CAR-T cell Therapy for Lymphoma

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Maloney Disclosures

- Research funding to Institution
  - Kite Pharma
  - Juno/Celgene/BMS
- Advisory board participation
  - Celgene/Juno/BMS
  - Pharmacyclics
  - Kite Pharma/Gilead
  - Novartis
- DMC participation
  - BioLine RX
- Scientific Advisory Board
  - A2 Biotherapeutics
- Stock options
  - A2 Biotherapeutics
- Patents
  - Juno Therapeutics, unlicensed

CD19 directed CAR-T cell therapy for NHL

- **Aggressive NHL**
  - Tisagenlecleucel
  - Axicabtagene ciloleucel
  - Lisocabtagene maraleucel

  Comparison: How to choose?

- **Mantle Cell lymphoma**
  - Brexucabtagene autoleucel

- **Follicular lymphoma**
  - Axicabtagene ciloleucel

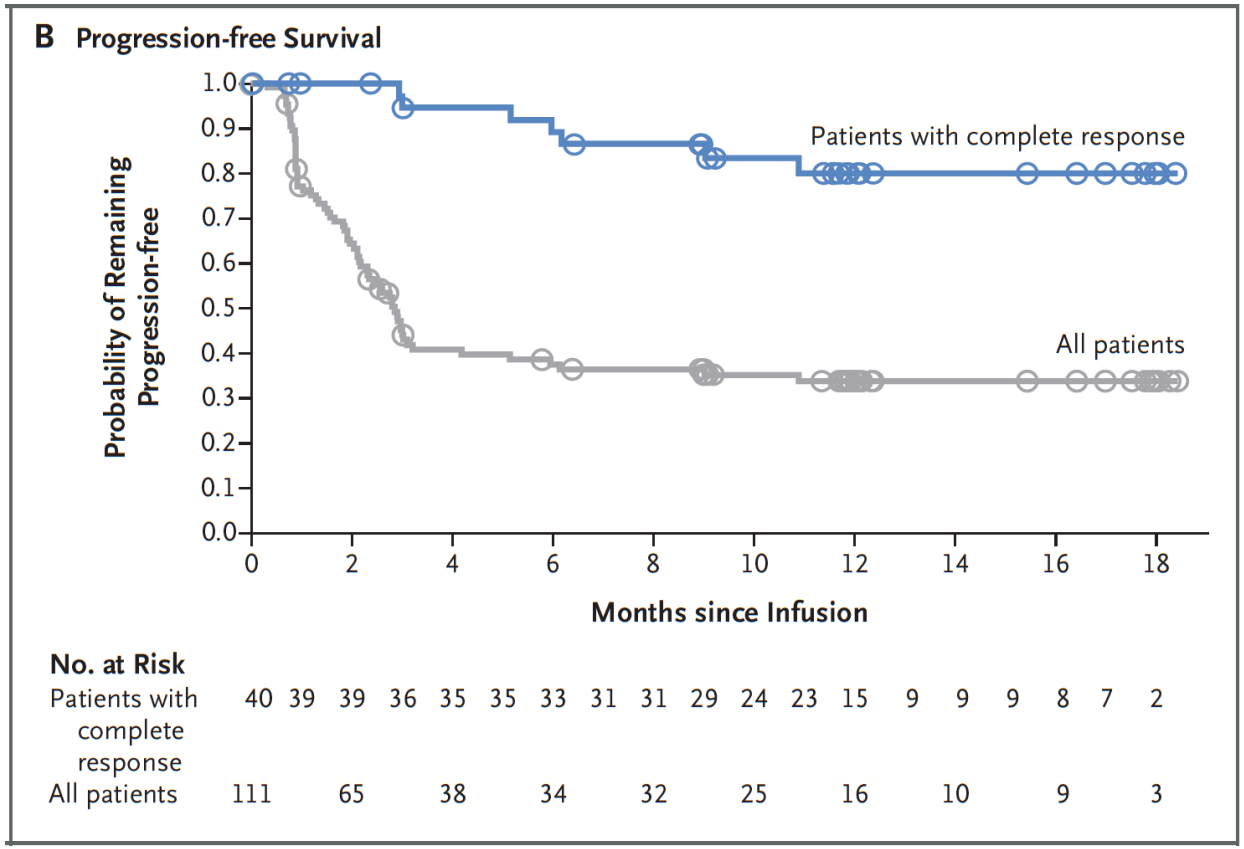
- **Future of CAR-T for NHL**

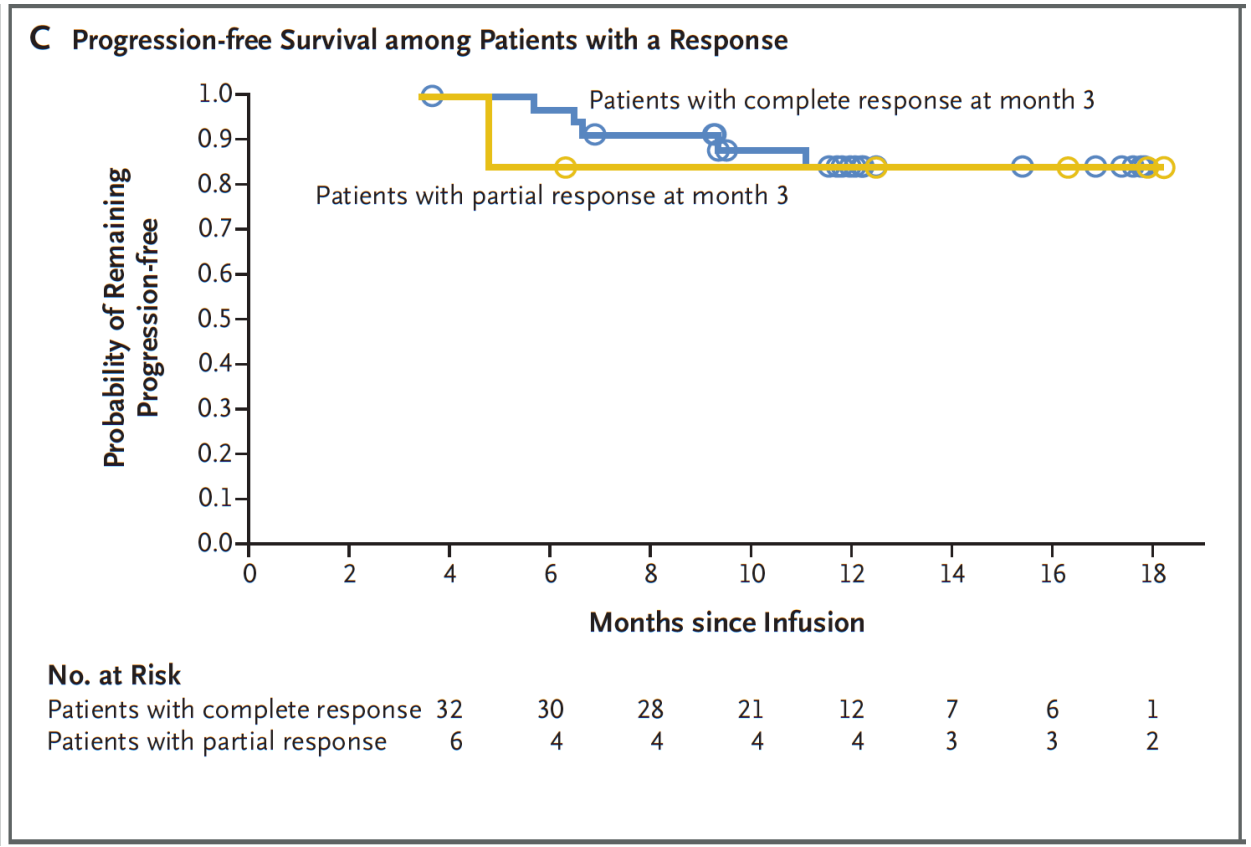
Aggressive Lymphoma: Commercial CD-19 CAR-T Cell Products

Feature	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel
