAR-T can be highly effective against T-ALL.
- ✓ Manufacturing has been feasible, using various strategies to overcome fratricide, with no reports of lymphoblast contamination.
- ✓ Significant hurdles remain: how to improve long-term survival without transplantation, how to reduce rates of antigen-negative relapse, how to minimize infectious toxicity, and the optimal approach to develop effective allogeneic products.
- ✓ Despite these challenges, it seems likely that cellular therapies may indeed provide a cure for more patients with T-cell malignancies in the near future (dual targeting? Others?)

Thank you!



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