Society for Immunotherapy of Cancer

Advances in Cancer Immunotherapy™

CAR-T Cell Therapy in Adults with Acute Lymphoblastic Leukemia

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#LearnACI

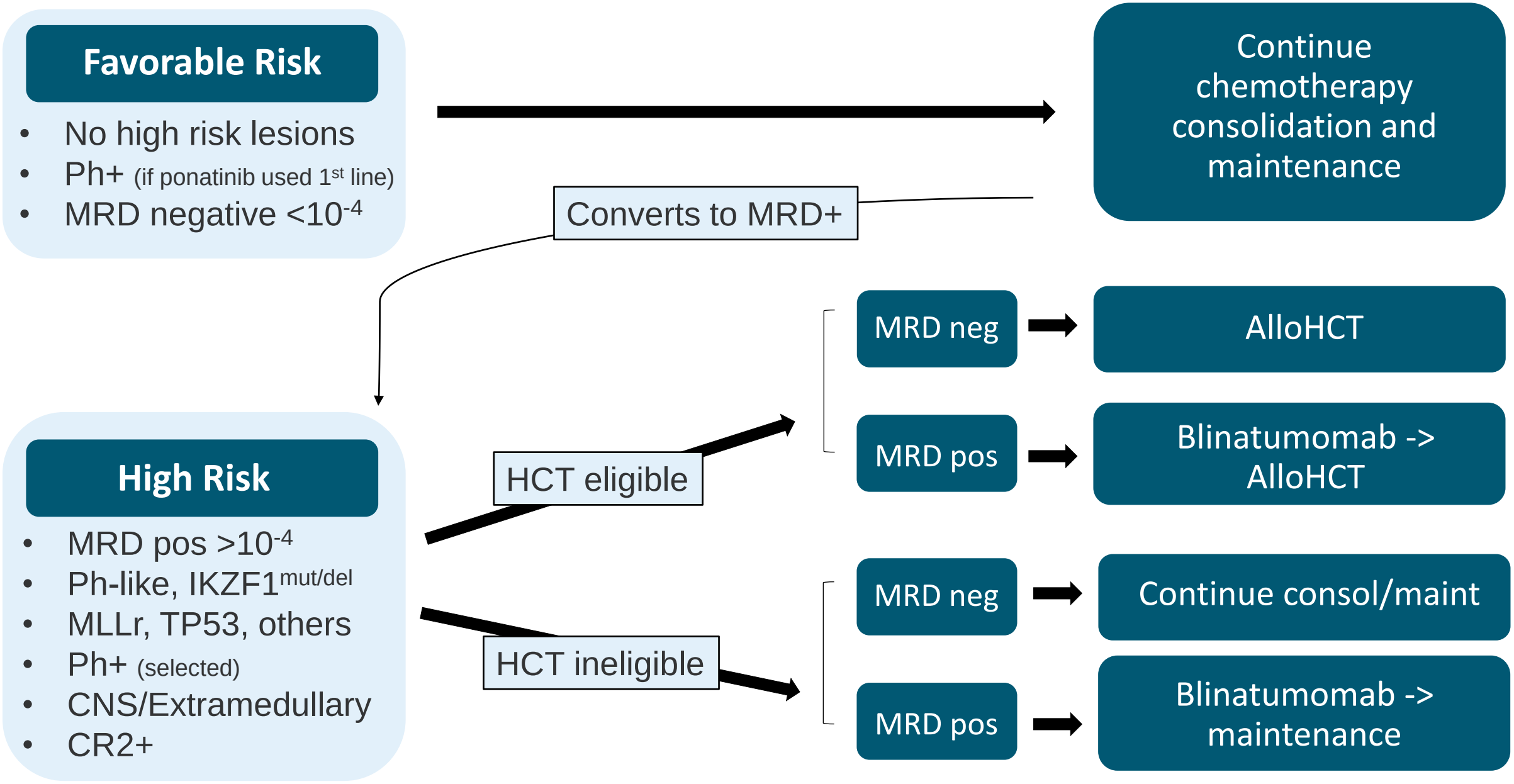
Disclosures

Research Funding: Amphivena, Astellas, Autolus, Jazz, Kadmon, Kite, Pharmacyclics

Consulting: Abbvie, Bristol-Meyers Squibb, Pfizer

I will be discussing non-FDA approved indications during my presentation.

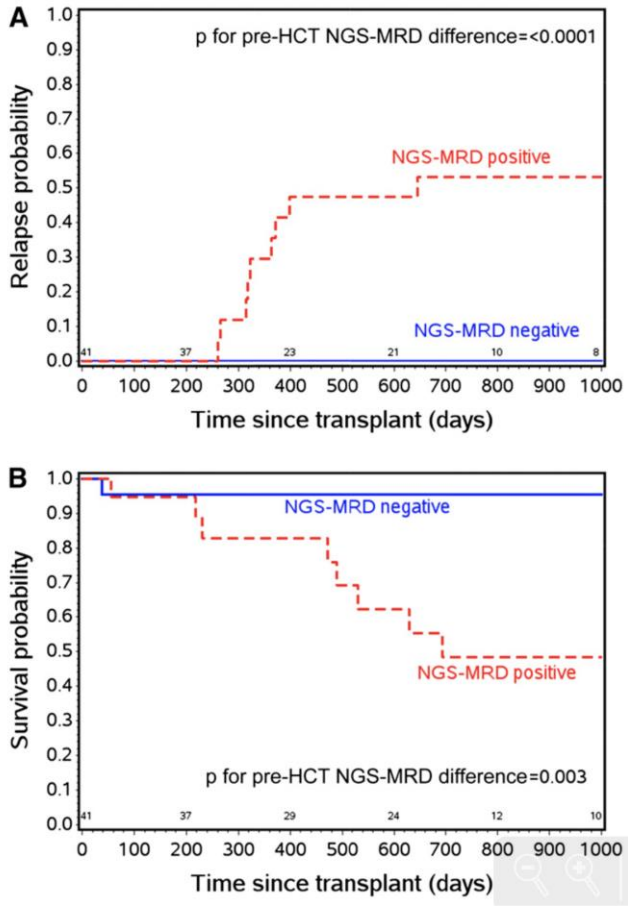
Management Algorithm for Adults with ALL in CR1



MRD+ B-ALL

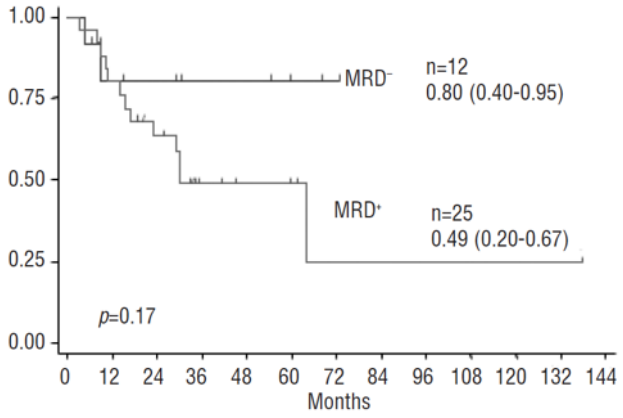
MRD Status Pre-HCT Predicts RFS and OS

- N=56, age 1-21
- COG ASCT0431
- MRD Quant: NGS

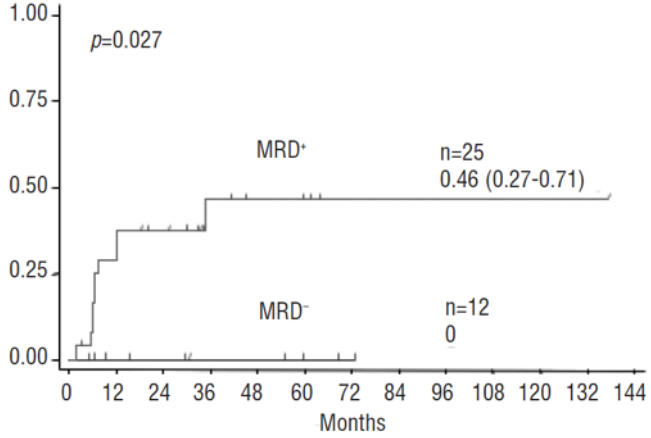


n=43, age 18-63
MAC alloHCT in CR1
MRD quant:
TCR/Ig ASO-PCR or BCR/ABL Q-PCR or
MLL/AF4 Q-PCR