Construct	FMC-63 murine scFv 41BB costim domain	FMC-63 murine scFv CD28 costim domain	FMC-63 murine scFv 41BB costim domain
Viral transfer	Lentiviral	Gamma retroviral	Lentiviral
Collection	Resting state apheresis, **Cryopreserved** Bulk cells	Resting state apheresis, Fresh only Bulk cells	Resting state apheresis, Fresh only, Selection CD4 and CD8
Manufacture	CD3/CD28 stim	CD3/CD28 stim	**CD4, CD8 selection** CD3/CD28 stimulation
Dose administered	0.6-6.0 x 10^8 CAR-T cells COA based on cell recovery	2 x 10^6/kg Max 200 x 10^6 No COA	100 x 10^6 (CD4/CD8) in separate vials (1:1) **Dose based on recovery**
Histology	DLBCL Transformed FL	DLBCL **PMBCL** Transformed FL	DLBCL, High grade **PMBCL** Transformed FL, **CLL, MCL**
CNS involvement	No	No	Secondary

Tisagenlecleucel: JULIET trial in DLBCL

- CD19 specific, 41BB containing CAR-T, bulk CD3 cells using a lentiviral vector
- N=93 infused: **CR=40%, PR=12%**
- Grade 3/4 CRS = 22% * U Penn grading, Grade 3/4 NT = 12%

