
CD19 directed CAR T-cells in Acute Lymphoblastic Leukemia

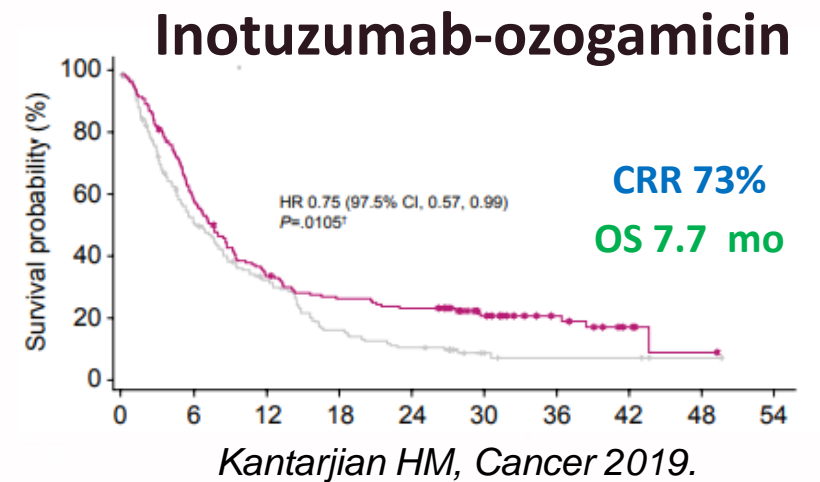
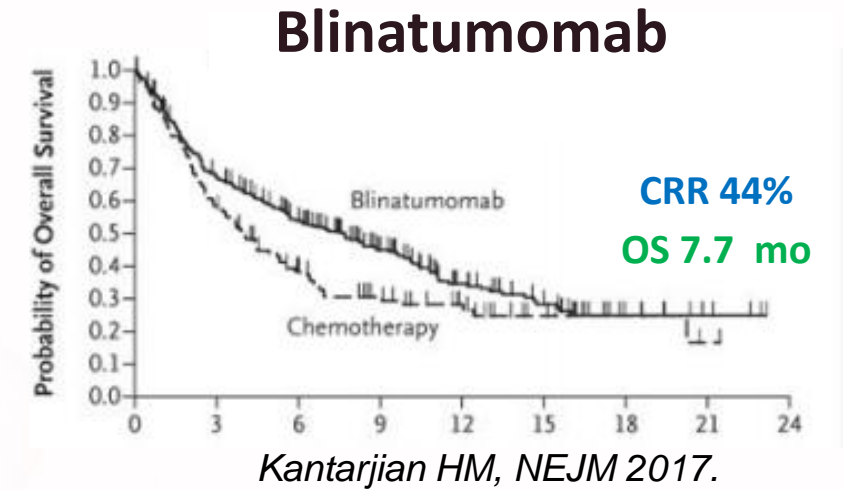
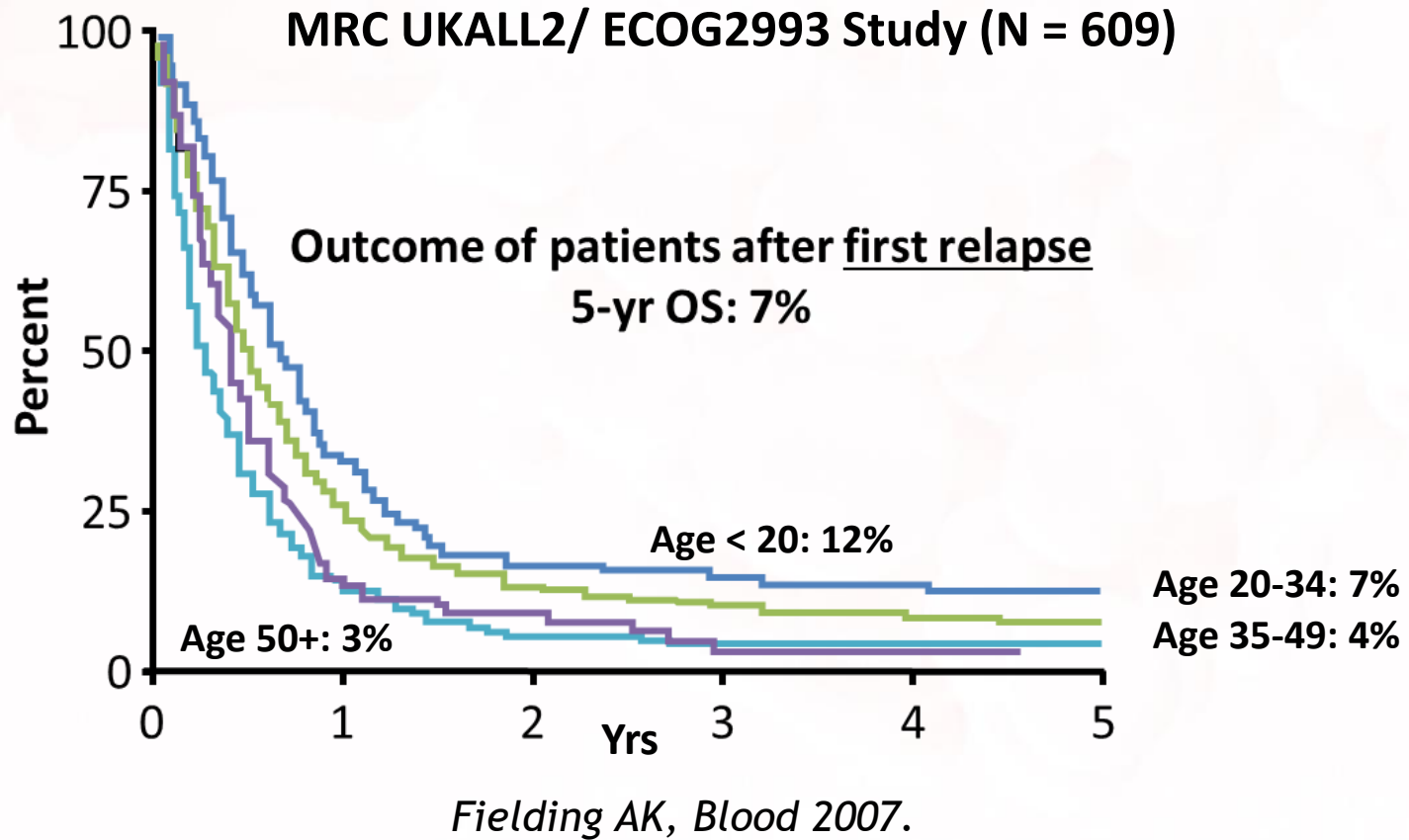
Valentín Ortiz-Maldonado

04/11/2021

Disclosures

- **Research grants:** Fundación Española de Hematología y Hemoterapia
- **Travel grants:** Kite, Celgene, Novartis, Roche, Takeda & Janssen
- **Consultant or advisory fees:** Kite, Celgene-BMS, Novartis & Janssen
- **Honoraria:** Kite
- **Employment:** Hospital Clínic de Barcelona

Prognosis of R/R B-ALL: an unmet need



CAR-T cell therapy for R/R ALL

Patients	Product	Scfv	ScFv Origin	Co-stimulaion	Group	Reference
PEDIATRICS + YOUNG ADULTS						
75 kids (up to 25y)	CTL019	FMC63	Murine	4-1BB	UPenn	Maude et al, NEJM 2018
24 kids (up to 20y)	KTE-X19	FMC63	Murine	CD28	Kite	Wayne AS et al, EHA 2021
45 kids (up to 25y)	JCAR017	FMC63	Murine	4-1BB	FHCRC	Gardner et al, Blood 2017
16 kids (+6 adults)	-	FMC63	Murine	CD28	Sheba MC	Jacoby E et al, Am J Hematol 2018
14 kids	AUTO1	CAT	-	4-1BB	UCL	Ghorashian S et al, Nat Med 2019
11 kids (up to 19y)	ARI-0001	A3B1	Murine	4-1BB	HCB	Ortiz-Maldonado et al, Mol Ther 2020
ADULTS						
53 adults	19E3/1928z	FMC63	Murine	CD28	MSKCC	Park et al, NEJM 2018
35 adults	CTL019	FMC63	Murine	4-1BB	UPenn	Frey et al, JCO 2019
53 adults	JCAR017	FMC63	Murine	4-1BB	FHCRC	Hay et al, Blood 2019
55 adults	KTE-X19	FMC63	Murine	CD28	Moffit	Shah et al, Lancet 2021
16 adults	AUTO1	CAT	-	4-1BB	UCL	Roddie et al, ASCO 2019
27 adults (> 18y)	ARI-0001	A3B1	Murine	4-1BB	HCB	Ortiz-Maldonado et al, Mol Ther 2020

Outcomes of CAR-T cells on ALL: **safety**

PEDIATRICS + YOUNG ADULTS					
Patients	Product	Co-stimulaion	Grade ≥3 CRS (%)	Grade ≥3 ICANS (%)	Reference
75 kids (up to 25y)	CTL019	4-1BB	47%	13%	Maude et al, NEJM 2018
24 kids (up to 20y)	KTE-X19	CD28	33%	21%	Wayne AS et al, EHA 2021
45 kids (up to 25y)	JCAR017	4-1BB	23%	21%	Gardner et al, Blood 2017
16 kids (+6 adults)	-	CD28	15%	30%	Jacoby E et al, Am J Hematol 2018
14 kids	AUTO1	4-1BB	21%	7%	Ghorashian S et al, Nat Med 2019
11 kids (up to 19y)	ARI-0001	4-1BB	18%	0%	Ortiz-Maldonado et al, Mol Ther 2020

ADULTS					
Patients	Product	Co-stimulaion	Grade ≥3 CRS (%)	Grade ≥3 ICANS (%)	Reference
53 adults	19E3/1928z	CD28	26%	42%	Park et al, NEJM 2018
35 adults	CTL019	4-1BB	71%	6%	Frey et al, JCO 2019
53 adults	JCAR017	4-1BB	12%	40%	Hay et al, Blood 2019
55 adults	KTE-X19	CD28	24%	25%	Shah et al, Lancet 2021
16 adults	AUTO1	4-1BB	0	19%	Roddie et al, ASCO 2019
27 adults (> 18y)	ARI-0001	4-1BB	11%	3%	Ortiz-Maldonado et al, Mol Ther 2020

Outcomes of CAR-T cells on ALL: efficacy

PEDIATRICS + YOUNG ADULTS					
Patients	Product	CRR, % (CI 95%)	PFS/EFS, median (CI 95%)	OS, median (CI 95%)	Reference
75 kids (up to 25y)	CTL019	81%	50% at 1y	76% at 1y	Maude et al, NEJM 2018
24 kids (up to 20y)	KTE-X19	75%*	5.2 mo	67% at 1y	Wayne AS et al, EHA 2021
45 kids (up to 25y)	JCAR017	93%	51% a 1y	69.5% at 1y	Gardner et al, Blood 2017
16 kids (+6 adults)	-	90%	76%** at 1y	90% at 1y	Jacoby E et al, Am J Hematol 2018
14 kids	AUTO1	86%	46% at 1y	63% at 1y	Ghorashian S et al, Nat Med 2019
11 kids (up to 19y)	ARI-0001	79%*	18.1 mo 82% at 1y	NA (7.1-NA) 78% at 1y	Ortiz-Maldonado et al, Mol Ther 2020