MRD status pre-HCT: OS



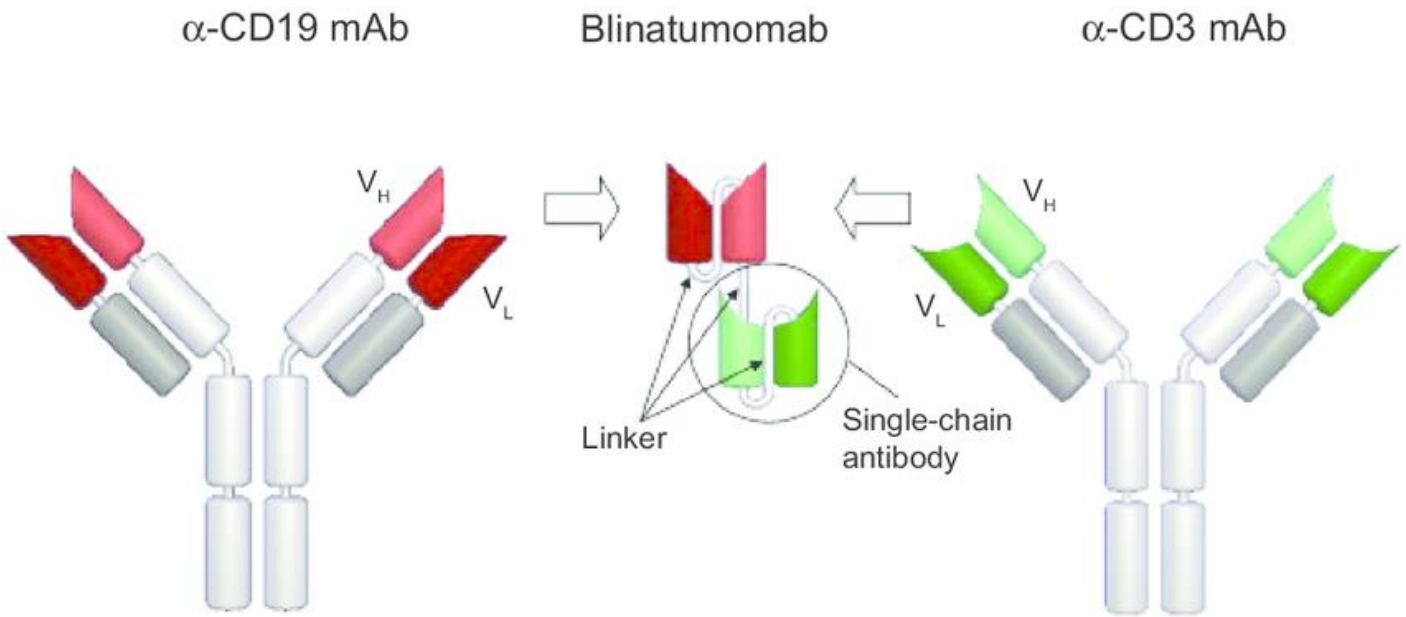
MRD status pre-HCT: CIR

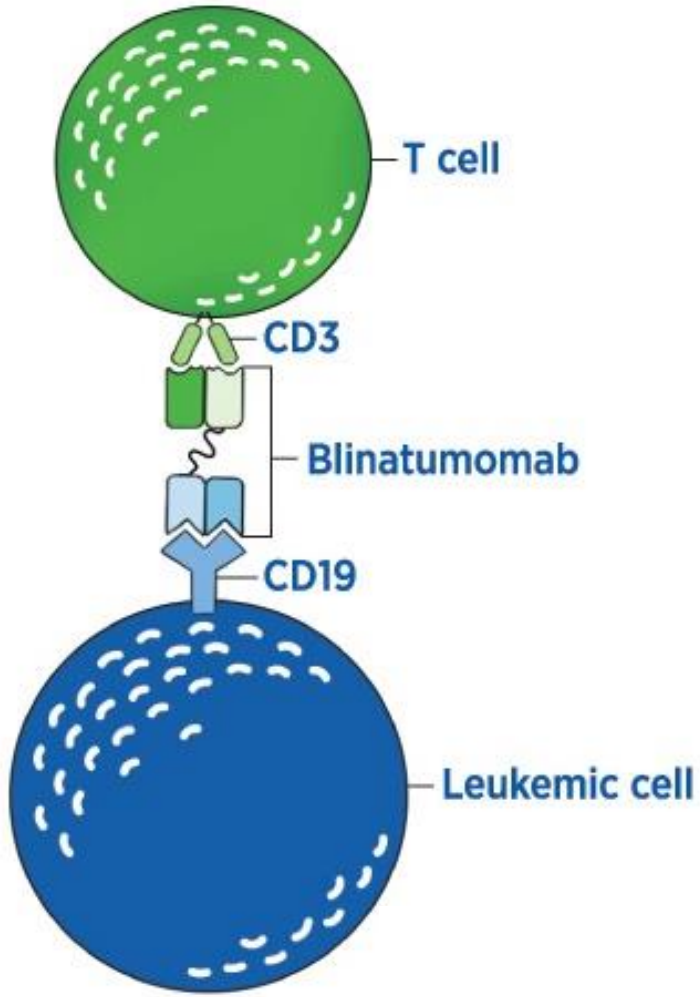


Pulsipher *et al*. Blood 2015; 125:3501-3508

Spinelli *et al*. Haematologica 2007; 92:612-618

Blinatumomab BLAST Trial: Preemption of ALL Relapse Using MRD-Directed Treatment





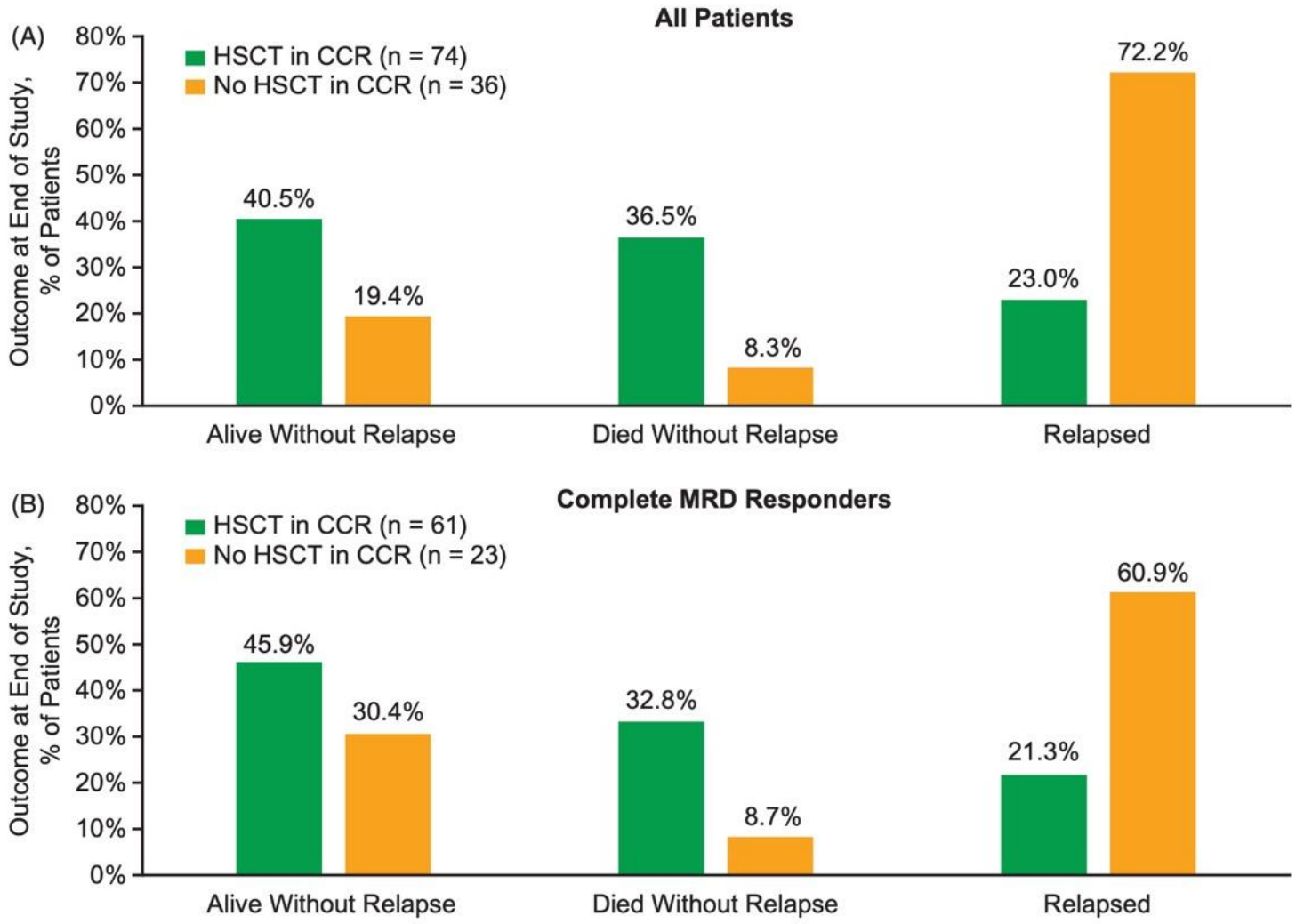
Honey K. AACR.ORG

Blinatumomab BLAST Trial: Preemption of ALL Relapse Using MRD-Directed Treatment

Blinatumomab administered for >10^{-3} MRD after ≥ 3 blocks of chemotherapy

-> 80% MRD response (achieved MRD <10^{-4})