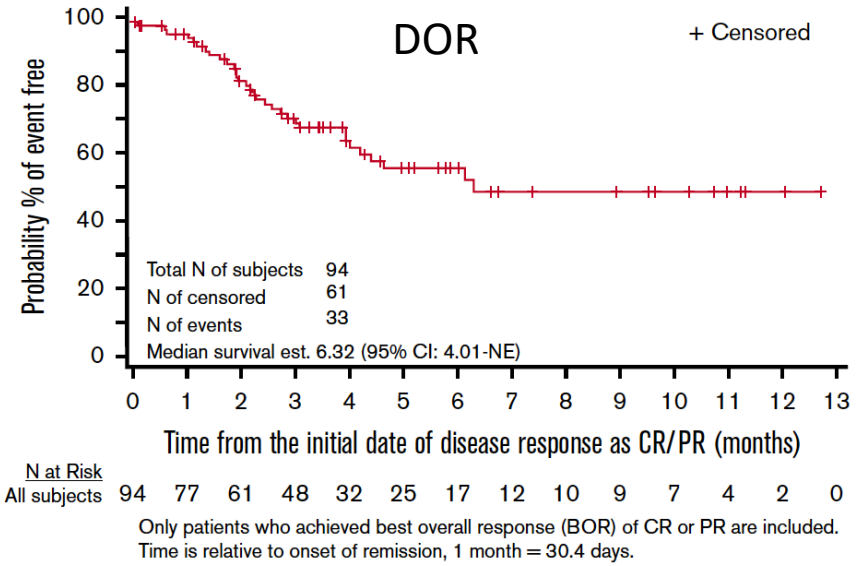


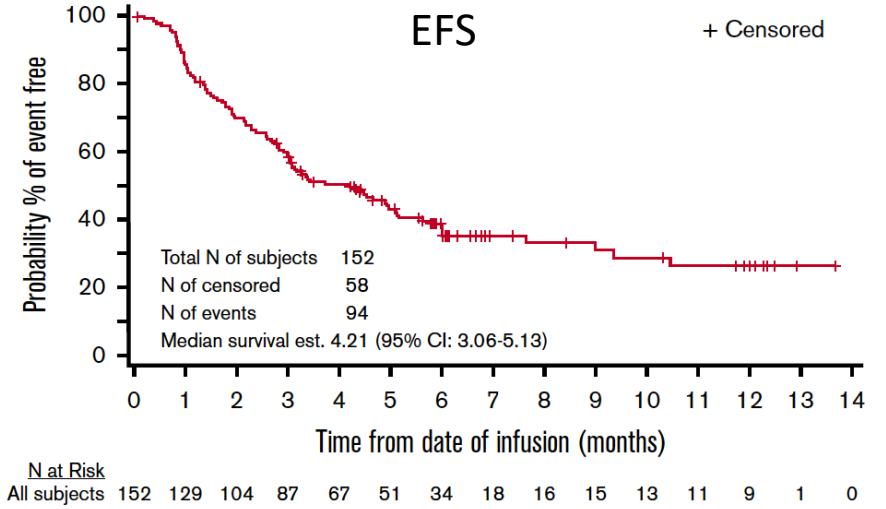


S. Schuster, NEJM 2018

Tisagenlecleucel: ”Real World Data NHL”

CIBMTR vs JULIET	(n = 152)	(n = 115)
ORR (CR + PR)	61.8 (53.6-69.6)	52.2 (42.7-61.6)
BOR of CR	39.5 (31.6-47.7)	38.3 (29.4-47.8)
DOR		
At 6 mo	55.3 (42.2-66.6)	66.6 (52.8-77.3)
At 12 mo	48.4* (33.9-61.5)	62.7 (48.7-73.9)
PFS		
At 6 mo	38.7 (30.5-46.9)	39.0 (29.7-48.2)
At 12 mo	26.4* (17.2-36.6)	34.7 (25.7-43.9)
OS		
At 6 mo	70.7 (62.2-77.6)	61.2 (51.6-69.5)
At 12 mo	56.3 (44.2-66.8)	48.2 (38.6-57.1)