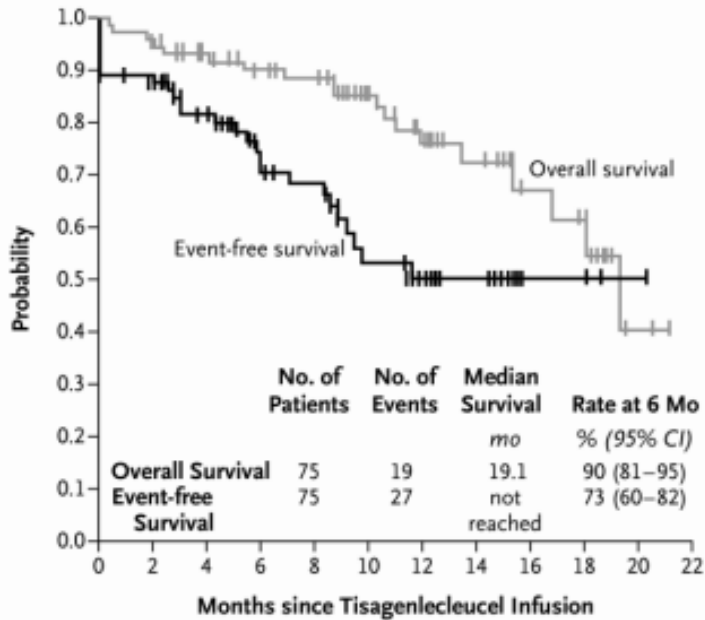
ADULTS					
Patients	Product	CRR, % (CI 95%)	PFS/EFS, median (CI 95%)	OS, median (CI 95%)	Reference
53 adults	19E3/1928z	83%	6.1 mo	12.9 mo	Park et al, NEJM 2018
35 adults	CTL019	69%	5.6 mo	19.1 mo	Frey et al, JCO 2019
53 adults	JCAR017	85%	7.6 mo	20.0 mo	Hay et al, Blood 2019
55 adults	KTE-X19	69%*	11.6 mo	18.2 mo	Shah et al, Lancet 2021
16 adults	AUTO1	84%	69% at 6 mo 52% at 1y	68% at 6 mo 63% at 1y	Roddie et al, ASH 2020
27 adults (> 18y)	ARI-0001	85%*	9.4 mo 34% at 1y	20.2 mo 65% at 1y	Ortiz-Maldonado et al, Mol Ther 2020

*MRD negative by FC
**all alloSCT post

RWE of approved CAR-T cells on **pediatric & YA ALL** pts

ELIANA trial

B Event-free and Overall Survival



Maude SL, NEJM 2018

N = 75

CRR 81%

1y EFS 52%

1y DOR 67%

1y OS 77%

sCRS 48%

sICANS 13%



N = 249

CRR 85%

1y EFS 57%

1y DOR 61%

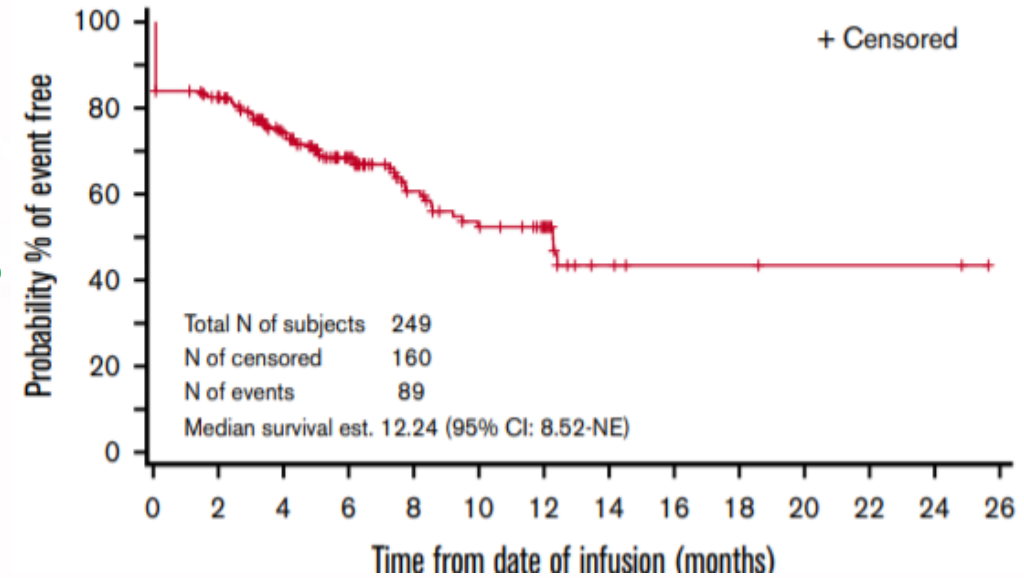
1y OS 77%

sCRS 16%

sICANS 9%

- **<3 yr**
- **37% in CR**
- **Early Toci**

CIBMTR (RWE)

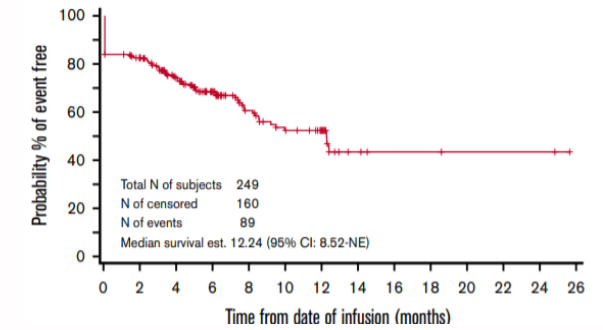


Pasquini MC, Blood Adv. 2020

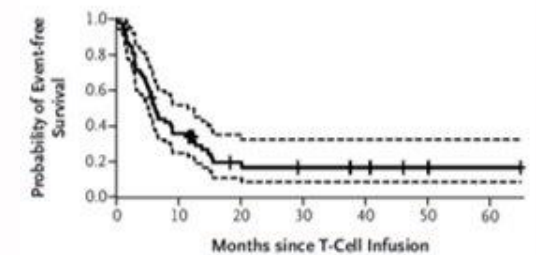
CAR-T cell in R/R ALL: high CRR but low DOR

PEDIATRICS + YA				
Patients	Product	CRR, % (CI 95%)	PFS/EFS, median (CI 95%)	Reference
75 kids (up to 25y)	CTL019	81%	50% at 1y	Maude et al, NEJM 2018
24 kids (up to 20y)	KTE-X19	75%*	5.2 mo	Wayne AS et al, EHA 2021
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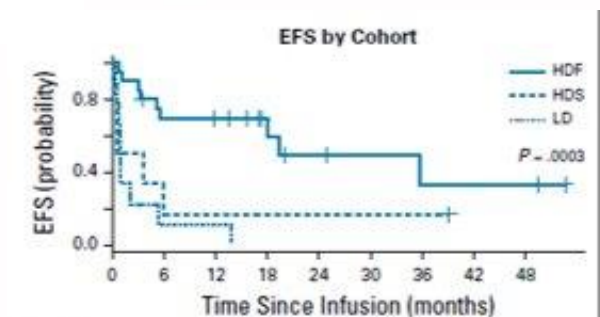
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Patients	Product	CRR, % (CI 95%)	PFS/EFS, median (CI 95%)	Reference
53 adults	19E3/1928z	83%	6.1 mo	Park et al, NEJM 2018
35 adults	CTL019	69%	5.6 mo	Frey et al, JCO 2019
53 adults	JCAR017	85%	7.6 mo	Hay et al, Blood 2019
55 adults	KTE-X19	69%*	11.6 mo	Shah et al, Lancet 2021
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Pasquini MC, Blood Adv. 2020



Park KA, NEJM 2019



Frey NV, JCO 2019

Prognostic factors for CAR-T cells in ALL

Pre-treatment variables

- Age
- Tumor burden
- Prior therapies
- Disease location
- Lymphodepletion
- CAR-T cell design
- CAR-T cell dose & dosage

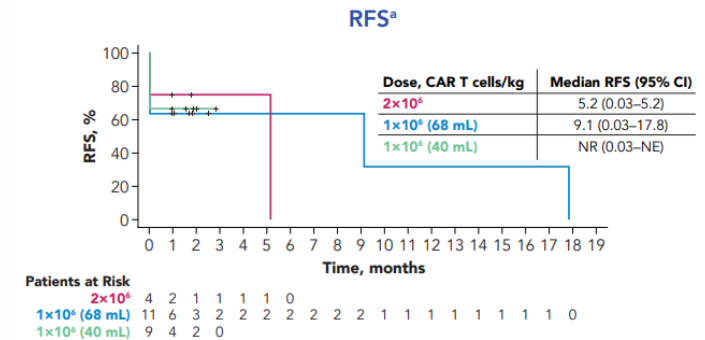
Post-treatment variables

- CAR-T cell expansion
- Depth of response
- CAR-T cell persistence (BCA)
- AlloSCT status

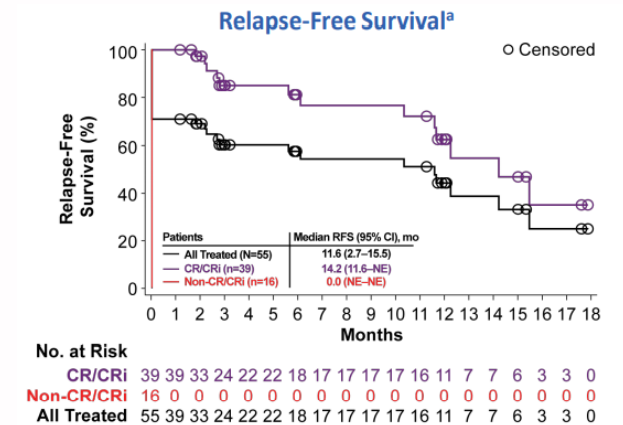
Prognostic factors for CAR-T cells in ALL: Age

Product	CRR		PFS		
	Peds + YA	Adults	Peds + YA	Adults	
KTE-X19	75% vs 69%		5.2 vs 11.6 mo		Wayne AS et al, EHA 2021 Shah et al, Lancet 2021
AUTO1	86% vs 84%		46% vs 52% at 1y		Ghorashian S et al, Nat Med 2019 Roddie et al, ASH 2020
CTL019	81% vs 69%		50% 1y vs 5.6 mo		Maude et al, NEJM 2018 Frey et al, JCO 2019
JCAR017	93% vs 85%		51% 1y vs 7.6 mo		Gardner et al, Blood 2017 Hay et al, Blood 2019
ARI-0001	79% vs 85%		82% vs 34% at 1y		Ortiz-Maldonado et al, Mol Ther 2020

Pediatric + YA



Adults



Prognostic factors for CAR-T cells in ALL: Age

Product	CRR		PFS	
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Wayne AS et al, EHA 2021
Shah et al, Lancet 2021

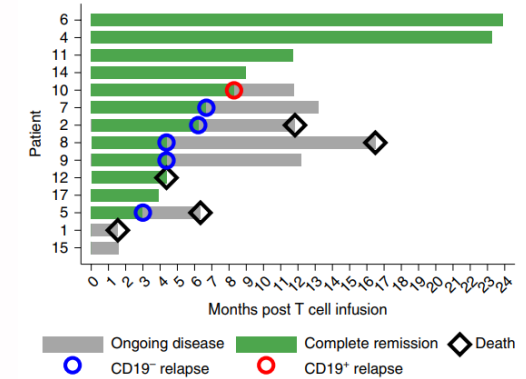
Ghorashian S et al, Nat Med 2019
Roddie et al, ASH 2020