-> 72% underwent alloHCT

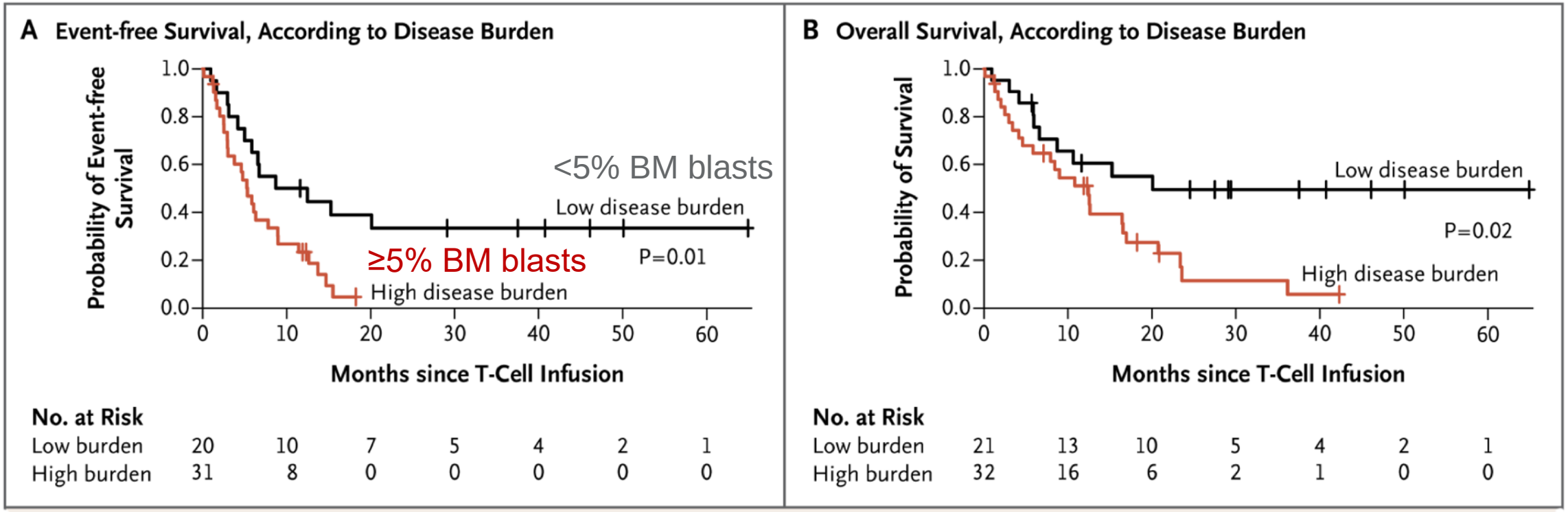


Gökbuget et al. Blood 2018; 131:1522-1531

Gökbuget et al. Leuk Lymph 2020; 61(11):2665-2673

CAR-T cells in MRD+ B-ALL

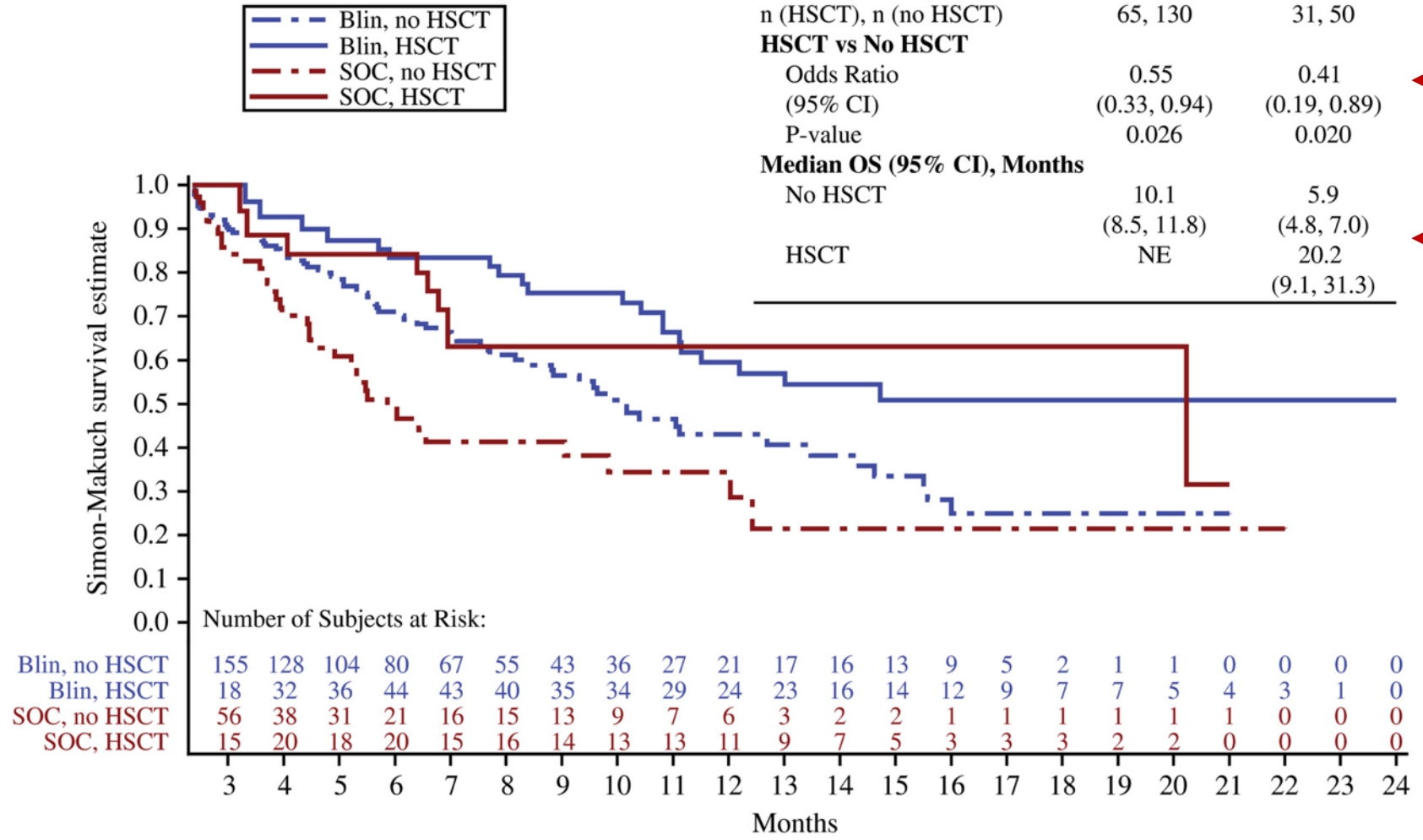
MSKCC experience with CD19-CD28z CAR-T



Park et al. NEJM 2018; 378(5):449-459

Relapsed/Refractory B-ALL

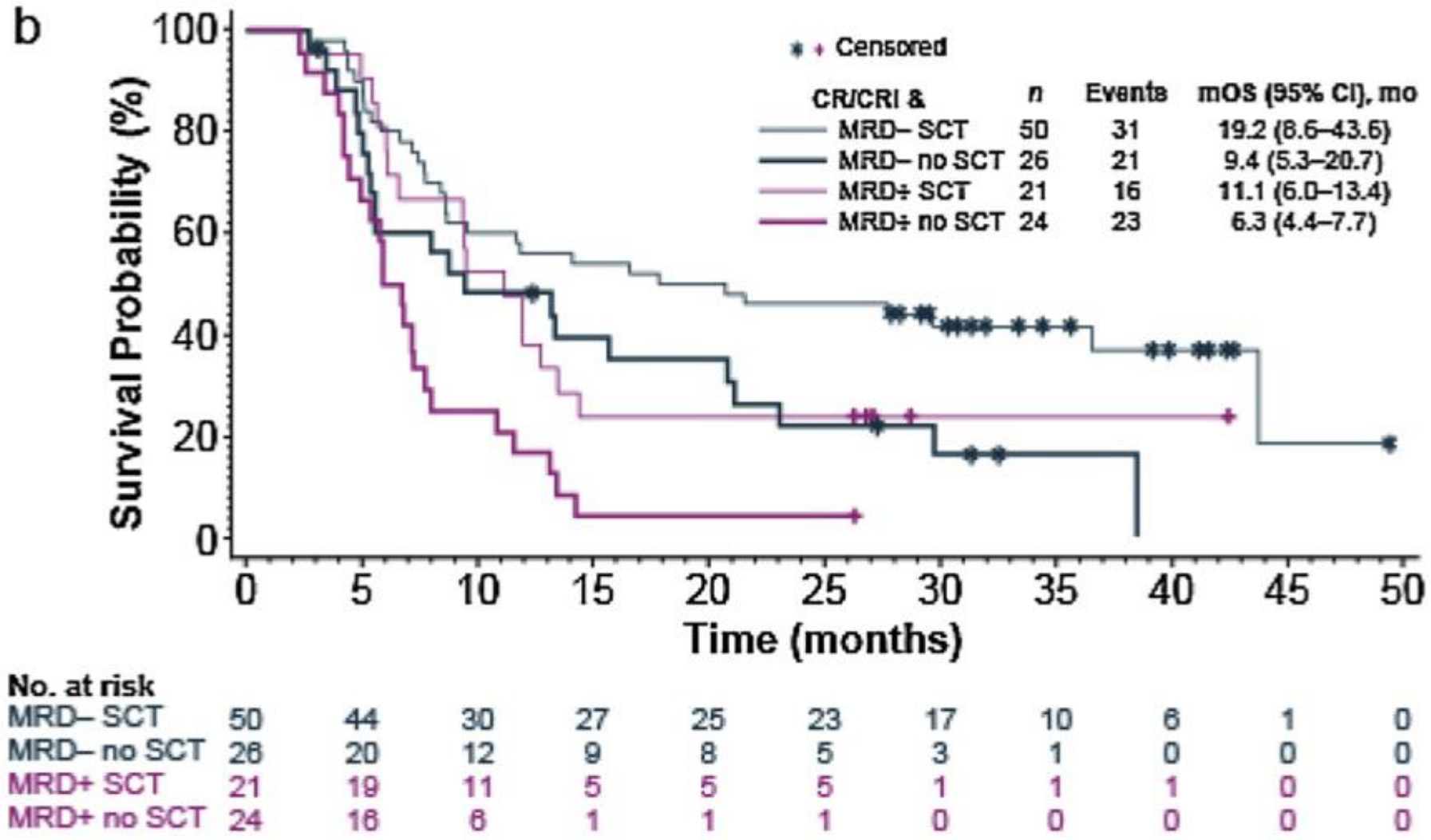
Blinatumomab as Bridge to Allo-HCT in R/R ALL



	Blin n = 195	SOC n = 81
n (HSCT), n (no HSCT)	65, 130	31, 50
HSCT vs No HSCT		
Odds Ratio	0.55	0.41
(95% CI)	(0.33, 0.94)	(0.19, 0.89)
P-value	0.026	0.020
Median OS (95% CI), Months		
No HSCT	10.1 (8.5, 11.8)	5.9 (4.8, 7.0)
HSCT	NE	20.2 (9.1, 31.3)

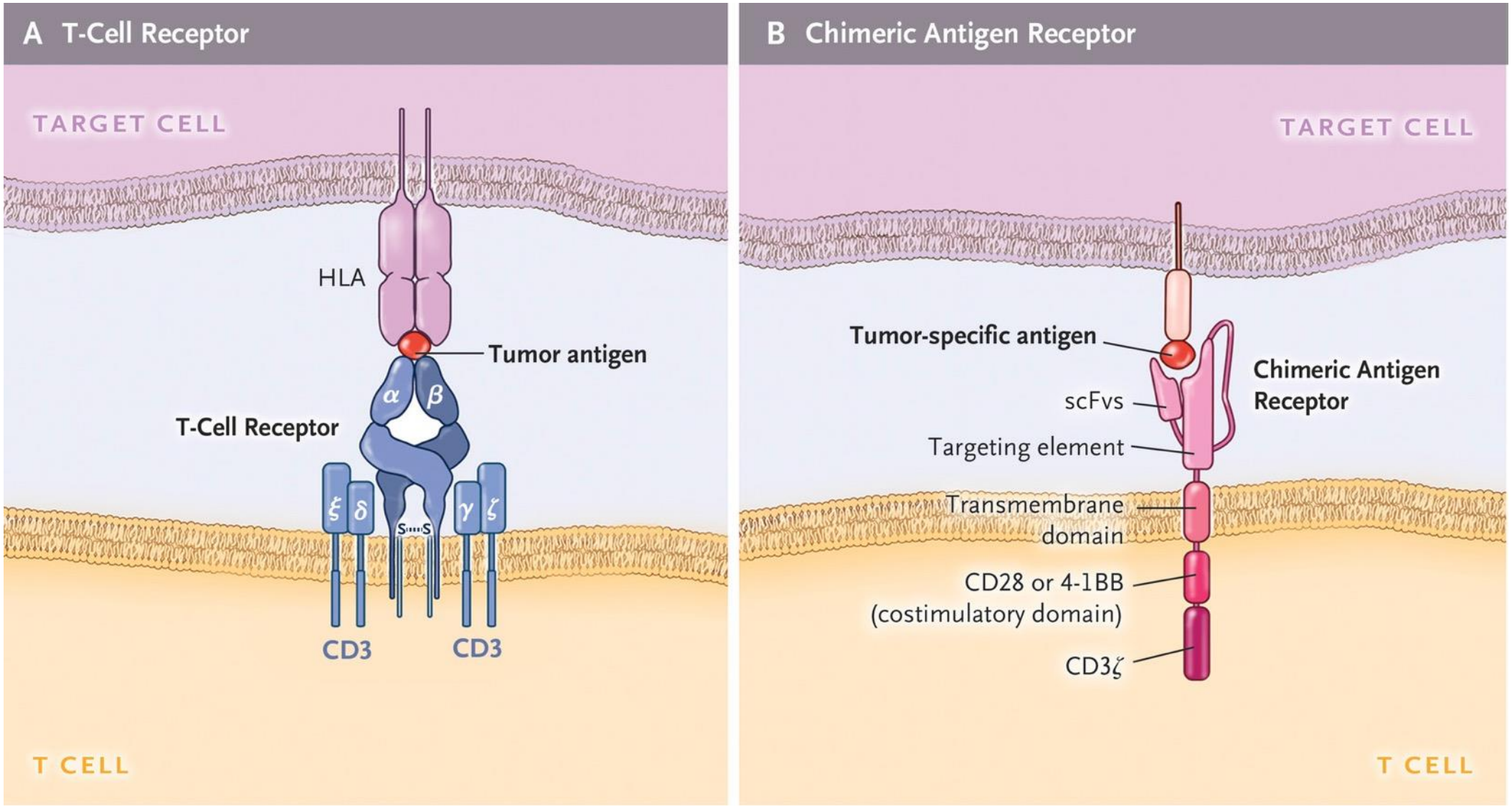
Jabbour et al. Cancer 2019; 125(23):4181-4192

Inotuzumab as Bridge to Allo-HCT in R/R ALL



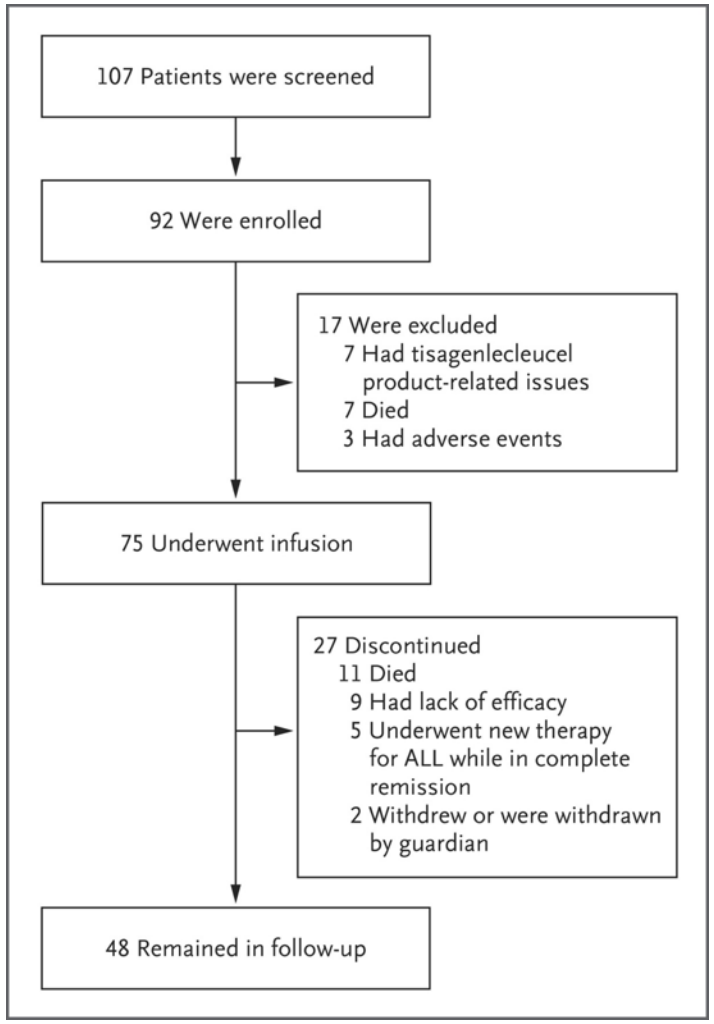
Jabbour et al. Leukemia Res 2020; 88:106283