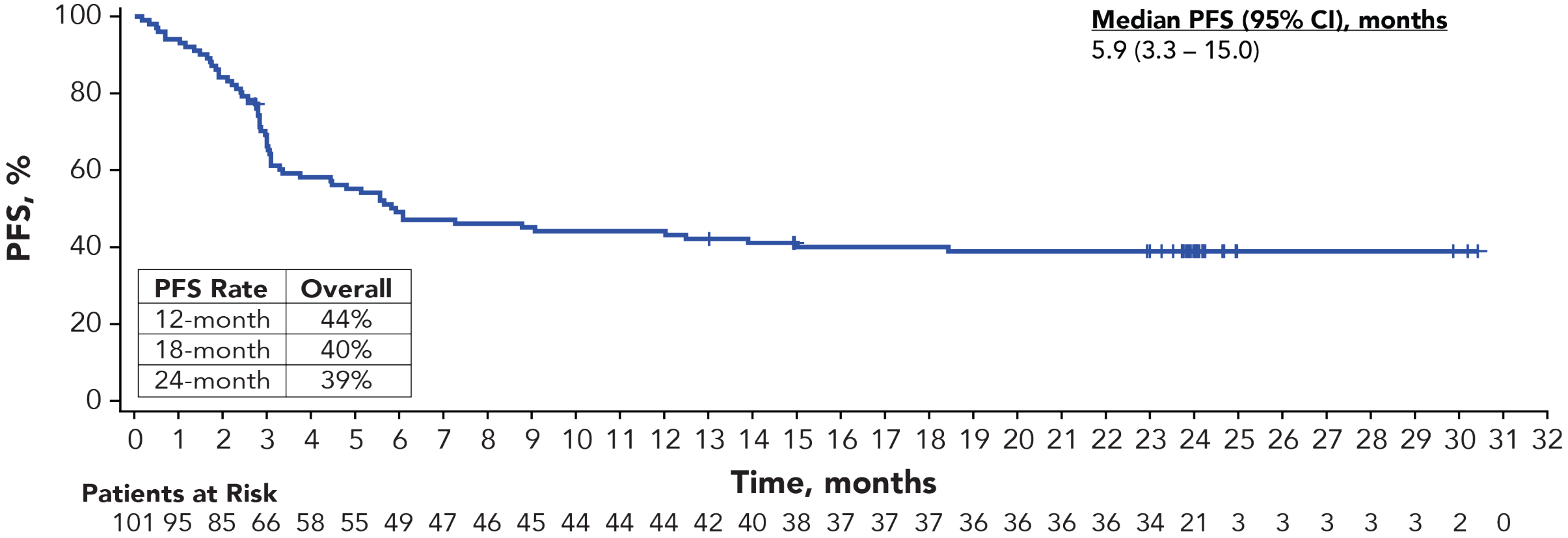




M. Pasquini Blood Advances, 2020

Axicabtagene ciloleucel ZUMA-1 TRIAL, PFS

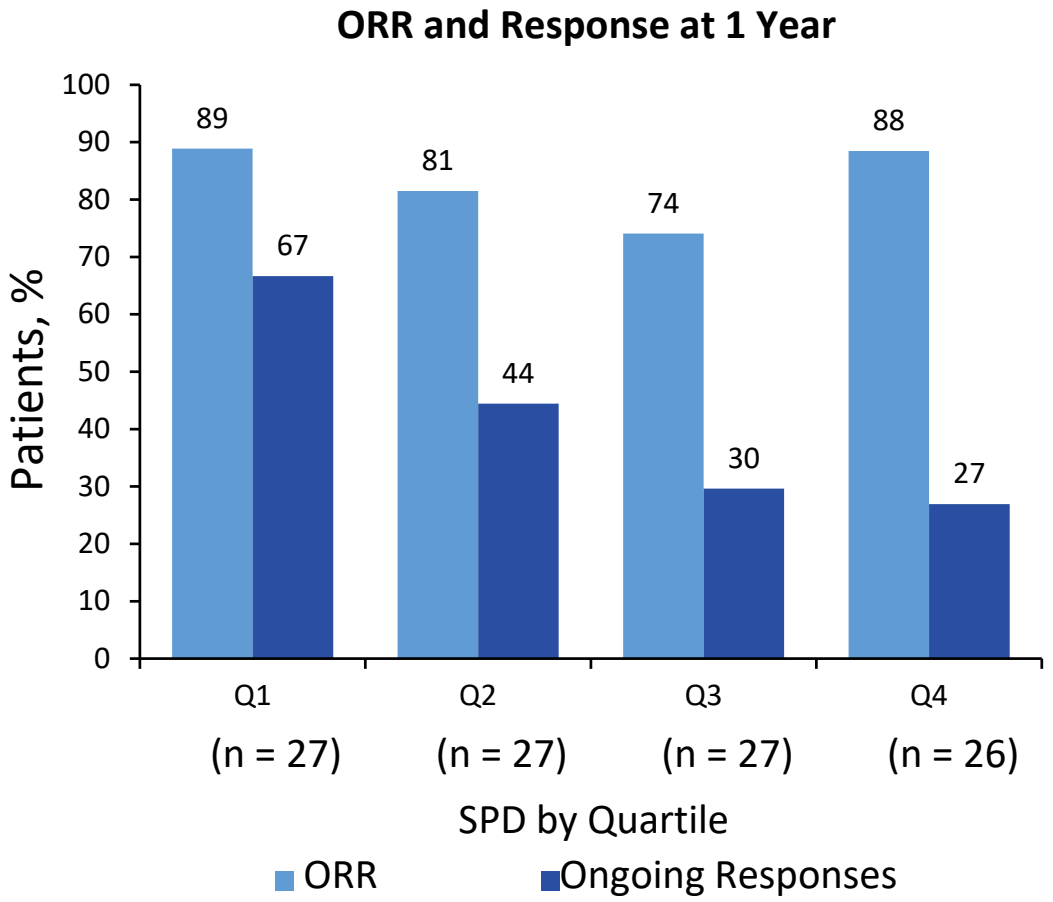
N= 101, ORR = 82%, CR = 54%
DLBCL, tFL, PMBCL