Maude et al, NEJM 2018
Frey et al, JCO 2019

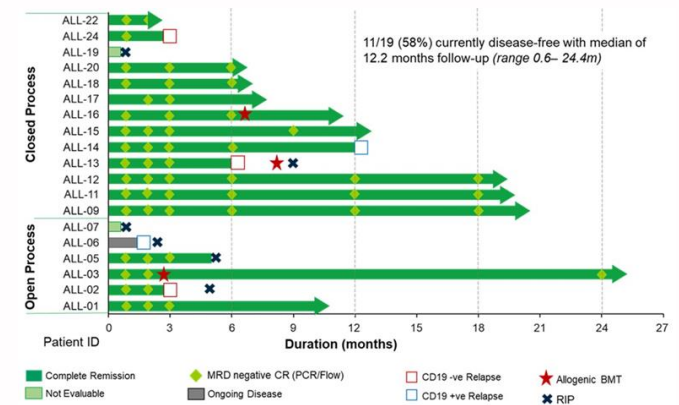
Gardner et al, Blood 2017
Hay et al, Blood 2019

Ortiz-Maldonado et al,
Mol Ther 2020

Pediatric + YA



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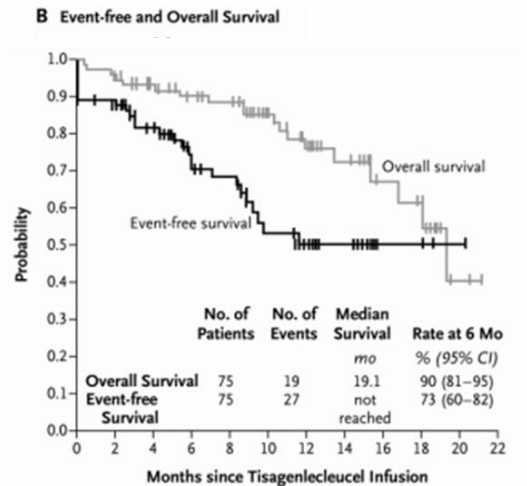
Ghorashian S et al, Nat Med 2019
Roddie et al, ASH 2020

Maude et al, NEJM 2018
Frey et al, JCO 2019

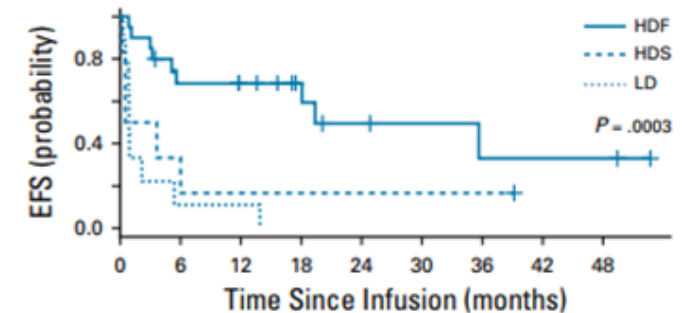
Gardner et al, Blood 2017
Hay et al, Blood 2019

Ortiz-Maldonado et al,
Mol Ther 2020

Pediatric + YA



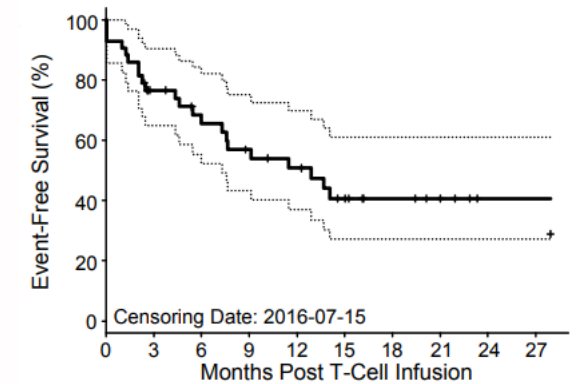
Adults



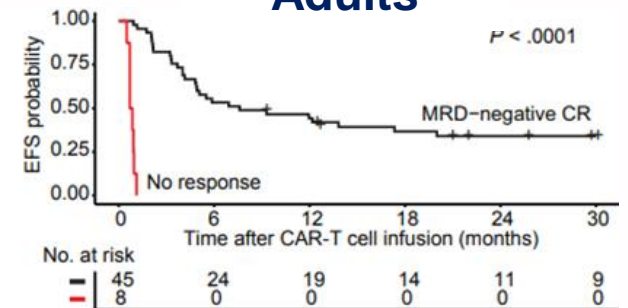
Prognostic factors for CAR-T cells in ALL: Age

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Pediatric + YA

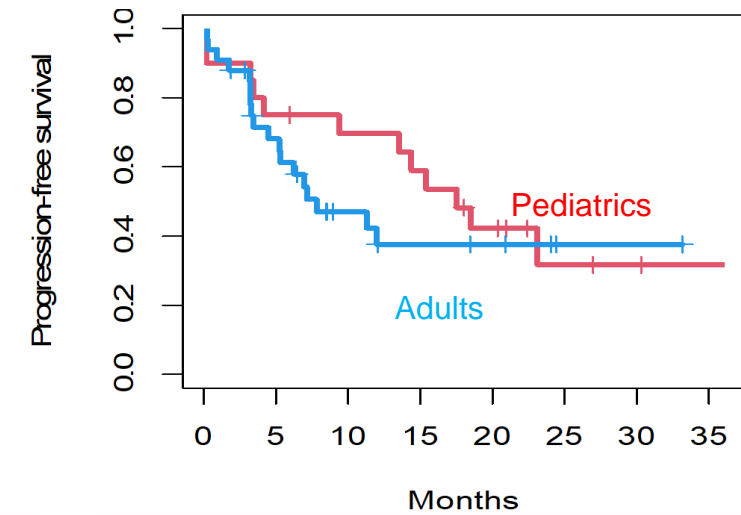


Adults



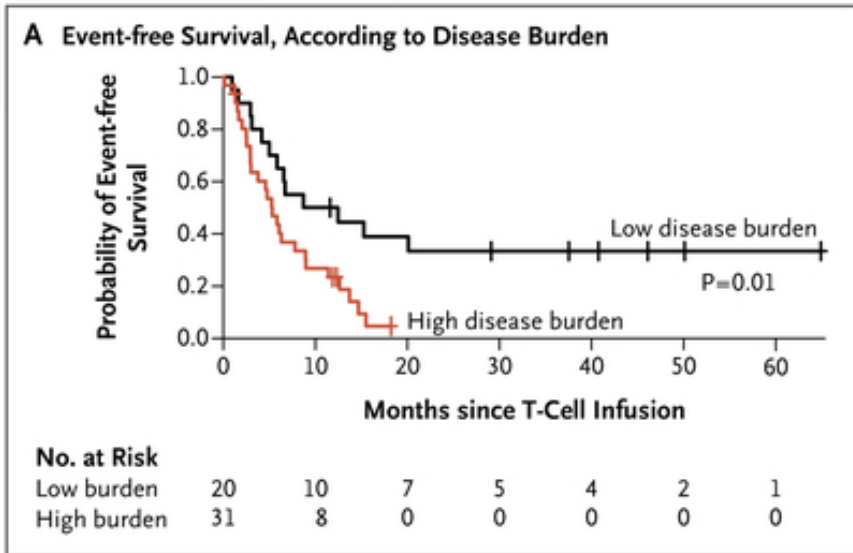
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AUTO1	86% vs 84%		46% vs 52% at 1y		Ghorashian S et al, Nat Med 2019 Roddie et al, ASH 2020
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Prognostic factors for CAR-T cells in ALL: Tumor burden (5%)

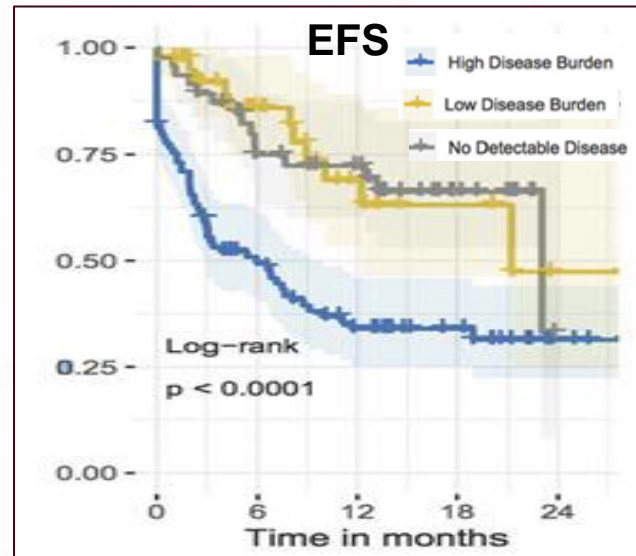
19E3/1928z



**EFS 10.6 mo vs 5.3 mo
(median) (p = 0.01)**

Park J, *NEJM* 2018

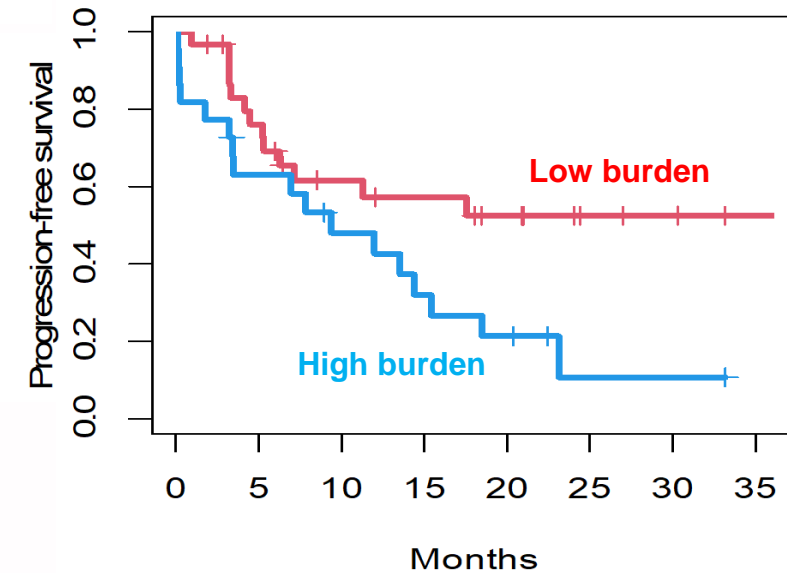
Tisagenlecleucel



	6mo OS	1y OS	6mo EFS	1y EFS
High Disease Burden	0.75	0.58	0.50	0.34
Low Disease Burden	0.94	0.85	0.86	0.69
No Detectable Disease	0.98	0.95	0.75	0.72