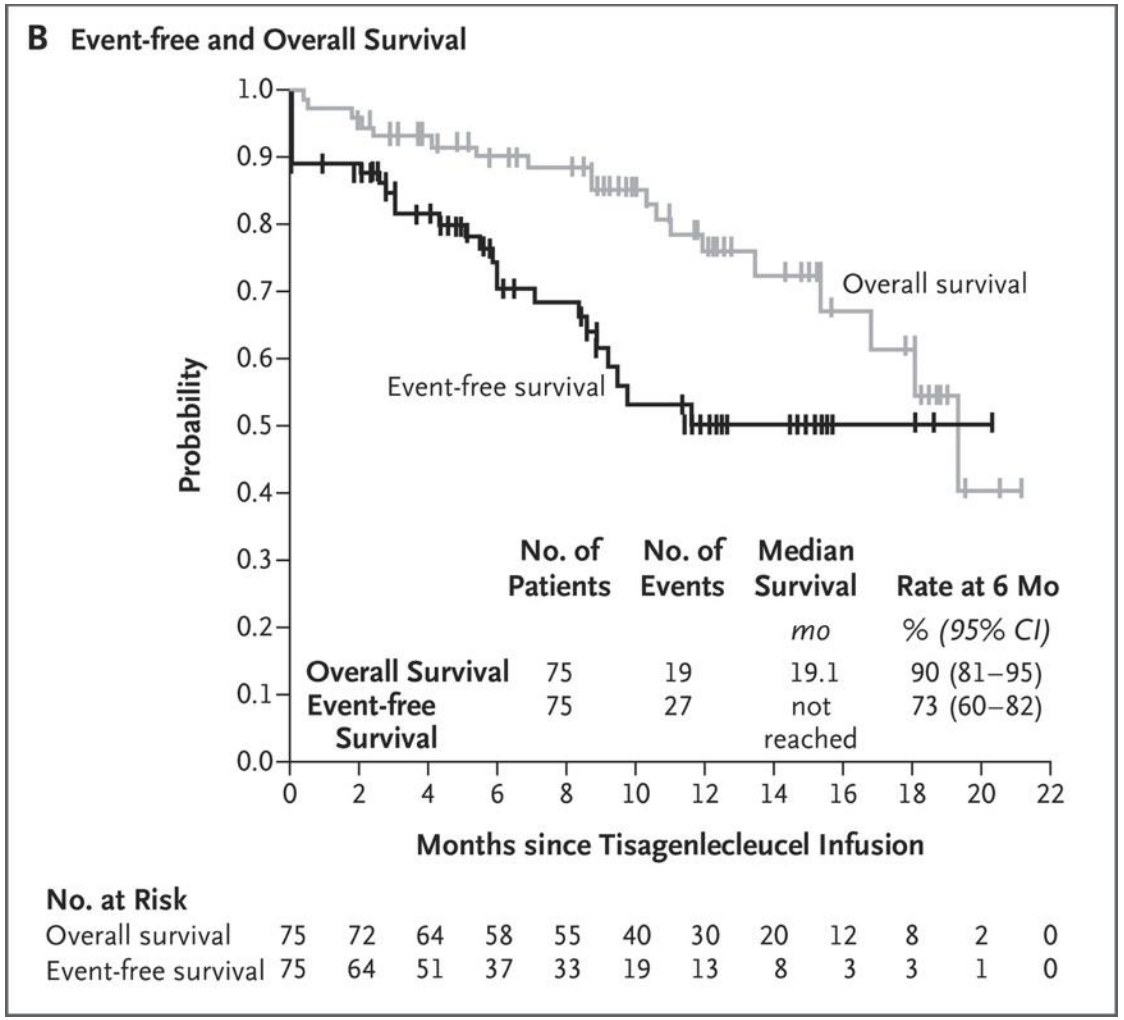
Chimeric Antigen Receptor (CAR)-T cells



June and Sadelain. N Engl J Med 2018; 379:64-73.

Treatment of Relapsed/Refractory ALL — Tisagenlecleucel (CD19/4-1BBz) (ELIANA)



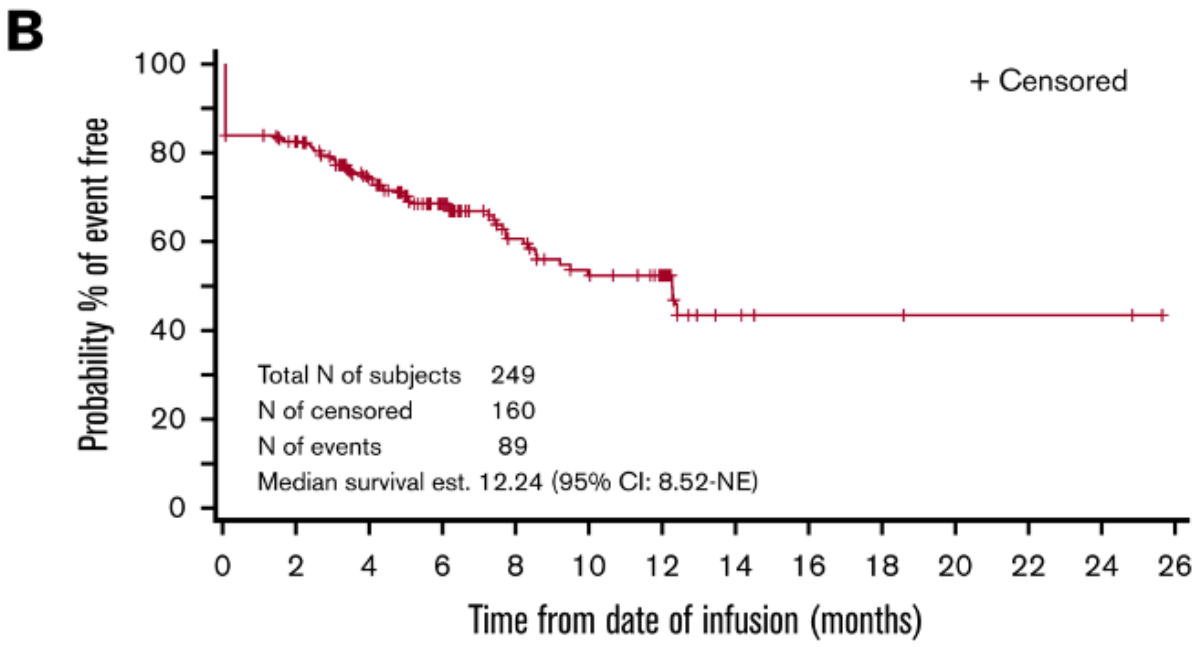


Maude et al. NEJM 2018; 378:439-448

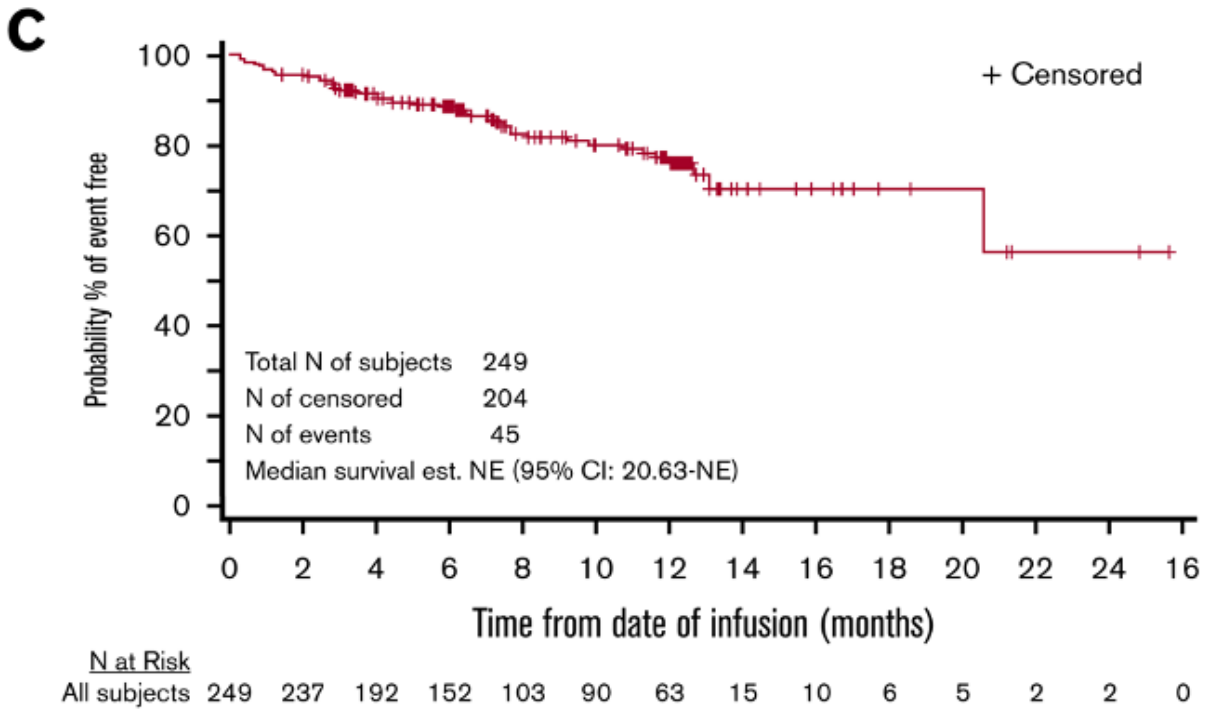
US FDA approved for treatment of relapsed/refractory B-ALL in ≤25yo 8/2017

Treatment of Relapsed/Refractory ALL — Tisagenlecleucel (CD19/4-1BBz) (CIBMTR)

EFS

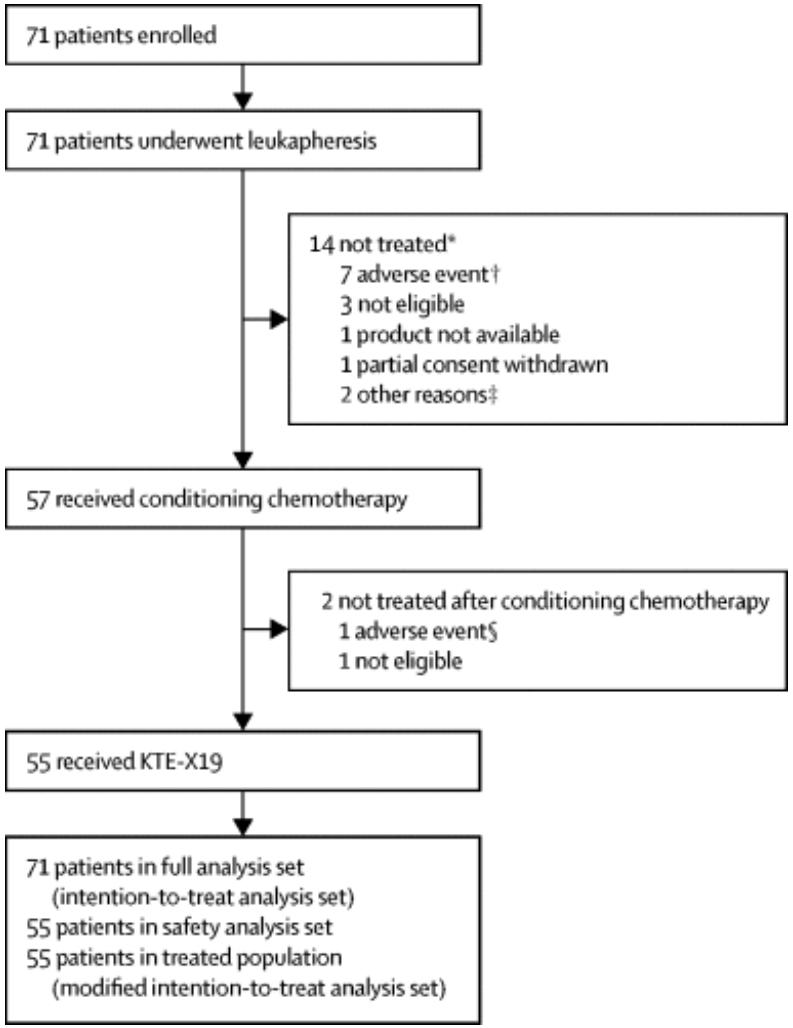


OS



Pasquini et al. Blood Advances 2020; 4(21):5414-5424

Brexucabtagene autoleucel(CD19/CD28z) in Adult R/R ALL



	Treated patients (n=55)
Overall complete remission or complete remission with incomplete haematological recovery	39 (71%)*
Complete remission	31 (56%)
Complete remission with incomplete haematological recovery	8 (15%)
Blast-free hypoplastic or aplastic bone marrow	4 (7%)
No response	9 (16%)
Unknown or not evaluable†	3 (5%)

Data are n (%). *95% CI 57–82, p<0·0001. †The three patients who were unknown or not evaluable died (at days 8, 15, and 18) before the first disease assessment.

Table 2: **Rate of overall complete remission or complete remission with incomplete haematological recovery based on central assessment**

Shah et al., Lancet 2021; 398:491-502

Brexucabtagene autoleucel(CD19/CD28z) in Adult R/R ALL

Intention to treat

Table S2. Efficacy Endpoints in Enrolled Patients in Phase 2 Based on Central Assessment (Phase 2, Full Analysis Set).

n (%)	N=71
Overall CR/CRi	39 (54·9)
CR	31 (43·7)
CRi	8 (11·3)
Blast-free hypoplastic or aplastic bone marrow	4 (5·6)
No response	11 (15·5)
Unknown or not evaluable	17 (23·9)
Median DOR (95% CI), mo	12·8 (8·7–NE)
Median RFS (95% CI), mo	7·0 (0·0–13·2)
Median OS (95% CI), mo	19·2 (10·4–NE)

CR=complete remission; CRi=complete remission with incomplete hematologic recovery; DOR=duration of remission; NE=not estimable; OS=overall survival; RFS=relapse-free survival.