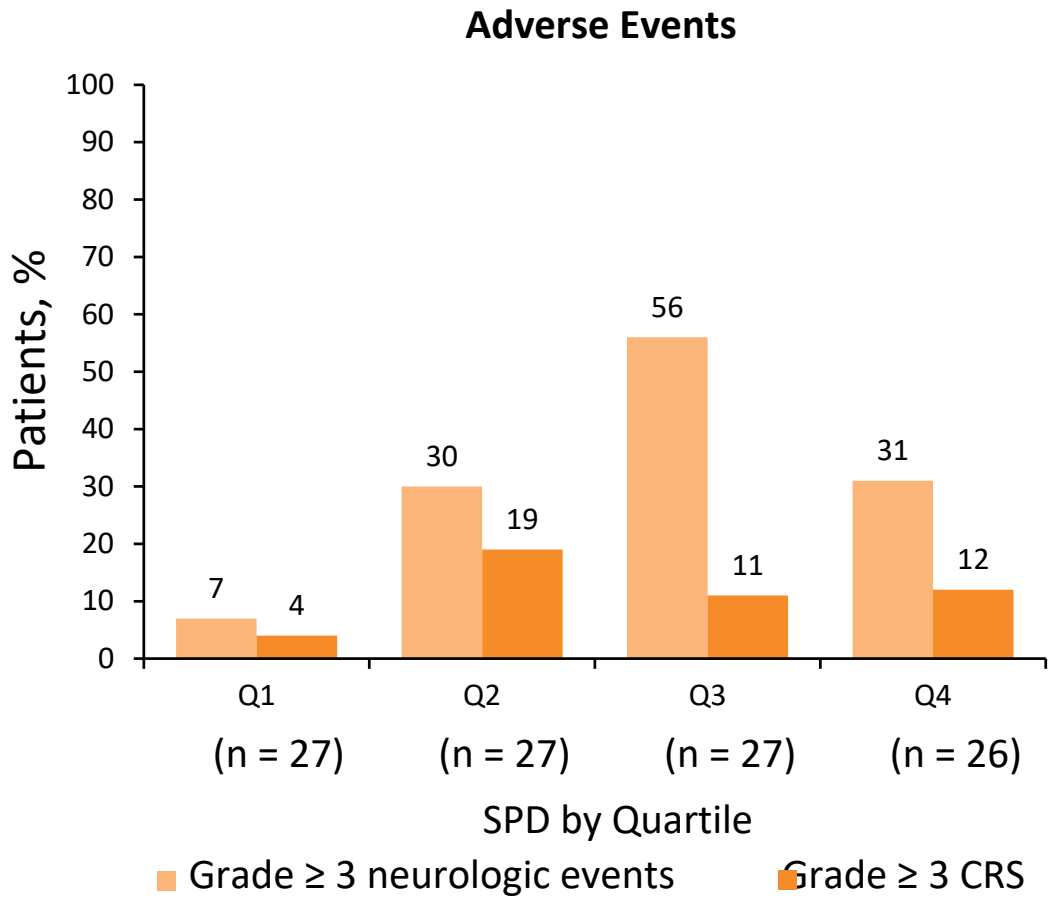


- The 6-month plateau was largely maintained, with only 10 patients progressing beyond the 6-month follow-up

PFS, progression-free survival.
Neelapu SS, et al. ASH 2018. Abstract #2967.

ZUMA-1 Predictors: Baseline Tumor Burden
Efficacy and Safety



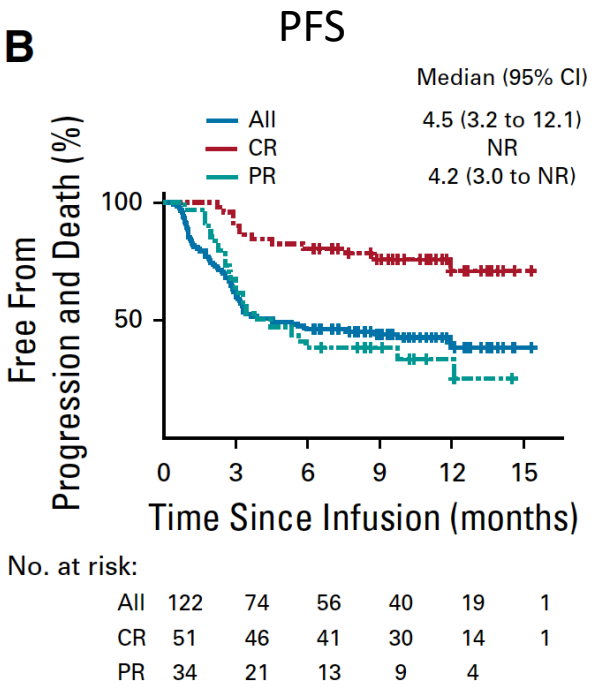


CRS, cytokine release syndrome; Q, quartile; SPD, sum of product diameters.
Locke FL, et al. *J Clin Oncol*. 2018;36(suppl, abstr):3039.

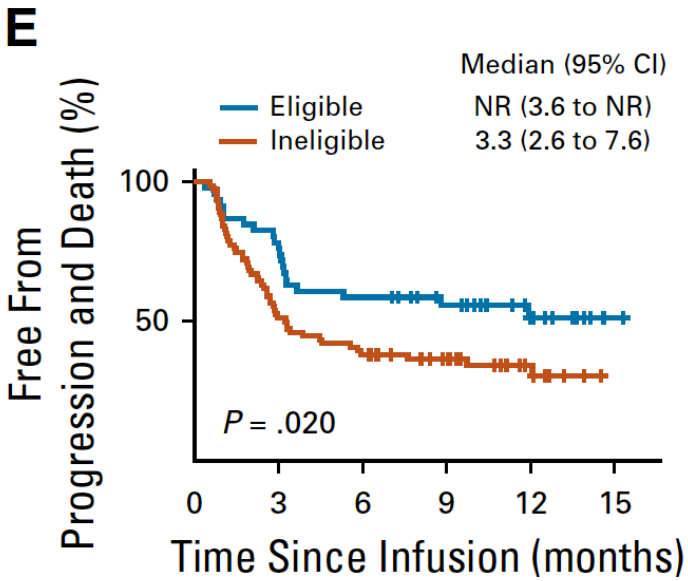
“Real World” Axicabtagene Ciloleucel (1)

Data from 7 US academic centers

Category	Percent
Not eligible for ZUMA-1	62%
ORR/CR	70%/ 50%
CRS > grade 2	16%
NT > grade 2	35%
CR in not eligible for Zuma-1	42% (vs 63%)