Schultz LM, *ASH* 2020

ARI-0001

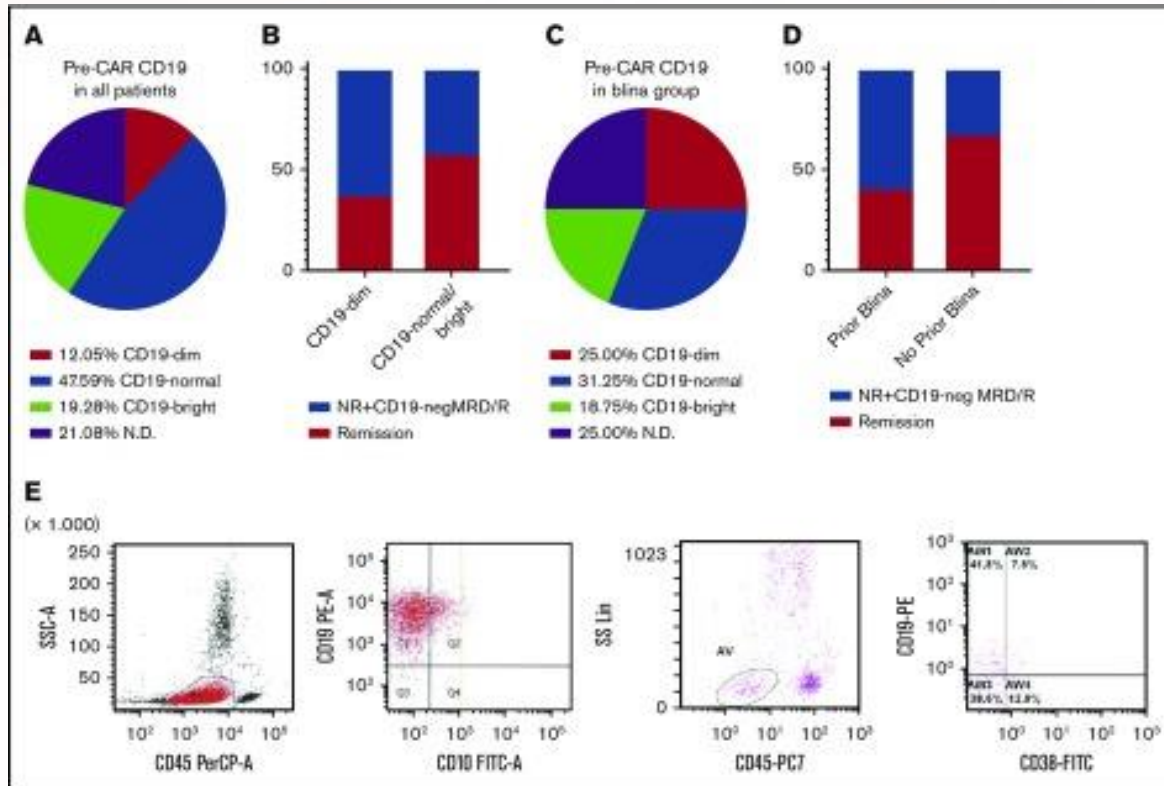


**2y PFS 52.5% vs 10.7%
(p = 0.077)**

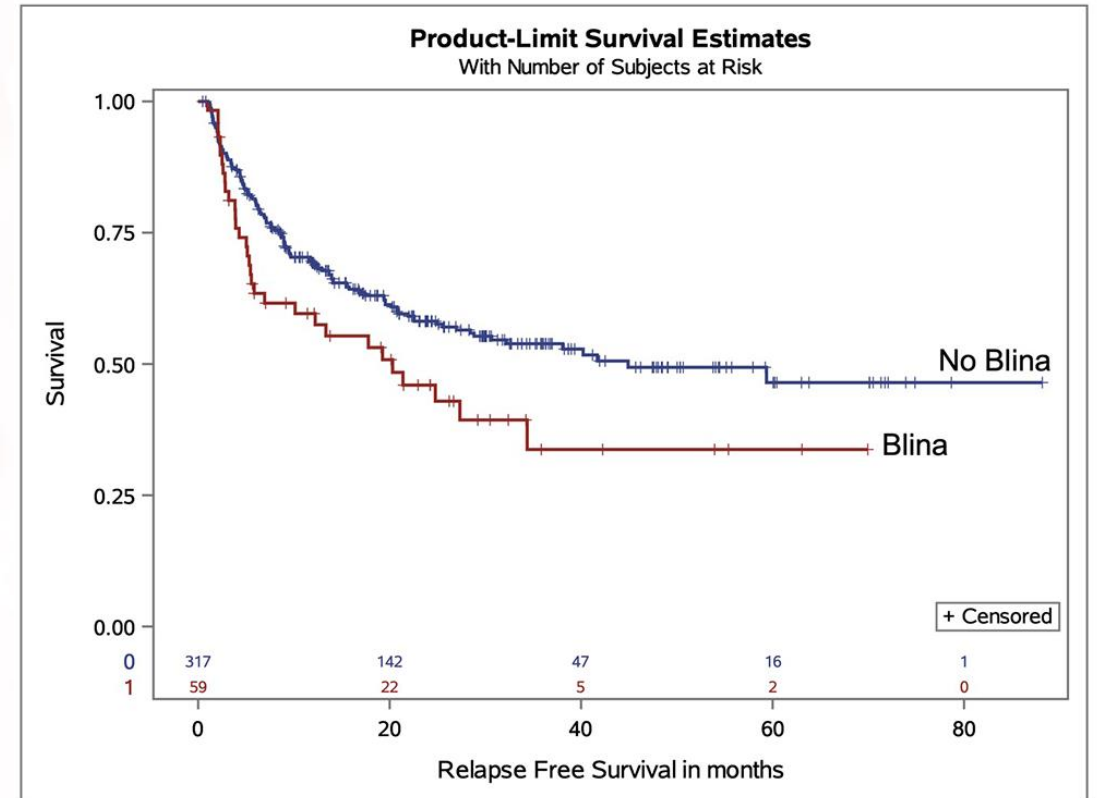
Ortiz-Maldonado V, *EHA* 2021

Prognostic factors for CAR-T cells in ALL: prior therapies

Prior Blinatumomab

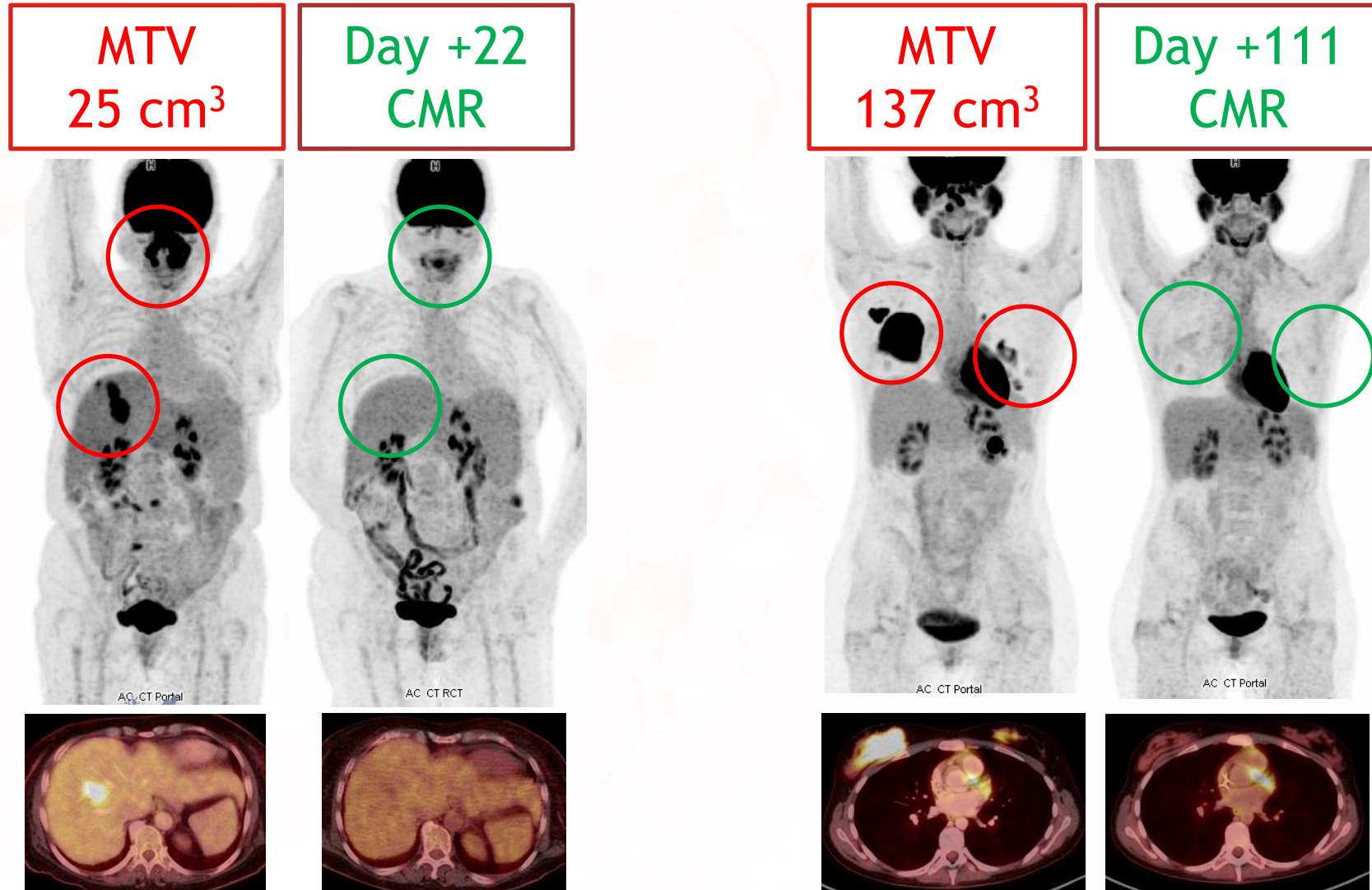


Vinodh Pillai, Blood Adv 2019



Nirali, ASH 2020

Especial situations for CAR-T cells in ALL: Extramedullary disease

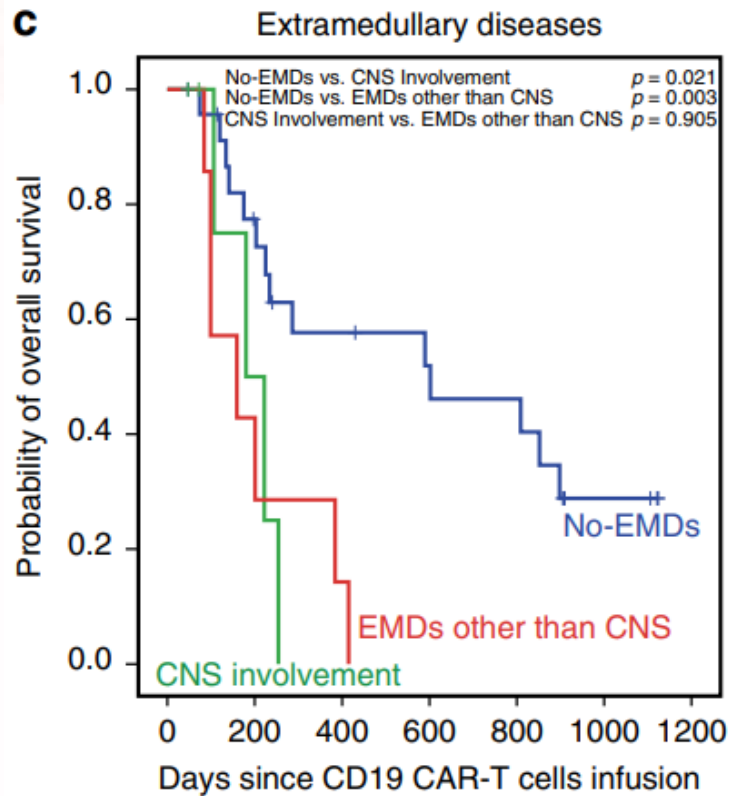


MTV, metabolic tumor volume; CMR, complete metabolic response.