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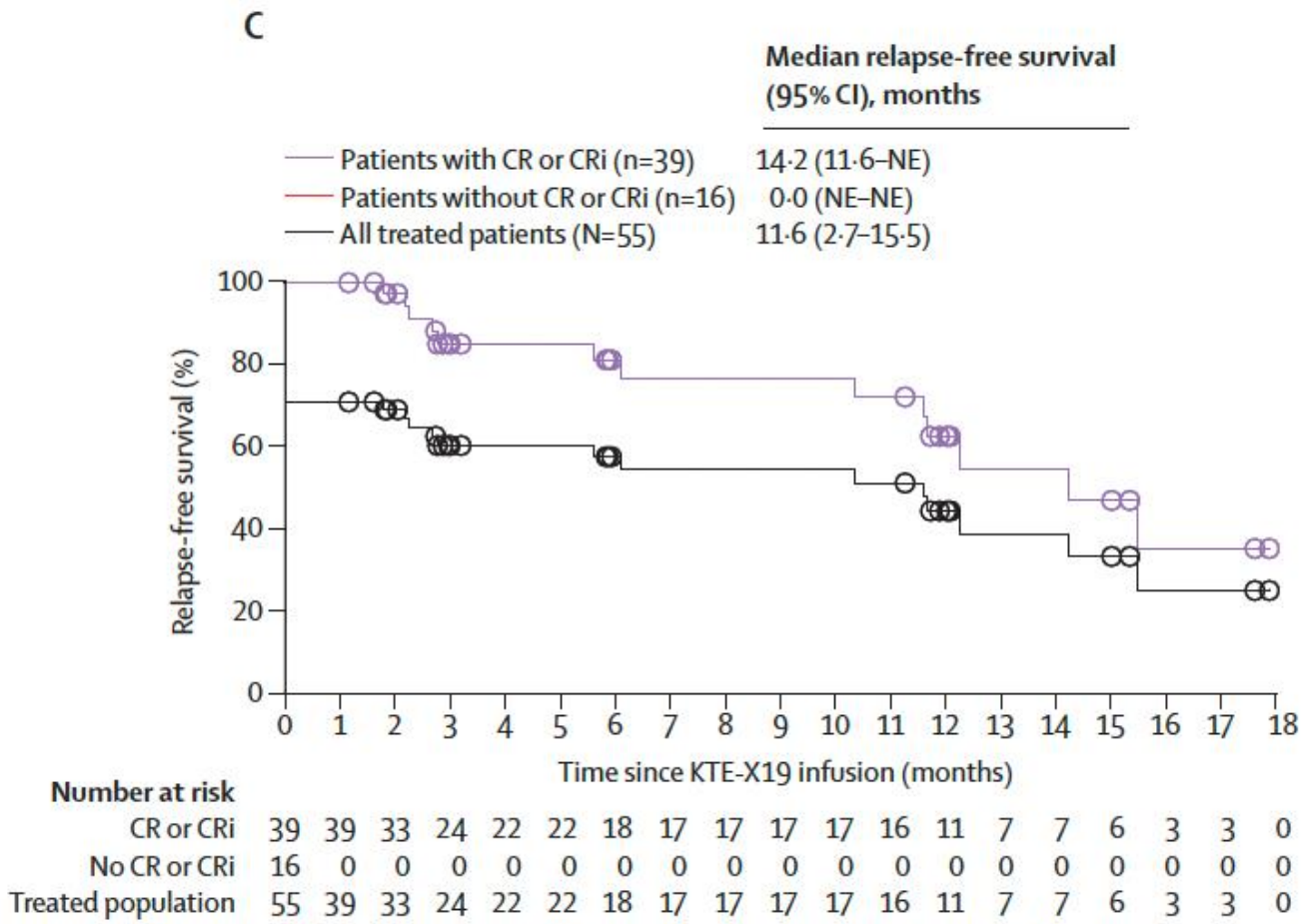
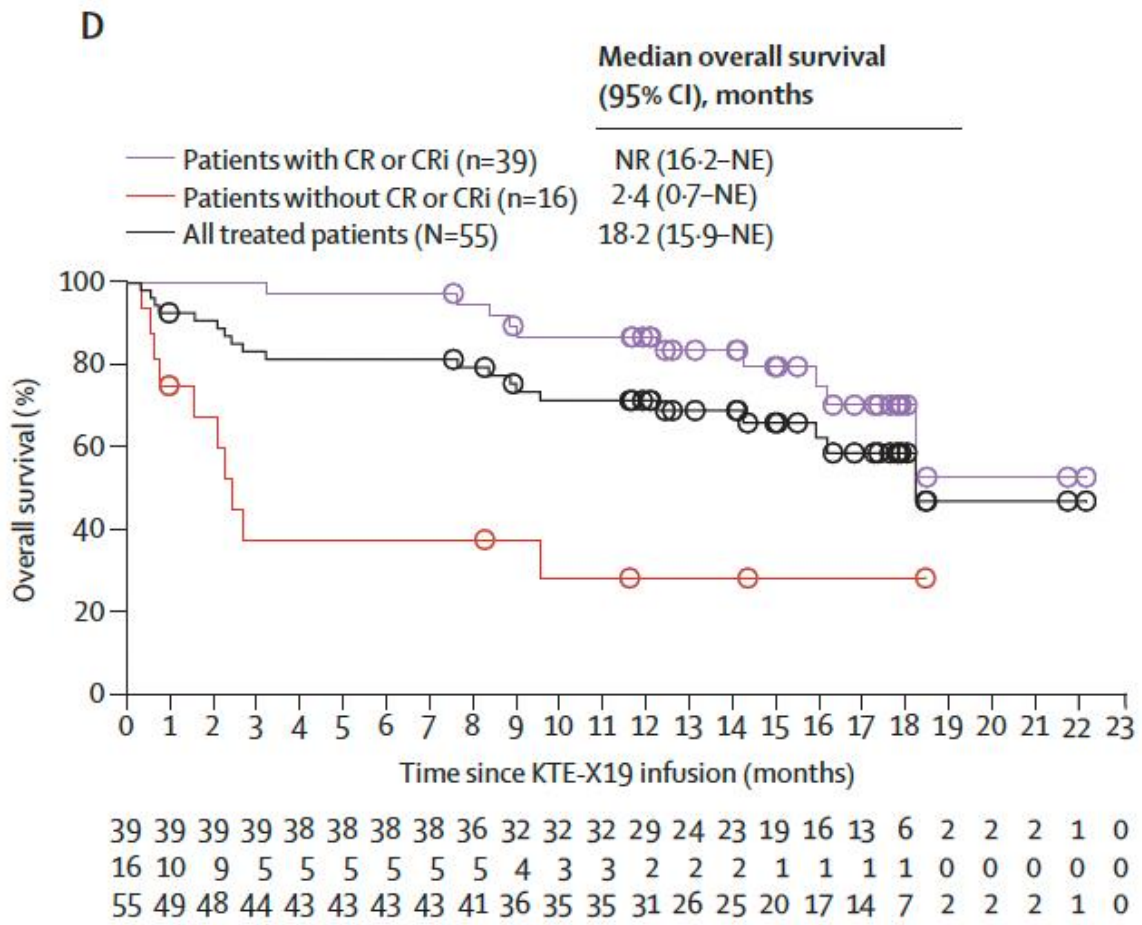


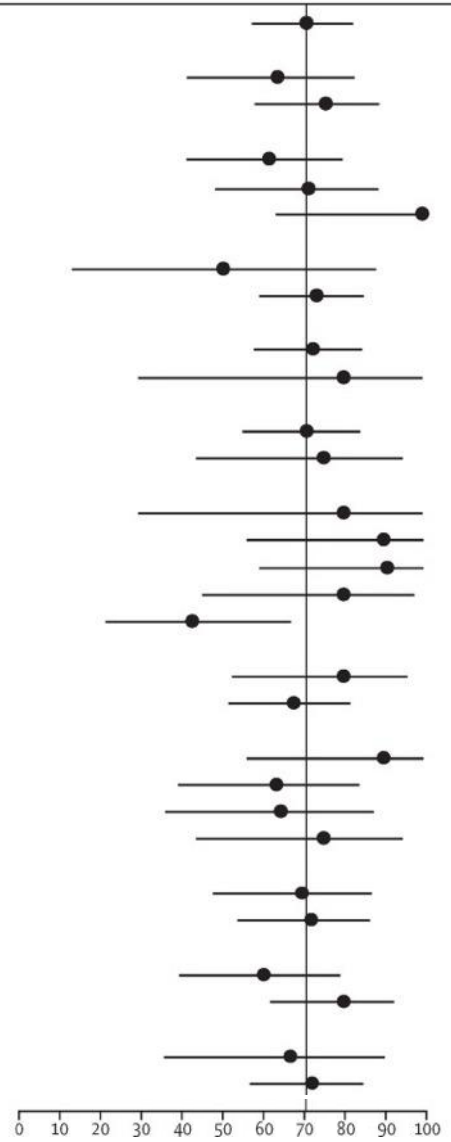


Shah et al., Lancet 2021; 398:491-502

US FDA approved for treatment of relapsed/refractory B-ALL 10/2021

Brexucabtagene autoleucel(CD19/CD28z) in Adult R/R ALL

	Total patients, N	Patients with CR or CRi, n	Proportion of patients with response, % (95% CI)
Overall	**55**	**39**	**71% (57–82)**
Sex			
Female	22	14	64% (41–83)
Male	33	25	76% (58–89)
Age, years			
18–39	26	16	62% (41–80)
40–64	21	15	71% (48–89)
≥65	8	8	100% (63–100)
Baseline extramedullary disease			
Yes	6	3	50% (12–88)
No	49	36	73% (59–85)
CNS status at screening			
CNS-1	47	34	72% (57–84)
CNS-2	5	4	80% (28–99)
CD19 lymphoblast baseline category, %			
≥95	41	29	71% (54–84)
<95	12	9	75% (43–95)
Blasts in bone marrow at baseline, %			
0–5	5	4	80% (28–99)
>5–25	10	9	90% (55–100)
>25–50	11	10	91% (59–100)
>50–75	10	8	80% (44–97)
>75–100	19	8	42% (20–67)
Philadelphia chromosome			
Yes	15	12	80% (52–96)
No	40	27	68% (51–81)
Previous lines of therapy			
1	10	9	90% (55–100)
2	19	12	63% (38–84)
3	14	9	64% (35–87)
≥4	12	9	75% (43–95)
Previous allogeneic SCT			
Yes	23	16	70% (47–87)
No	32	23	72% (53–86)
Previous blinatumomab			
Yes	25	15	60% (39–79)
No	30	24	80% (61–92)
Previous inotuzumab ozogamicin			
Yes	12	8	67% (35–90)
No	43	31	72% (56–85)