PFS based on ZUMA-1 Eligibility



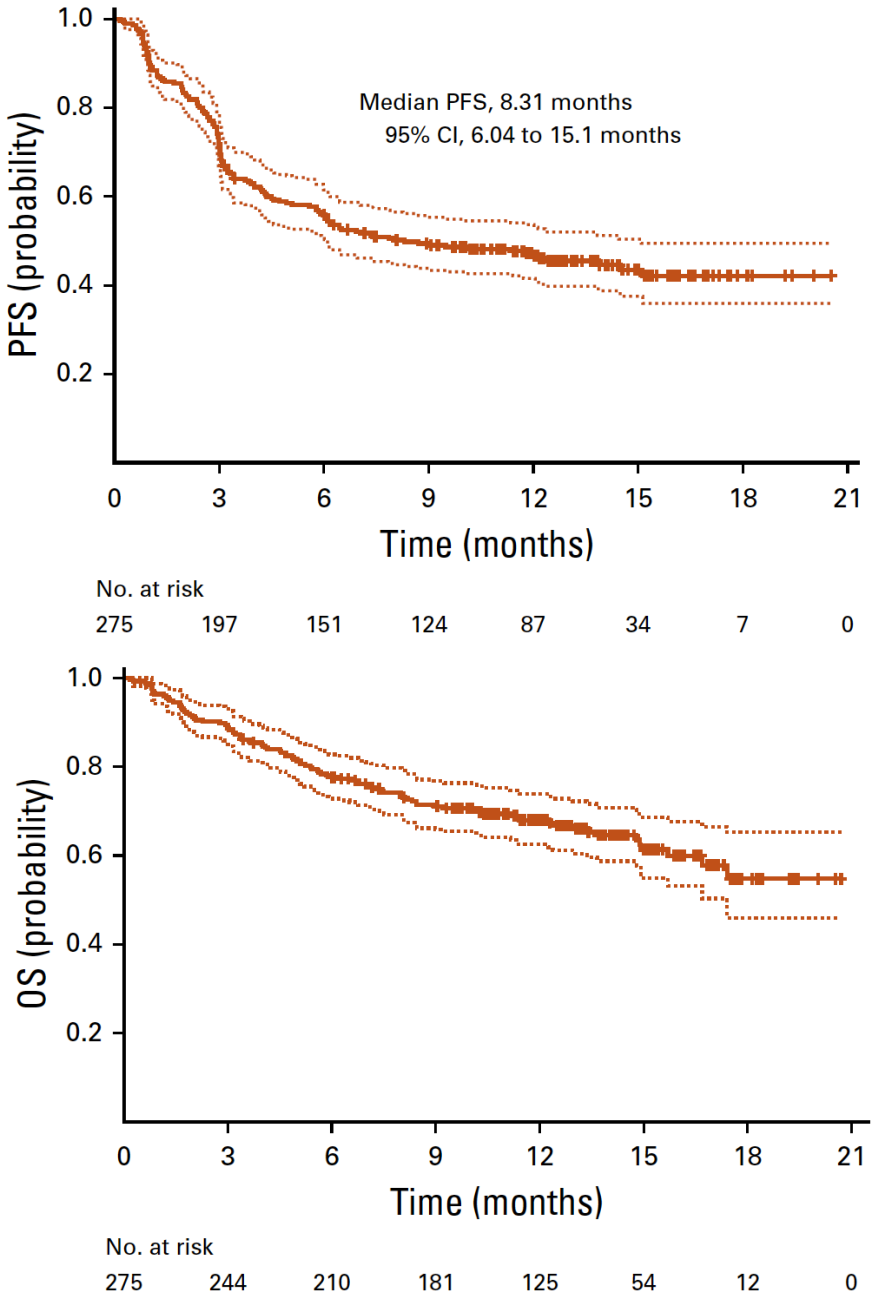
Jacobson, CA et al, JCO 2020

“Real World” Axicabtagene Ciloleucel (2)

Data from 17 US Academic centers, 43% not eligible for Zuma-1

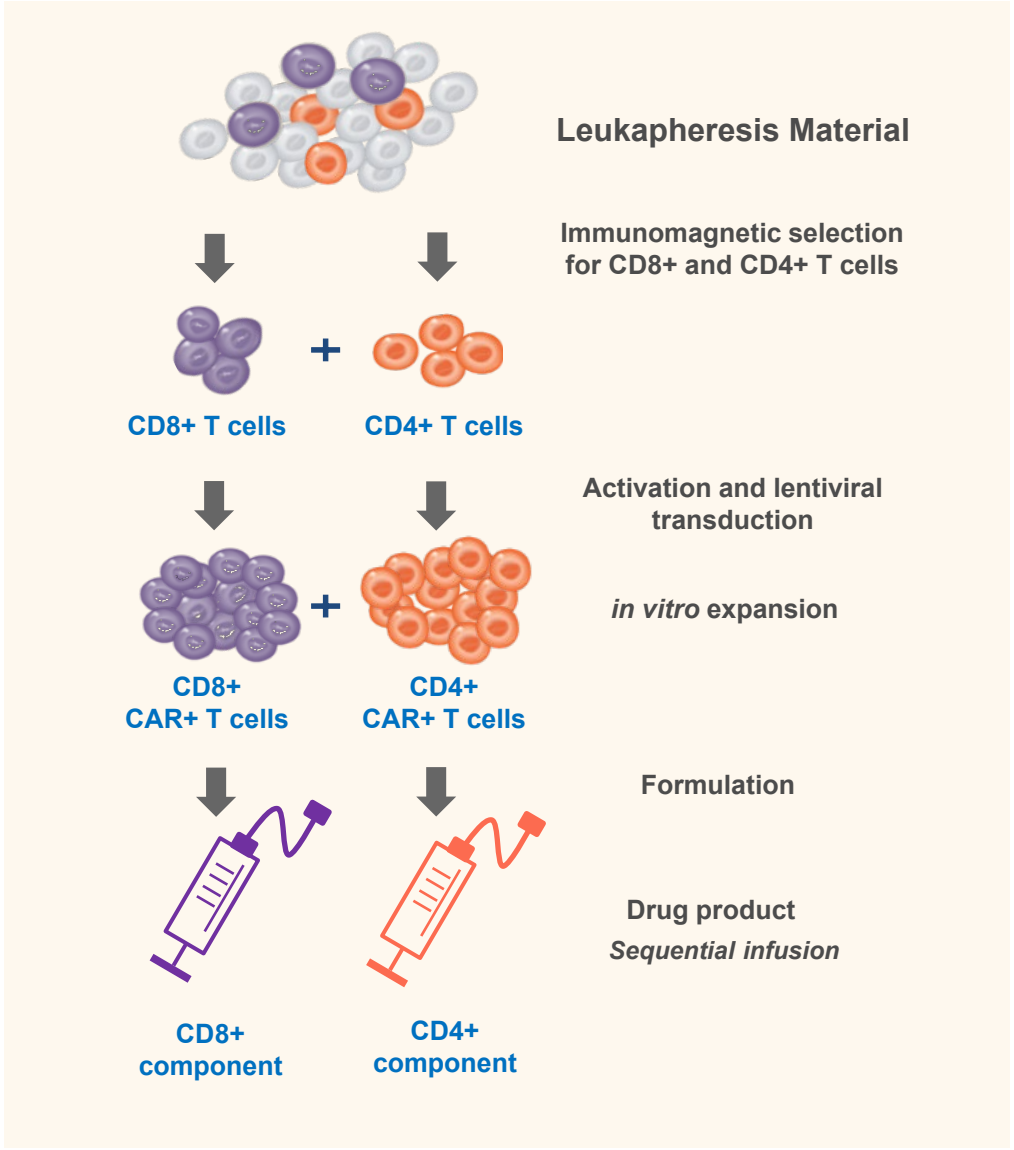
	mITT (N = 275)	ZUMA-1[1] (N = 108)
Tocilizumab usage, %	63	45
Corticosteroid usage, %	54	29
Median hospital stay, d	14 (3-66)	N/A
ICU stay, n (%)	91 (33)	N/A
Grade 5 AEs, n (%)	7 (3)	4 (4)