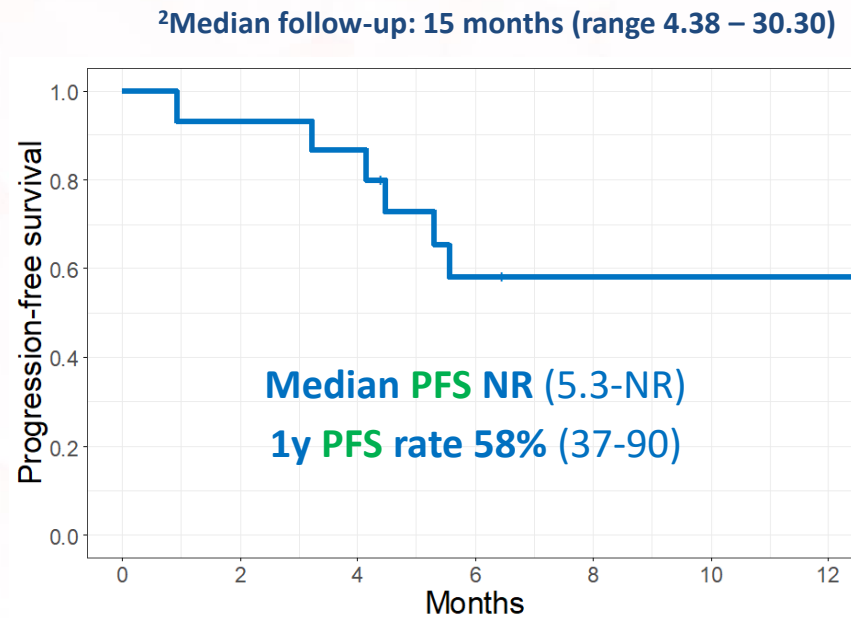
Ortiz-Maldonado V, et al. 3rd European CAR-T cell Meeting. 2021

Especial situations for CAR-T cells in ALL: Extramedullary disease

Medullar + extramedullary disease \neq Isolated extramedullary disease



An F, Nature Com 2020

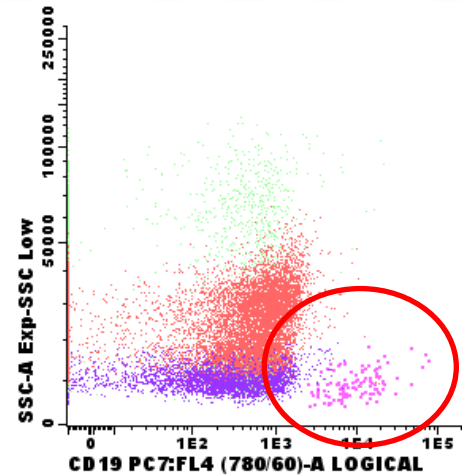
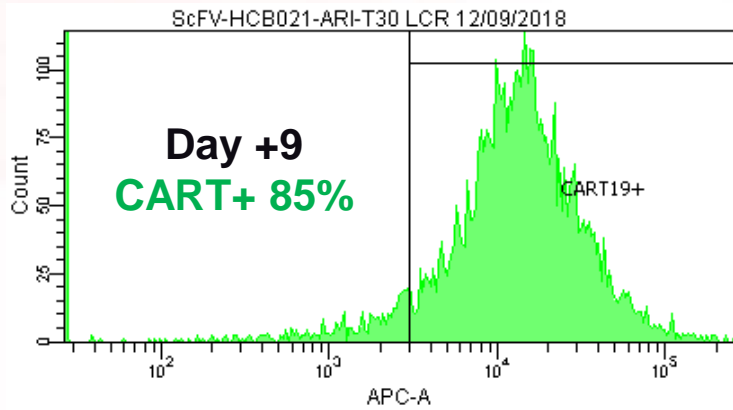


Population	CART19-BE-01 ¹	IEM ²
n	38	15
MRD-negative + imaging* CRR, at best response	84.2% (32/38)	86.6% (13/15)
PFS, median (CI 95%)	12.0 mo (4.2-20.2) 47% (27-67) at 1y	NR (5.3-NR) 58% (37-90) at 2y
DOR, median (CI 95%)	14.8 mo (6.0-NA) 59% (34-83) at 1y	NR (4.1-NR) 62% (34-83) at 2y
OS, median (CI 95%)	20.2 mo (10.4-NA) 69% (49-88) at 1y	NR (11.5-NR) 70% (49-99) at 2y

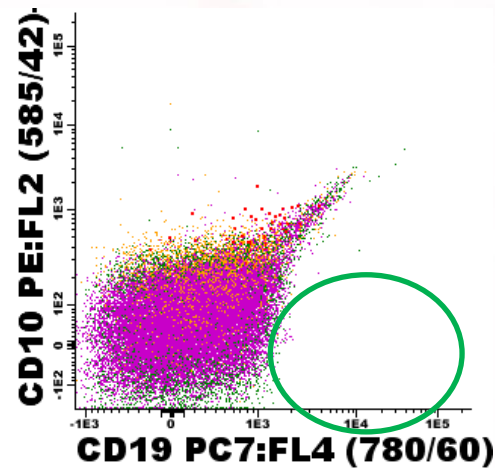
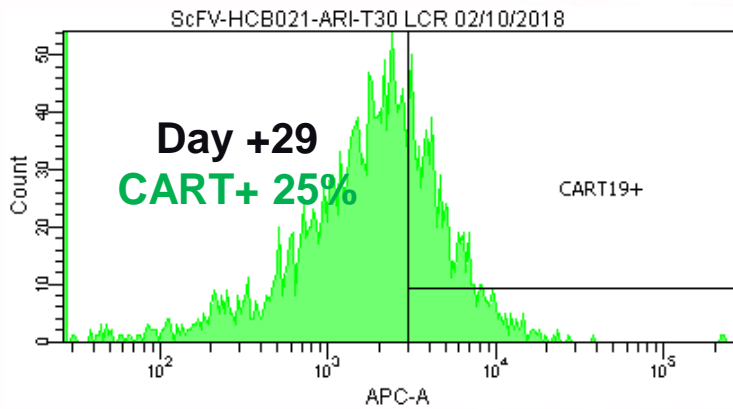
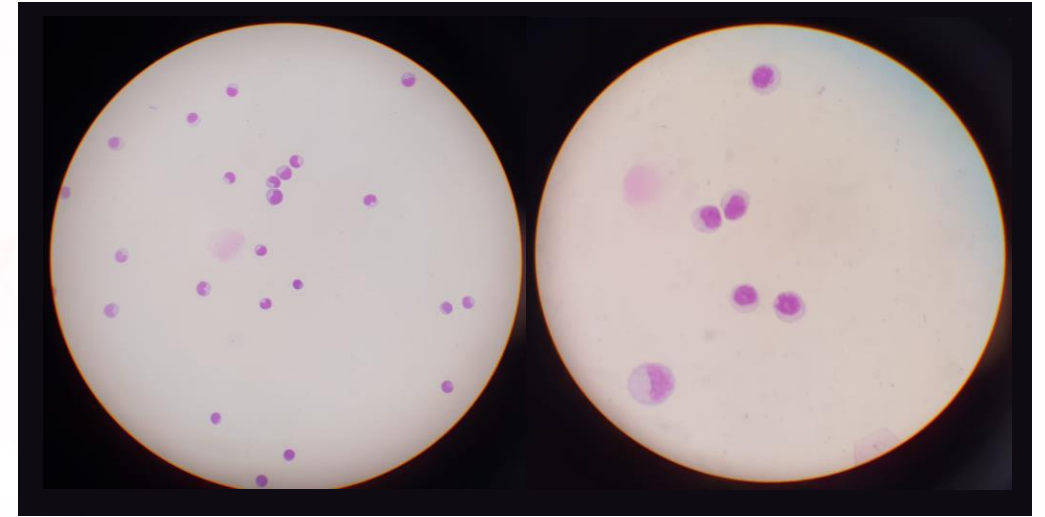
¹Ortiz-Maldonado V, Mol Ther. 2020

²Ortiz-Maldonado V, 3rd European CAR-T cell Meeting. 2021

Especial situations for CAR-T cells in ALL: CNS affection



Blasts 0.5%

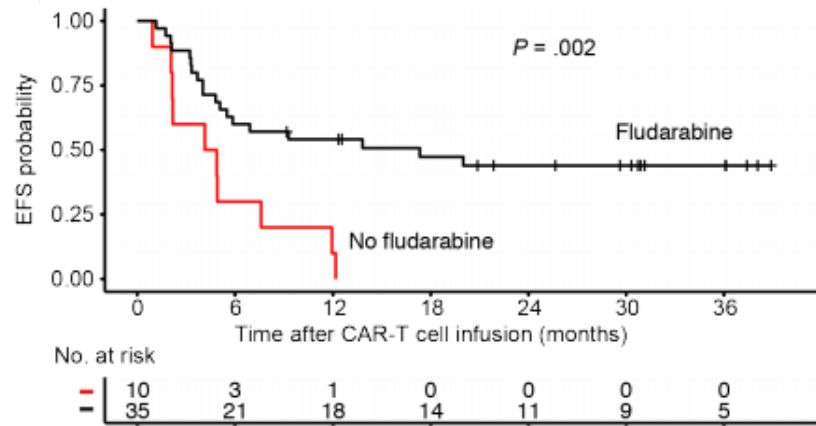
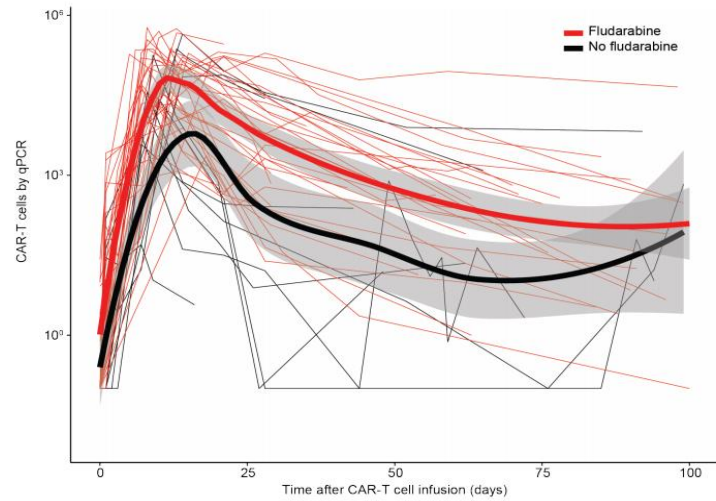