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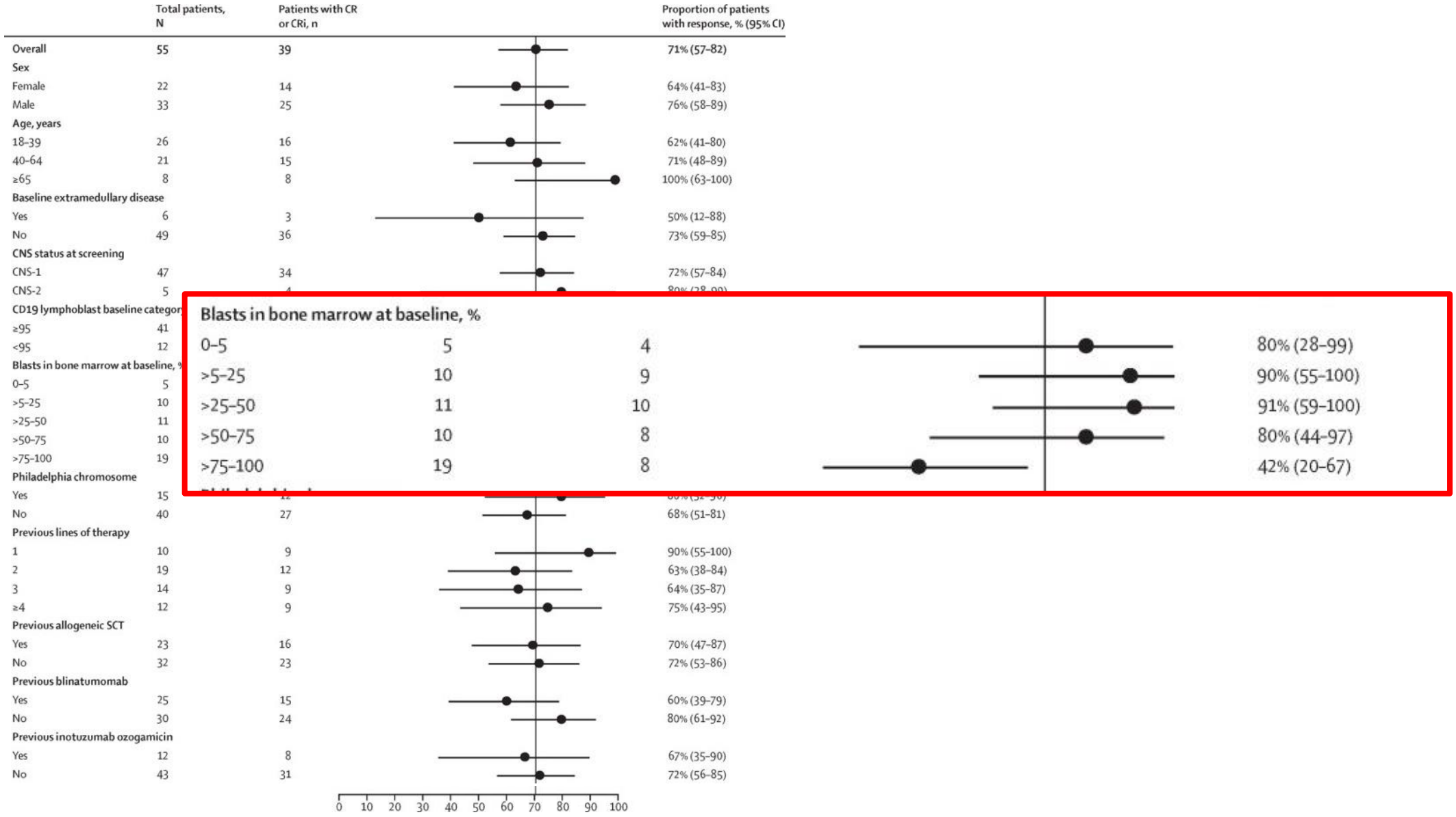
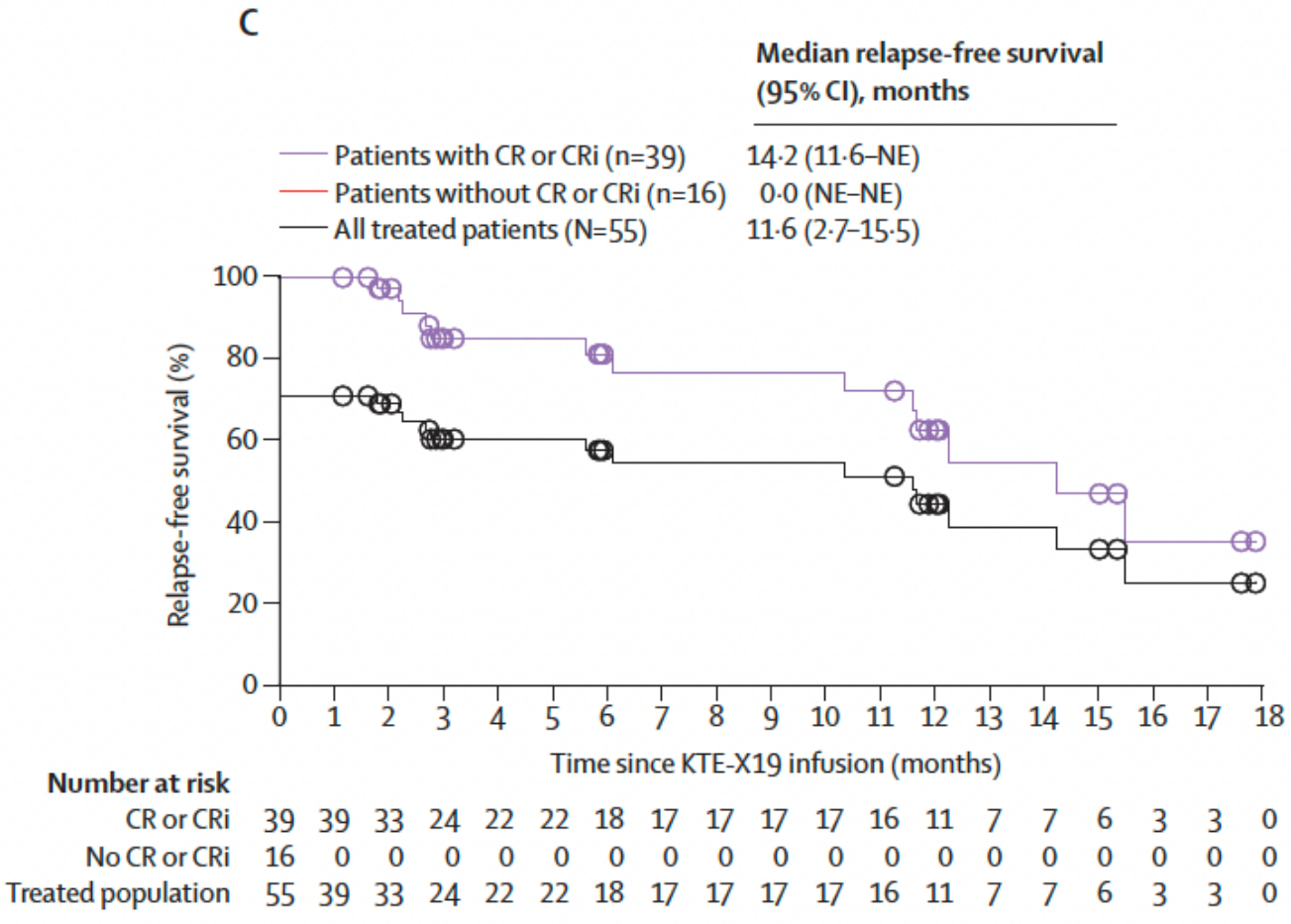


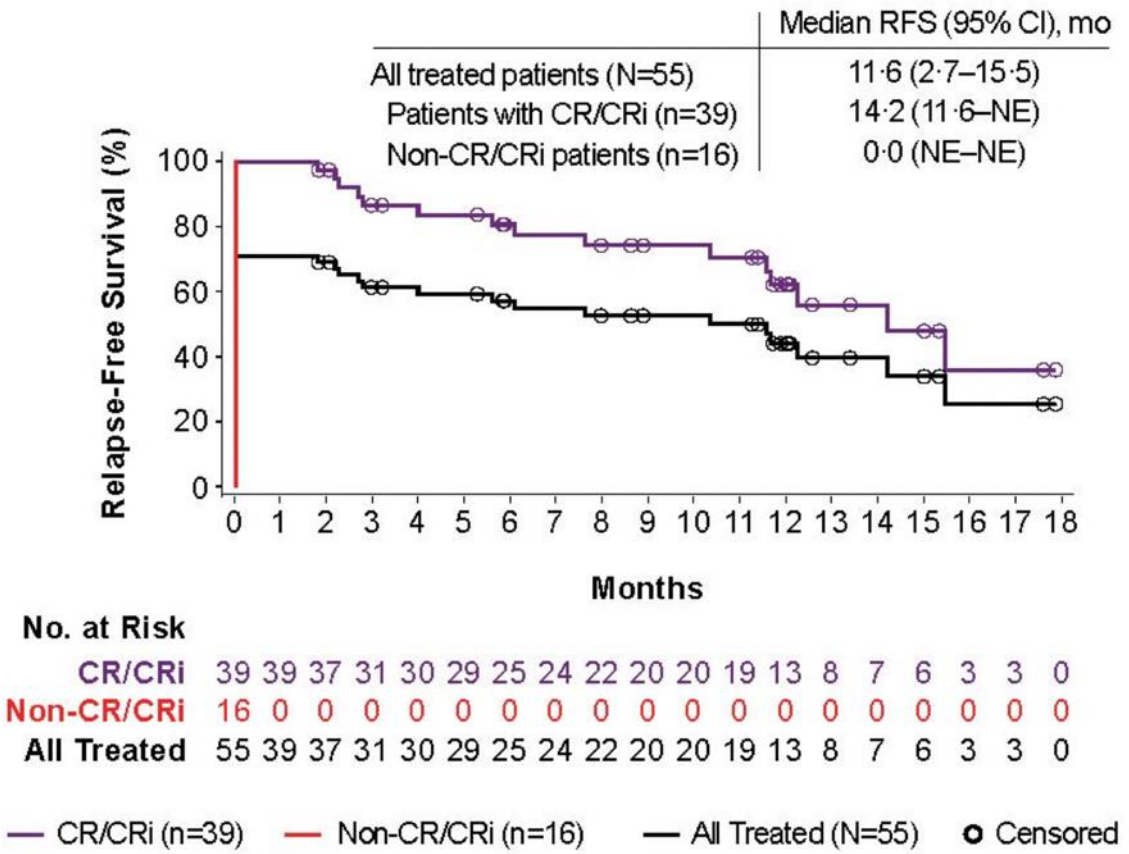
Shah et al., Lancet 2021; 398:491-502

Brexucabtagene autoleucel(CD19/CD28z) in Adult R/R ALL

Censored for alloHCT



Not censored for alloHCT
(n=10 underwent HCT after Brexu-cel)

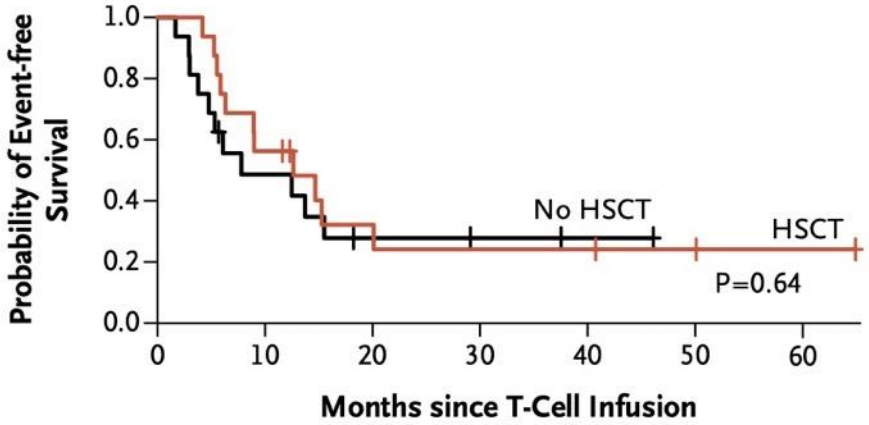


Shah et al., Lancet 2021; 398:491-502

CAR-T as Bridge to AlloHCT for R/R ALL

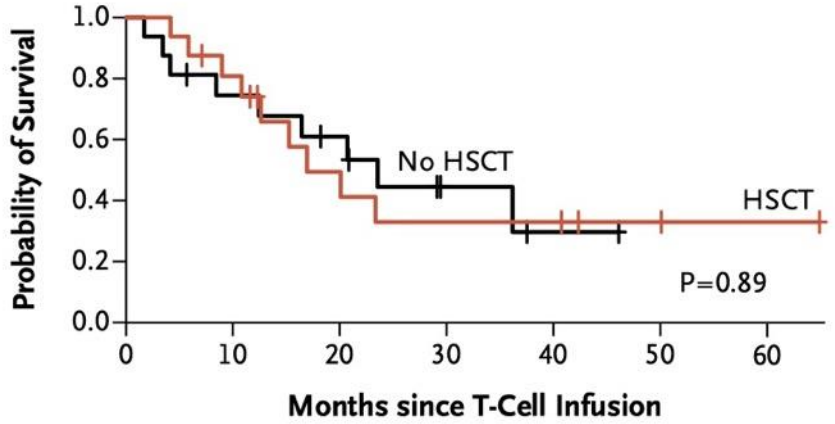
(CD19/CD28z)