Best response
ORR = 82%,
CR = 64%



Nastoupil, LJ et al, JCO 2020

Lisocabtagene maraleucel (liso-cel; JCAR017)
CD19-Directed, Defined Composition, 4-1BB CAR T Cell Product



CD8+ and CD4+ CAR+ T cell components are administered separately at equal target doses of CD8+ and CD4+ CAR+ T cells

The defined composition of liso-cel results in:

- Consistent administered CD8+ and CD4+ CAR+ T cell dose
- Low variability in the CD8+/CD4+ ratio

Dose and ratio of CD8+ and CD4+ CAR+ T cells may influence the incidence and severity of CRS and neurological events[1–3]

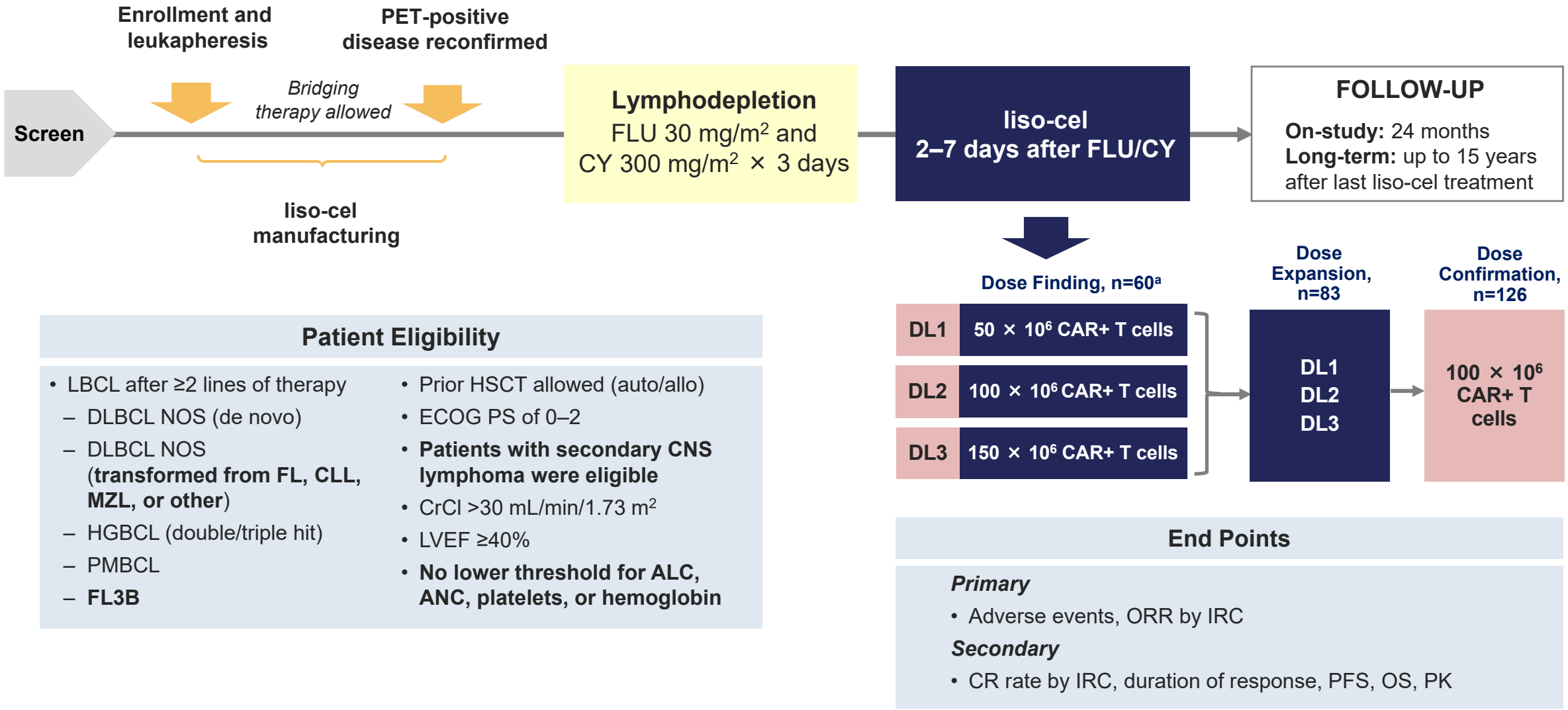
Abramson JS, Lancet 2020

CAR, chimeric antigen receptor; CRS, cytokine release syndrome.