Blasts 0%

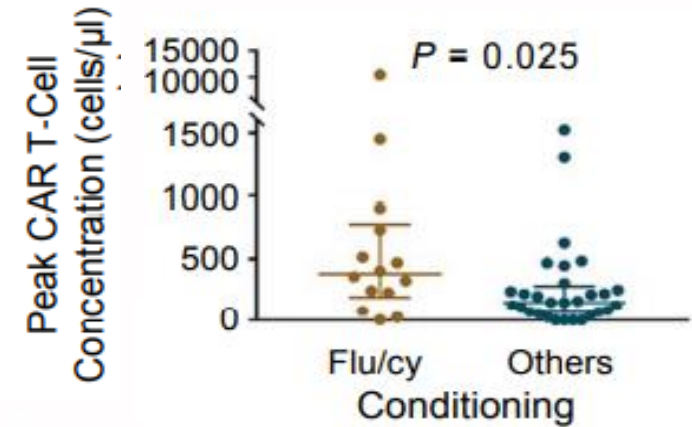
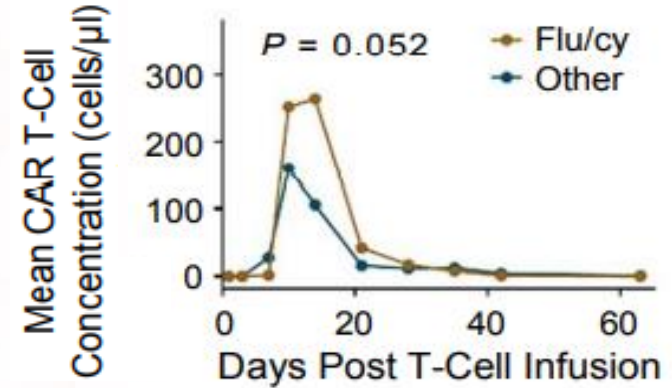
- **CNS+ usually excluded from CAR-T trials**
- Safety & efficacy concerns
- Tisagenlecleucel not approved in CNS relapse
- Scarce experience (trials & RWE)
- **CAR-T cells able to enter BBB (CNS)**
- **7/7 MRD neg CRR (ARI-0001)**

Prognostic factors for CAR-T cells in ALL: **Lymphodepletion**

Figure S5



Hay KA, Blood 2019

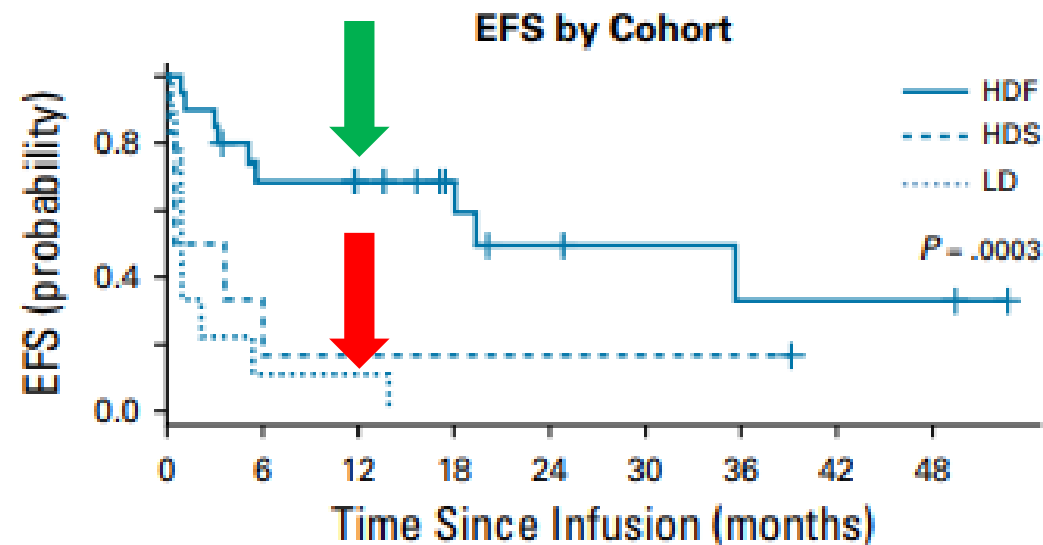


Gardner RA, Blood 2017

Prognostic factors for CAR-T cells in ALL: Cell dose

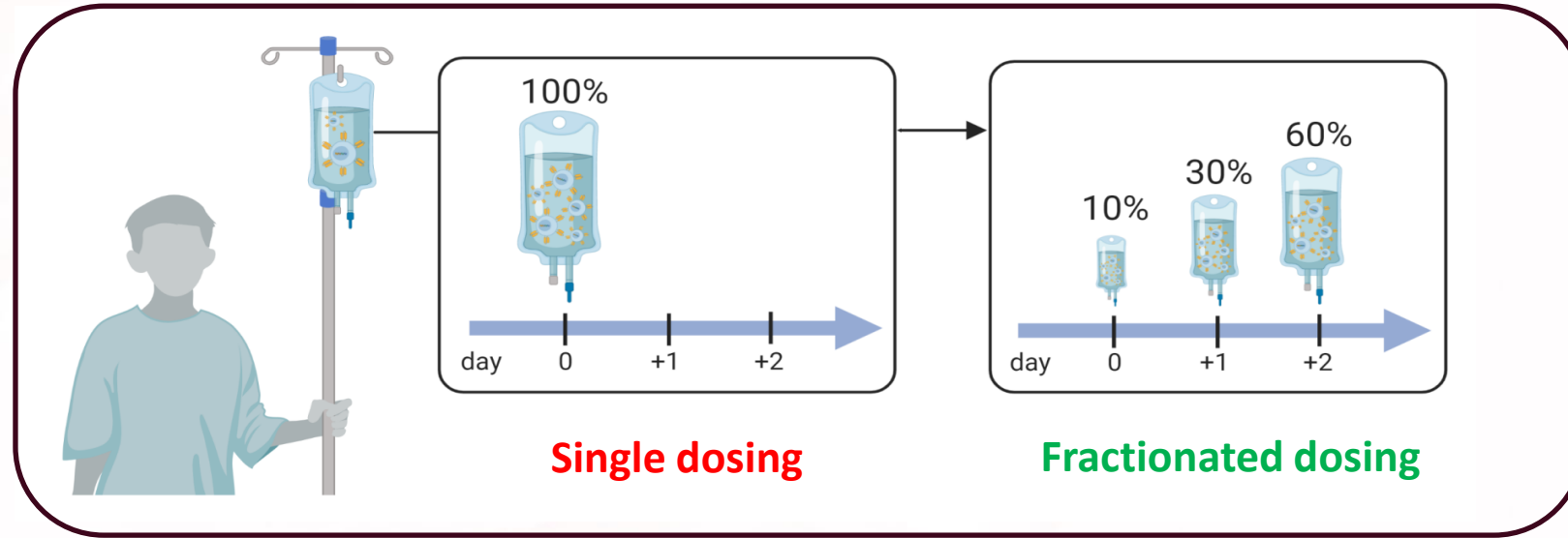
Patients	Cell dose	CRR, % (CI 95%)	PFS/EFS, median (CI 95%)	OS, median (CI 95%)	Reference
35		69% (51-83%)	5.6 mo (2.2-19.4)	19.1 mo (6.2-NA)	Frey et al, JCO 2019
6 (HDS)	7 x10 ⁶ CAR-T/kg	50%	2.1 mo (0.2-NA) 17% (0.8-52) at 2y	3.4 mo (0.2-NA) 17% (0.8-52) at 2y	
9 (LDS/F)	0.7 x10 ⁶ CAR-T/kg	33%	0.9 mo (0.3-5.4) 0% (0-33) at 2y	5.7 mo (0.3-25.4) 22% (3-51) at 2y	
20 (HDF)	7 x10 ⁶ CAR-T/kg	90%	19.4 mo (5.1-NR) 49.5% (21-73) at 2y	Not reached 73% (46-88) at 2y	

Dose matters!



But it's limited by toxicity...

Prognostic factors for CAR-T cells in ALL: Dosaje form

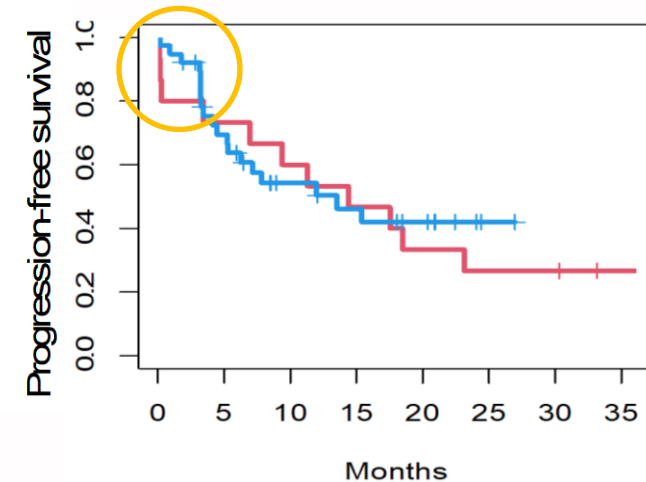


Patients	Cell dose	CRR, % (CI 95%)	OS, median (CI 95%)
35		69% (51-83%)	19.1 mo (6.2-NA)
6 (HDS)	7 x10 ⁶ CAR-T/kg	50%	3.4 mo (0.2-NA) 17% (0.8-52) at 2y
9 (LDS/F)	0.7 x10 ⁶ CAR-T/kg	33%	5.7 mo (0.3-25.4) 22% (3-51) at 2y
20 (HDF)	7 x10 ⁶ CAR-T/kg	90%	Not reached 73% (46-88) at 2y

PRM 50%



PRM 0%



PRM 20%



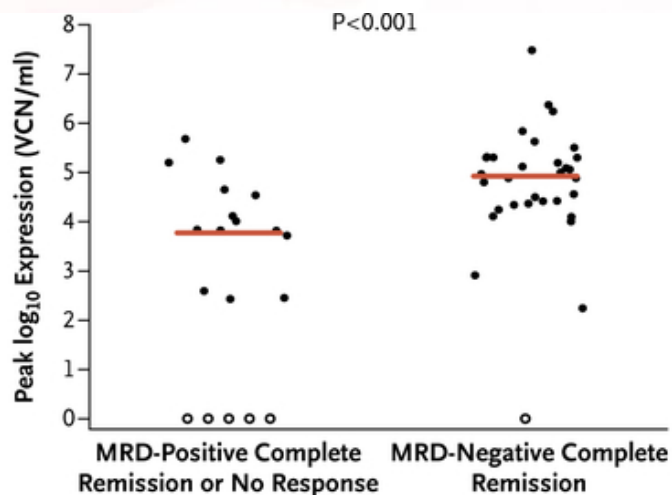
PRM 0%

Frey et al, JCO 2019

Ortiz-Maldonado V, Mol Ther. 2020

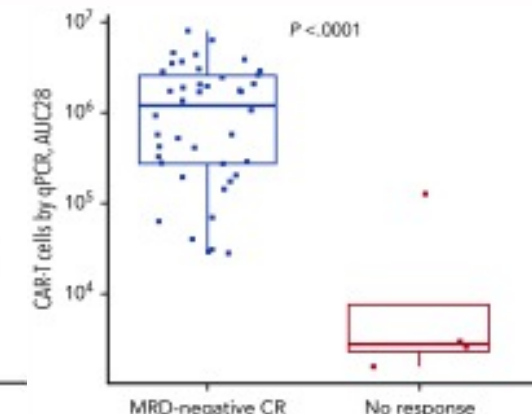
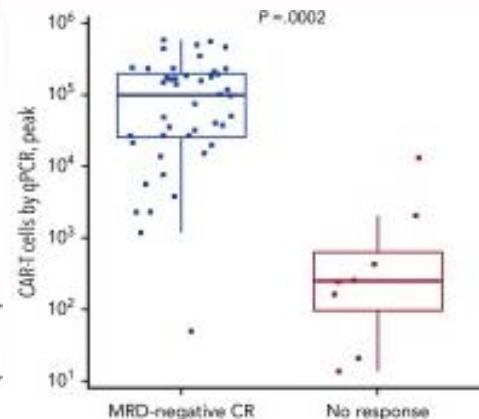
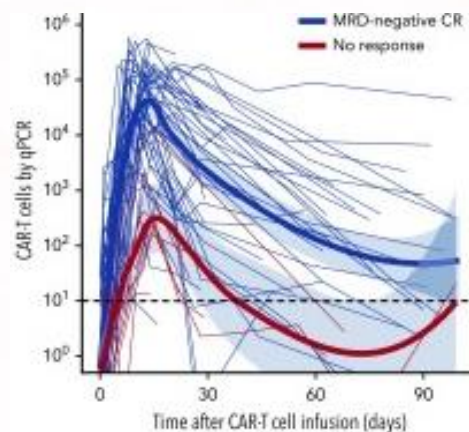
Prognostic factors for CAR-T cells in ALL: Cell expansion