E Event-free Survival, According to HSCT Status



No. at Risk							
No HSCT	16	7	3	2	1	0	0
HSCT	16	9	4	3	3	2	1

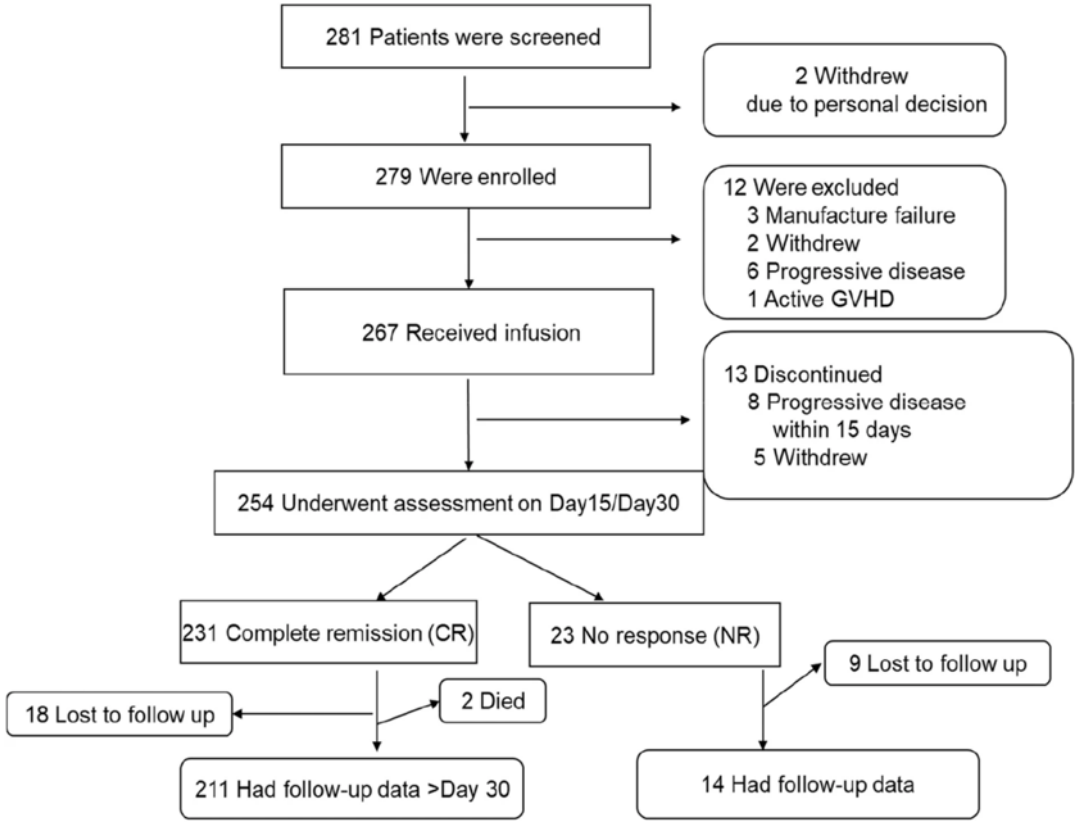
F Overall Survival, According to HSCT Status

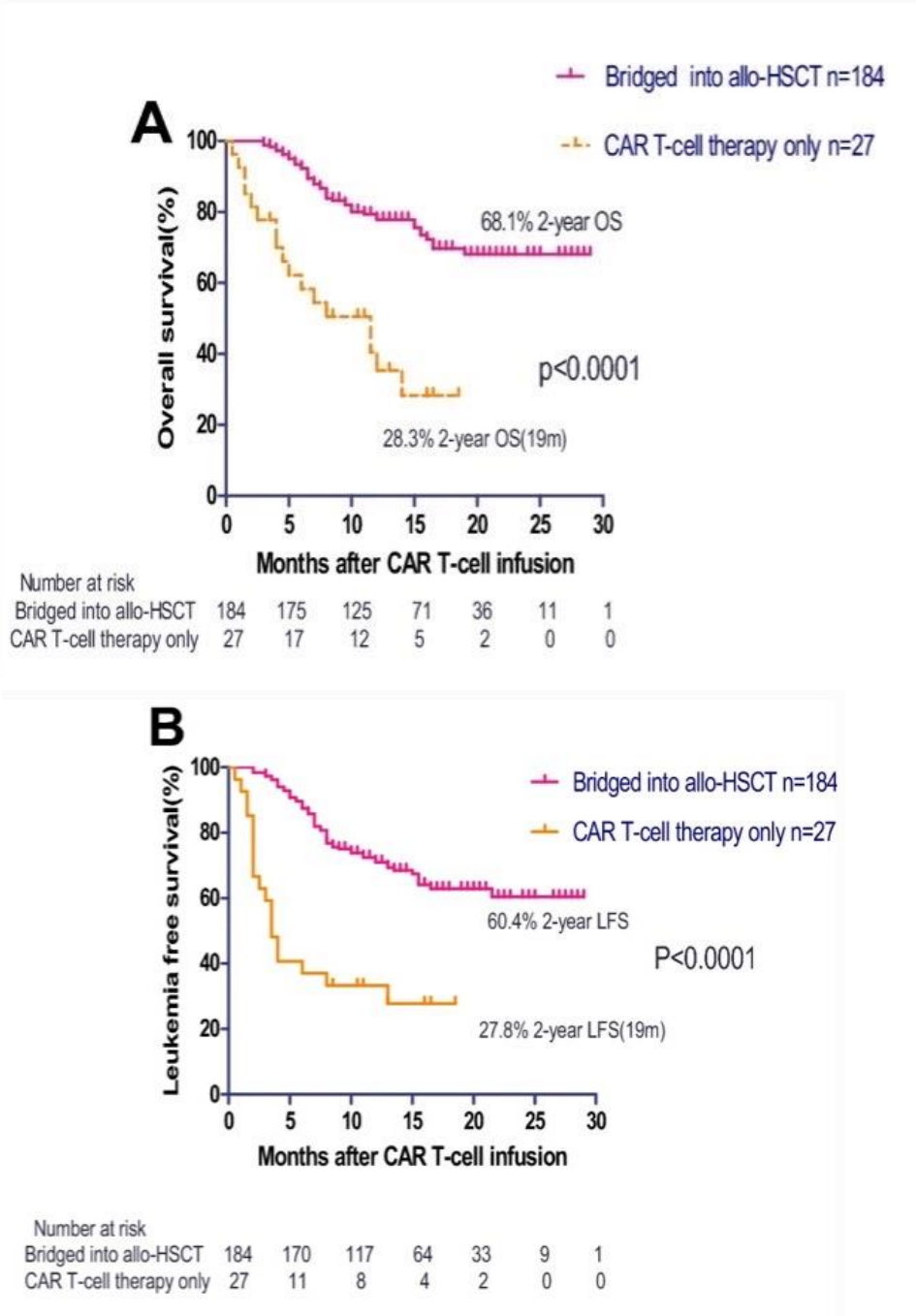


No. at Risk							
No HSCT	16	11	8	3	1	0	0
HSCT	16	12	6	4	4	2	1

Park *et al*. NEJM 2018; 378:449-459

CAR-T as Bridge to AlloHCT for R/R ALL

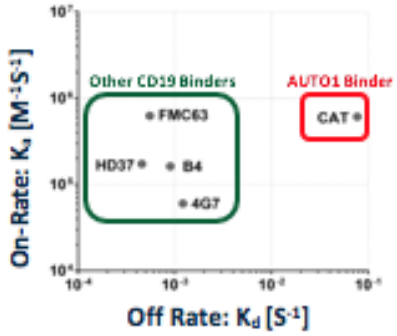




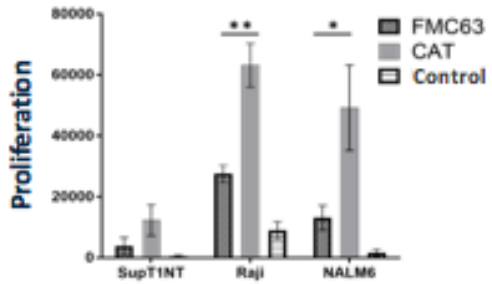
Zhang *et al*. Cancer Immunol Immunother 2021; 378:449-459

Future Development in CAR-T cells for ALL — Autolus low-affinity CD19 targeting (CD19*/4-1BBz)