19E3/1928z



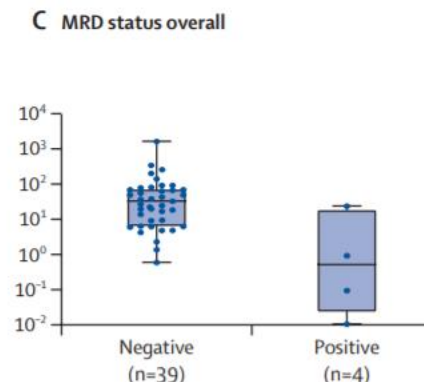
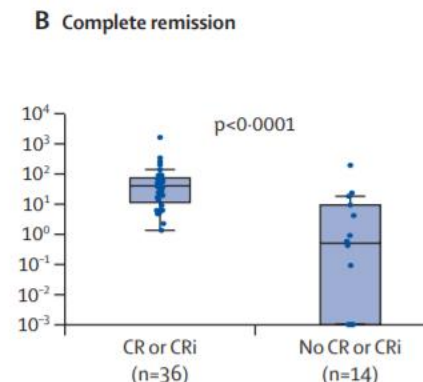
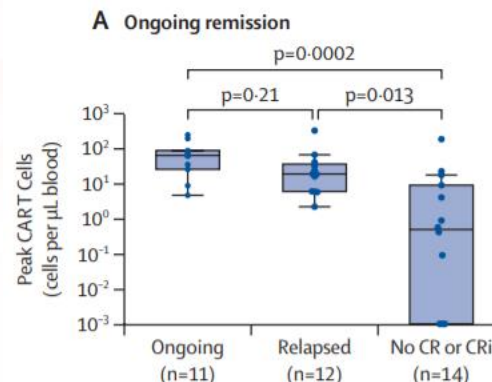
Park J, NEJM 2018

JCAR017



Hay KA, Blood 2019

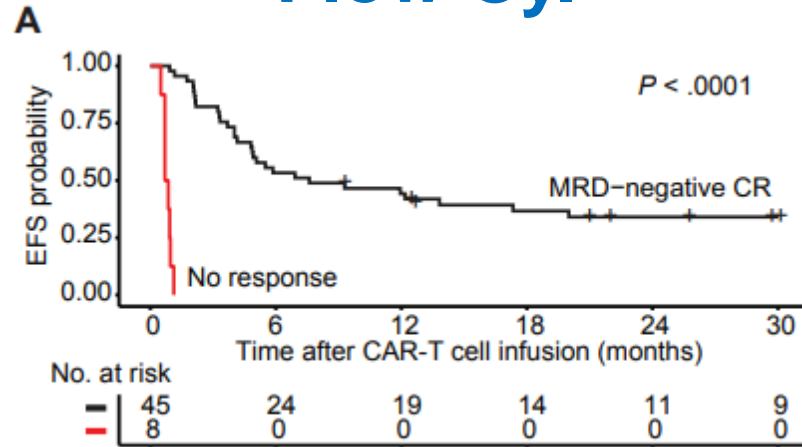
KTE-X19



Shah, Lancet 2021

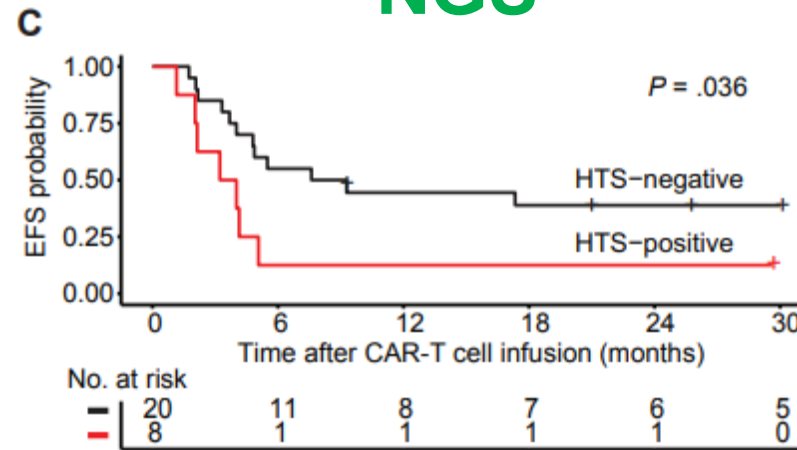
Prognostic factors for CAR-T cells in ALL: Depth of response

Flow Cy.



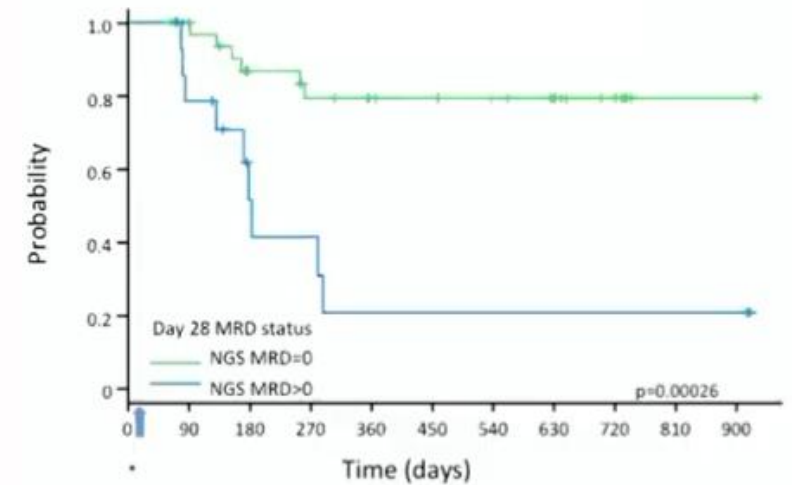
Hay KA, Blood 2019

NGS



Hay KA, Blood 2019

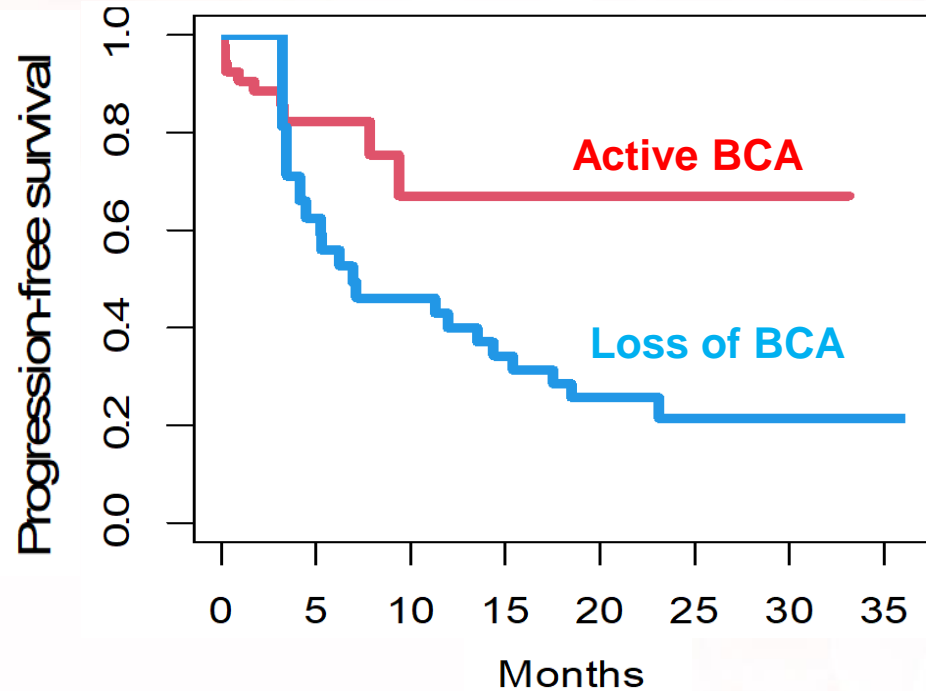
NGS



Pulsipher MA, ASH 2018

Prognostic factors for CAR-T cells in ALL: Cell persistence

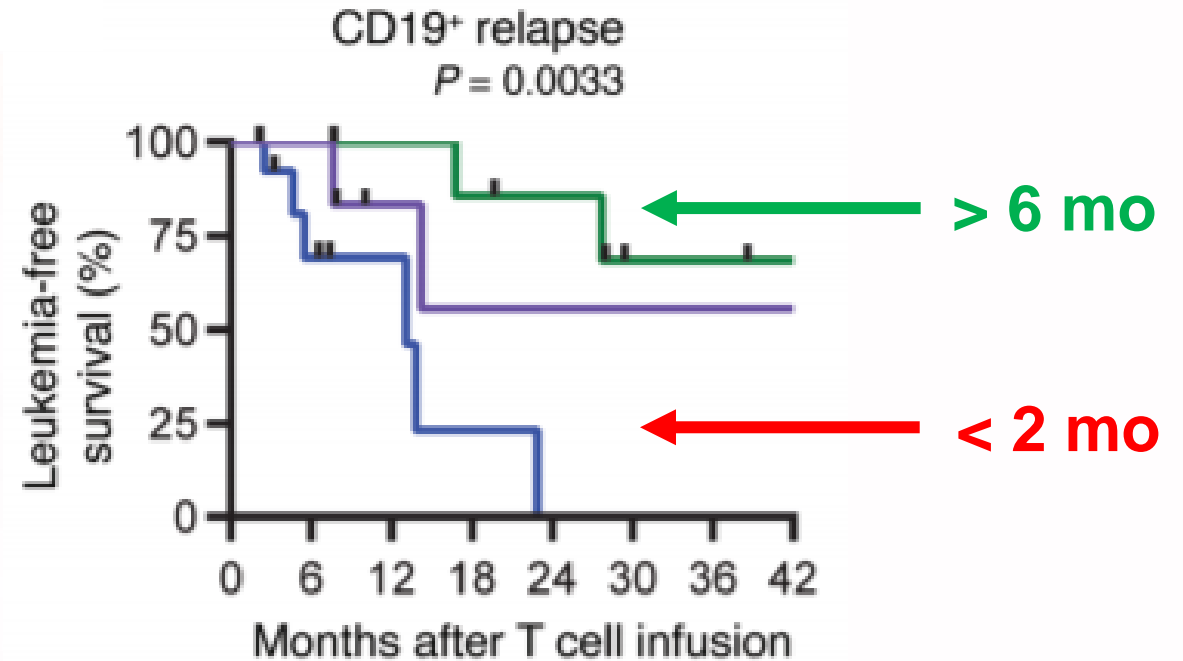
ARI-0001



HR 4.41
(p = 0.017)