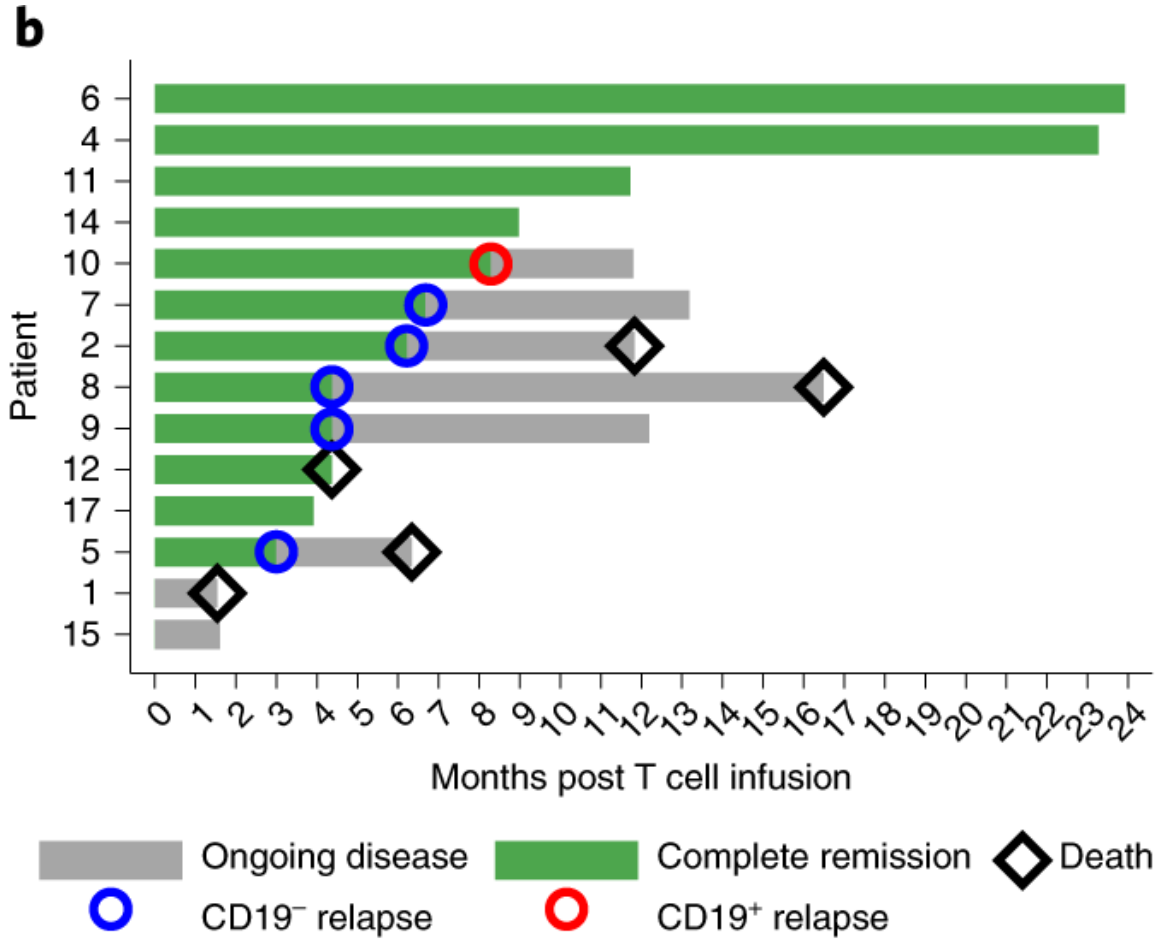
Fast Off-Rate



Enhanced Proliferation

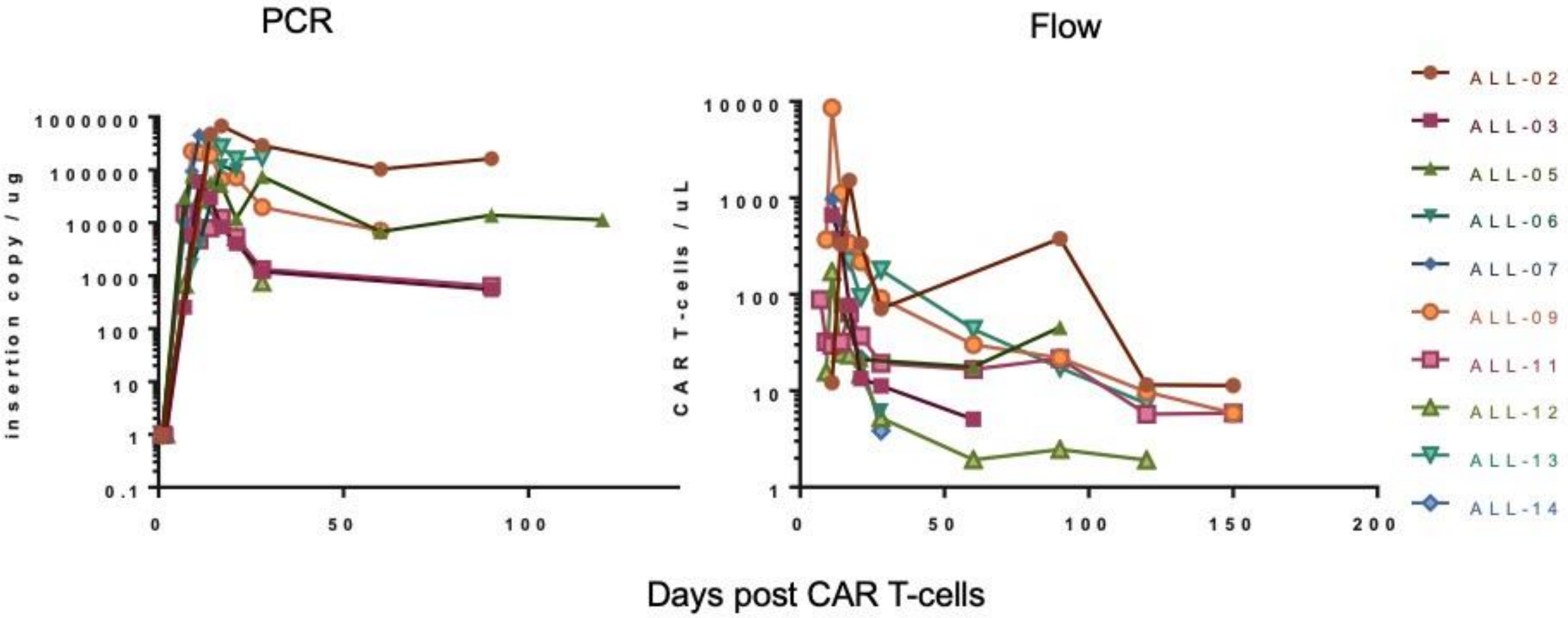


1. Similar binders are used in Yescarta and JCAR-017
2. Pule at al., Keystone Symposia: Emerging Cellular Therapies 2



Ghorashian et al., Nat Med 2019; 25:1408-1414.

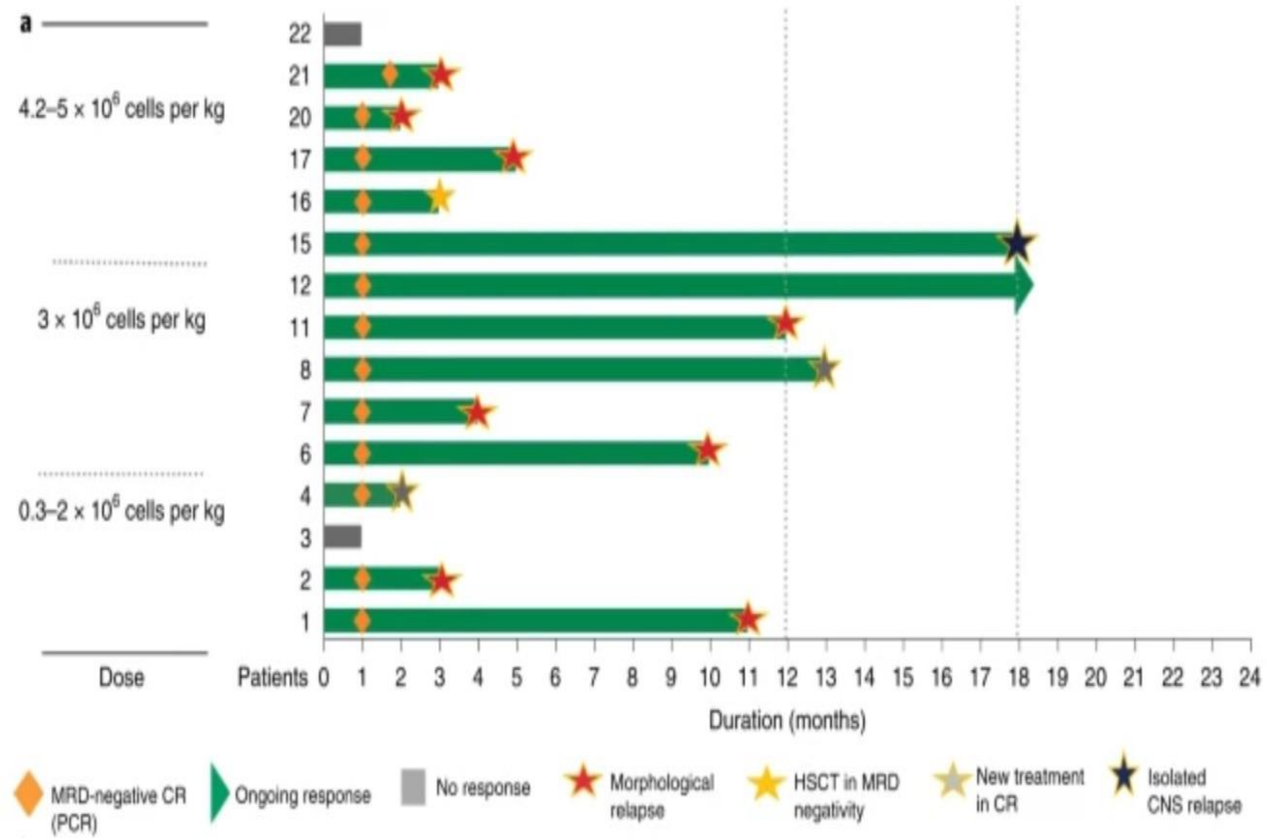
Future Development in CAR-T cells for ALL — Autolus low-affinity CD19 targeting (CD19*/4-1BBz)



Ghorashian et al., Nat Med 2019; 25:1408-1414.

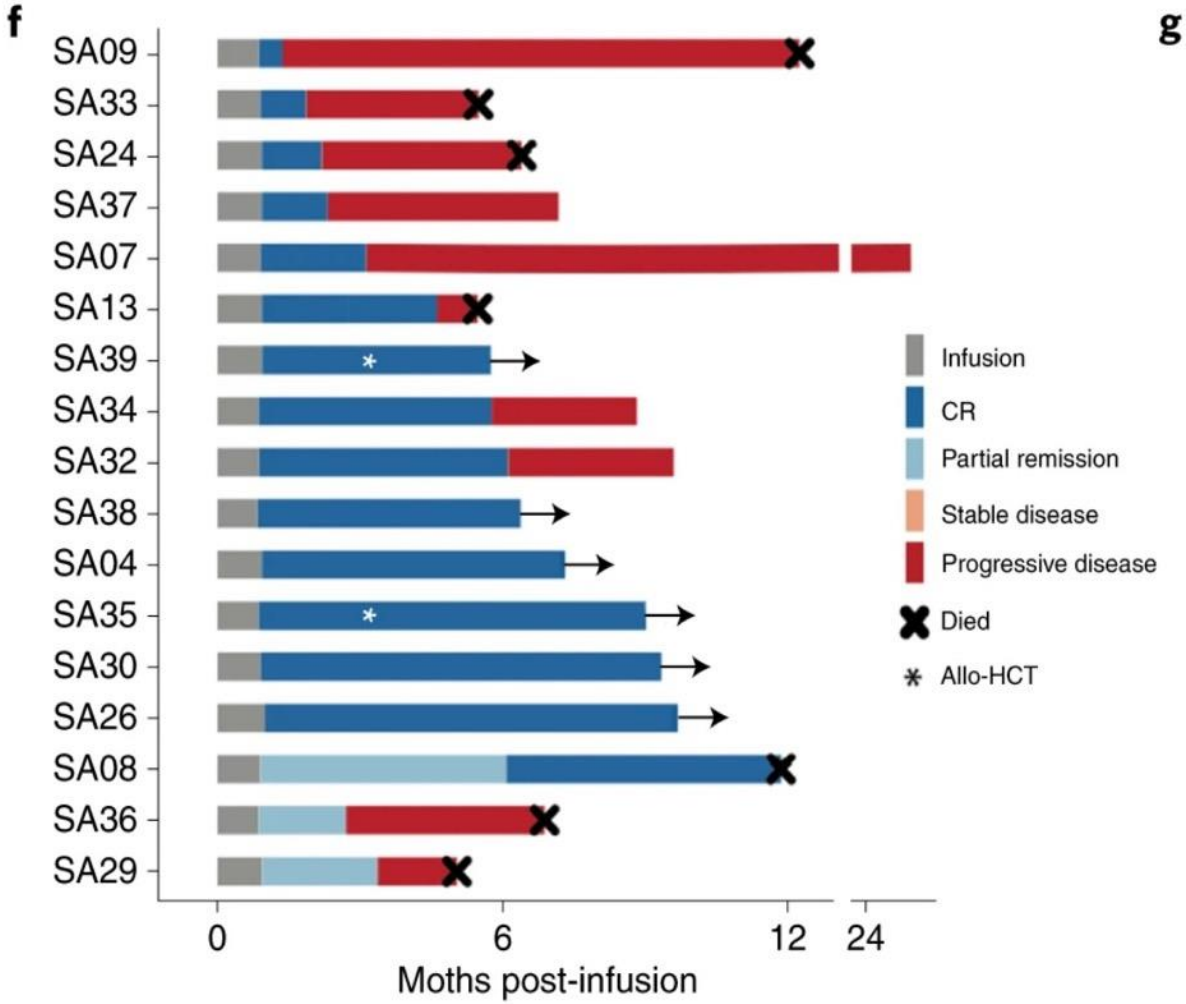
Future Development in CAR-T cells for ALL — CD22 targeting

(CD22/4-1BBz)



Cordoba et al., Nat Med 2021; 27:1797-1805.

(CD19/CD22/4-1BBz)



Speigel et al., Nat Med 2021; 27:1419-1431.

Management Algorithm for Adults with ALL

MRD+ B-ALL →

- **Blinatumomab → AlloHCT (preferred)**
- CAR-T → AlloHCT
- CAR-T

Remains to be determined

R/R B-ALL →

- **Blinatumomab → AlloHCT (preferred)**
- Inotuzumab → AlloHCT (option; need to limit Ino pre-HCT)
- Low dose Inotuzumab +/- chemo +/- Blin → AlloHCT
- Chemo → AlloHCT *(not preferred)*
- **CAR-T → AlloHCT (emerging*)**
- **CAR-T (emerging*)**

Remains to be determined which is preferable

***Preferred for post-Blin/Ino relapse, post-HCT relapse ?maybe instead of Blin/Ino in some settings**

CAR-T cells in Adult ALL:

- It remains unclear if there are patients for whom CAR-T should be preferred destination therapy (ie, no consideration of subsequent alloHCT)
- Currently, alloHCT will generally be a preferred destination for MRD+ and R/R B-ALL patients
- Further studies needed to optimize approaches to alloHCT after CAR-T
- Both alloHCT and CAR-T yield unsatisfactory results that need further improvement:
  - AlloHCT: High NRM due to GVHD/infections undermines lower relapse risk
  - CAR-T: Unsatisfactory cure rate with current CAR-T cell constructs
    - Remains to be determined whether cure rate can be improved with alternative constructs: eg, low affinity targeting, 4-1BB vs CD28 costim, and/or multiple antigen targeting


Thank you!