Ortiz-Maldonado V, EHA 2021

CAR19 41BB (1:1 CD4/CD8 ratio)



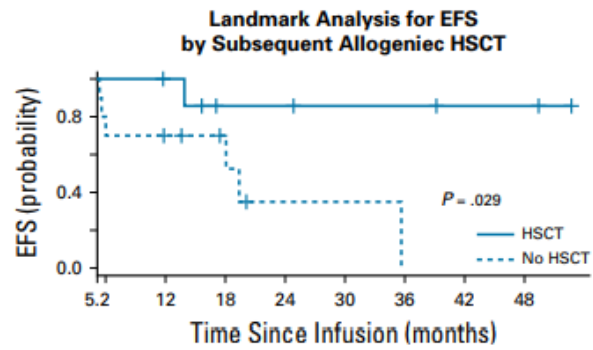
HR 34
(p = 0.01)

Finney OC, JCI 2019

Relapse	CD19 ⁺ , n (%)
longBCA	2 (22.2)
mediumBCA	2 (50.0)
shortBCA	6 (75.0)

Role of alloSCT for ALL in the CAR-T era

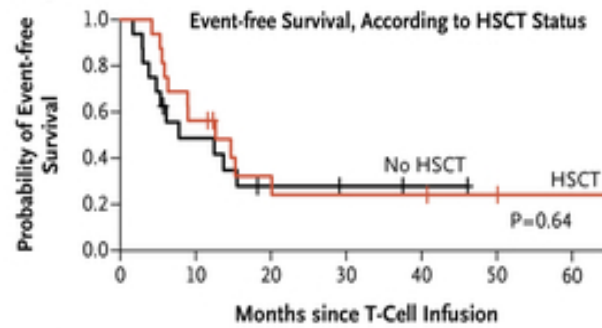
1st alloSCT post CAR-T



No. at risk:	5.2	12	18	24	30	36	42	48
HSCT	8	7	4	4	3	3	2	2
No HSCT	10	6	4	1	1	0	0	0

Frey, JCO 2020

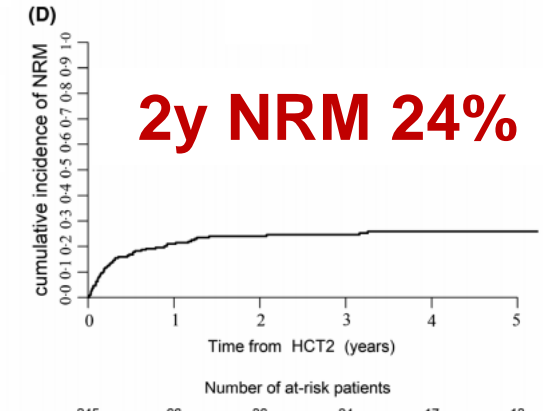
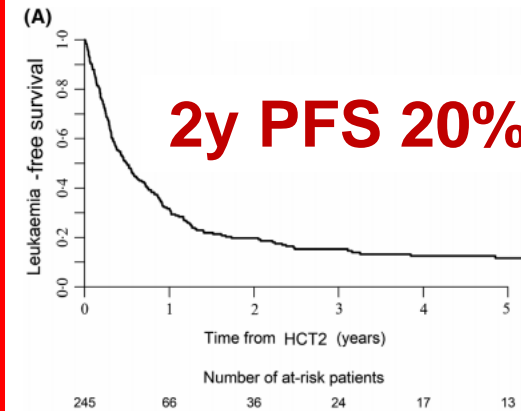
1st alloSCT post CAR-T



No. at Risk	0	10	20	30	40	50	60
No HSCT	16	7	3	2	1	0	0
HSCT	16	9	4	3	3	2	1

Park J, NEJM 2018

2nd alloSCT in ALL



Nagler A, BJH 2019

Role of alloSCT in ALL in the CAR-T era

2nd (and 1st?) AlloSCT post CAR-T:

- a) Should be performed to all patients?
- b) Should be guided by B-cell aplasia?
- c) Should be guided by tumor burden?
- d) Should be guided by age?
- e) All except 'a' are correct?



Approved CAR-T products in ALL



FDA News Release

FDA approval brings first gene therapy to the United States

CAR T-cell therapy approved to treat certain children and young adults with B-cell acute lymphoblastic leukemia

For Immediate Release

August 30, 2017



Approved by*:

- ✓ FDA: Aug, 2017
- ✓ EMA: Aug, 2018

*From 3 to 25 yr



October 03, 2021 | 1 min read

SAVE

FDA approves Tecartus for B-cell precursor ALL

[ADD TOPIC TO EMAIL ALERTS](#)

The FDA approved brexucabtagene autoleucel for treatment of adults with relapsed or refractory B-cell precursor acute lymphoblastic leukemia.



Approved by*:

- ✓ FDA: Oct, 2021
- *>18 yr



February 10 2021

AEMPS authorises Hospital Clínic's CAR-T ARI-0001 for patients with acute lymphoblastic leukaemia

The Spanish Agency of Medicines and Medical Devices (AEMPS) has approved CAR-T ARI-0001, developed by Hospital Clínic, as an advanced therapy drug of non-industrial production for its use in patients over 25 years of age with lymphoblastic leukaemia that is resistant to conventional treatments. It is the first CAR-T developed entirely in Europe to be approved by a regulatory agency.

ARI-0001

Approved by*:

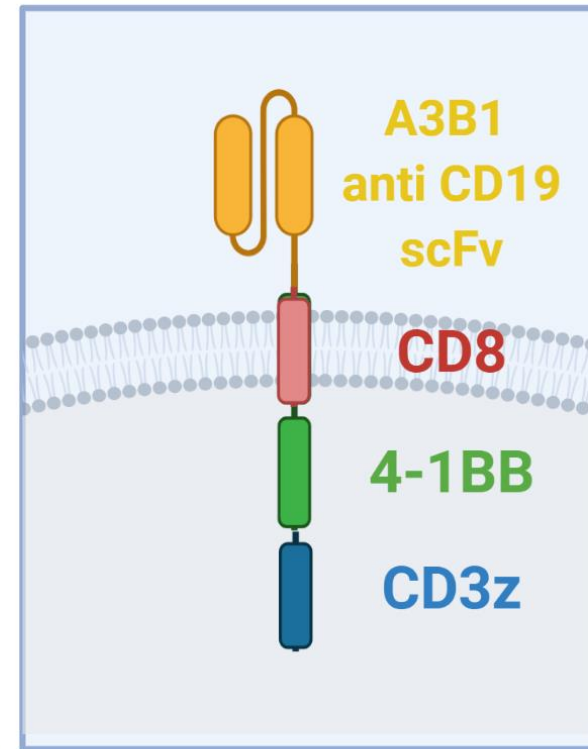
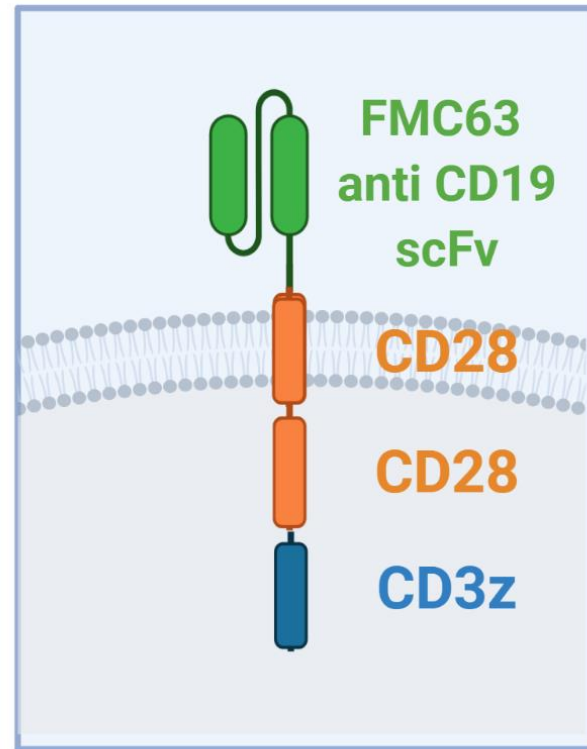
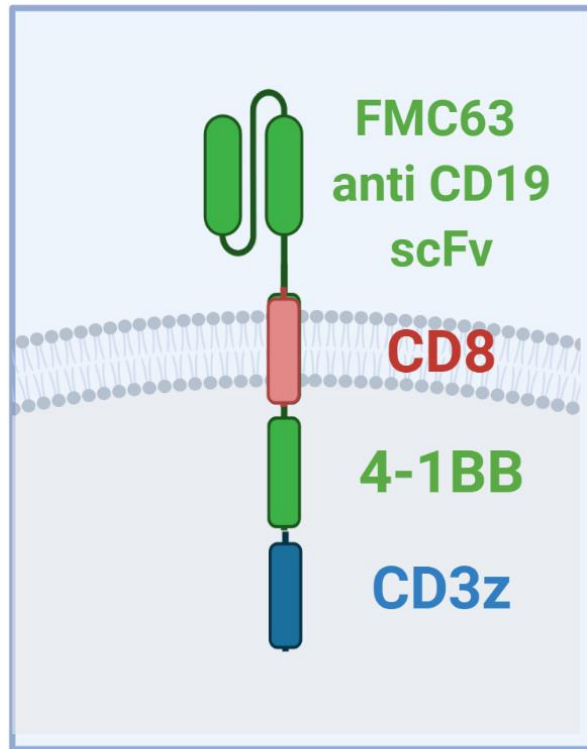
- ✓ AEMPS: Feb, 2021
- *>25 yr

Approved CAR-T products in ALL

KYMRIAH[®]
(tisagenlecleucel) Suspension for IV infusion

TECARTUS[®]
(brexucabtagene autoleucel) Suspension for IV infusion

ARI-0001



Antigen-recognition domain
Hinge + transmembrane domains
Signaling domains

Future challenges for CAR-T cells in ALL

- **Improve safety**

- Optimization of CRS management (high tumor burden)
- Patient tailored cell dosing (**one size does not fit all**)

- **Improve efficacy**

- Reduce tumor burden: optimization of bridging therapy
- Increase cell dose: AEs mitigation strategies
- **Reduce CD19+ relapses**: increase CAR-T persistence
- Reduce CD19- relapses: improve cell-grip (bi-specific CARs)
- **One-step solution enough?** → or multi-step solution? (multiple infusions)

Conclusions for current CAR-T therapy in B-ALL

1. Very high-risk patients:

- Fragile patients
- Bone marrow involvement (cytopenias)
- Disease localization: direct CRS
- AlloSCT issues: comorbidity, GvHD, SOS

2. High CRR but low long-term DOR:

- BCA-based approach?
- Tumor burden-based approach?

3. Role of alloSCT:

- 1st allo *currently* unchallenged (*to be continued*)
 - *Peds and young adults*
 - *Adults?*
- 2nd allo *definitely* challenged

4. Optimal timing and dosing of CAR-T

- Biological differences due to age
- Single CAR-T infusion enough?

THANKS FOR YOUR ATENTTION!