1. Turtle CJ, et al. *Sci Transl Med*. 2016;8(355):355ra116; 2. DeAngelo DJ, et al. *J Immunother Cancer*. 2017;5(Suppl 2):116: Abstract P217; 3. Neelapu SS, et al. *N Engl J Med*. 2017;377:2531–2544.

TRANSCEND NHL 001 (NCT02631044)

Pivotal Phase 1, Multicenter, Seamless Design Study



Patient Eligibility

- LBCL after ≥2 lines of therapy
  - DLBCL NOS (de novo)
  - DLBCL NOS (**transformed from FL, CLL, MZL, or other**)
  - HGBCL (double/triple hit)
  - PMBCL
  - **FL3B**
- Prior HSCT allowed (auto/allo)
- ECOG PS of 0–2
- **Patients with secondary CNS lymphoma were eligible**
- CrCl >30 mL/min/1.73 m^2
- LVEF ≥40%
- **No lower threshold for ALC, ANC, platelets, or hemoglobin**

End Points

Primary

- Adverse events, ORR by IRC

Secondary

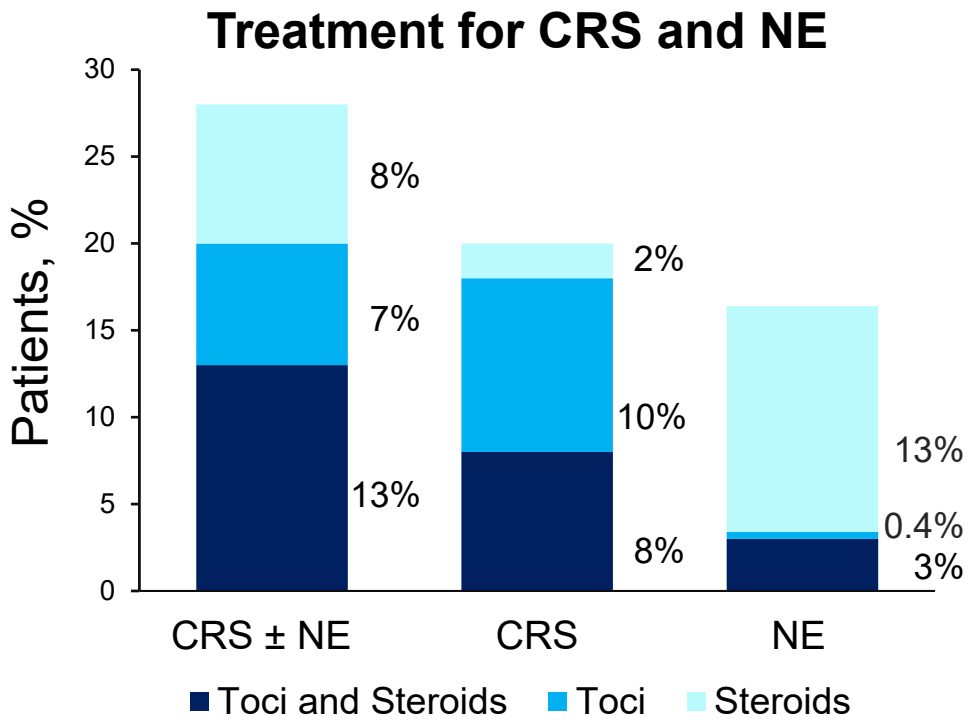
- CR rate by IRC, duration of response, PFS, OS, PK

[a]DL1 was also tested as a 2-dose regimen, with a second dose of liso-cel given 14 days after the first dose.

ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; CrCl, creatinine clearance; CY, cyclophosphamide; DL, dose level; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; FL3B, follicular lymphoma grade 3B; FLU, fludarabine; HGBCL, high-grade B-cell lymphoma; HSCT, hematopoietic stem cell transplantation; IRC, independent review committee; LBCL, large B-cell lymphoma; LVEF, left ventricular ejection fraction; MZL, marginal zone lymphoma; NOS, not otherwise specified; ORR, objective response rate; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetics; PMBCL, primary mediastinal large B-cell lymphoma.

Patient Incidence and Management of CRS and NE

	All liso-cel–Treated Patients (N=269)
CRS[a]	
Any grade, n (%)	**113 (42)**
Grade 3, n (%)	4 (1)
Grade 4, n (%)	2 (1)
Time to onset, median (range), days	5 (1–14)
Time to resolution, median (range), days	5 (1–17)
NE[b]	
Any grade, n (%)	**80 (30)**
Grade 3, n (%)	23 (9)
Grade 4, n (%)	4 (1)
Time to onset, median (range), days	9 (1–66)
Time to resolution, median (range), days	11 (1–86)
CRS or NE, n (%)	**127 (47)**
ICU admissions,[c] n (%)	**19 (7)**
For CRS and/or NE	12 (4)



- 3% of patients received vasopressors for CRS or NE
- 2 patients received other anti-inflammatory/anticytokine agents

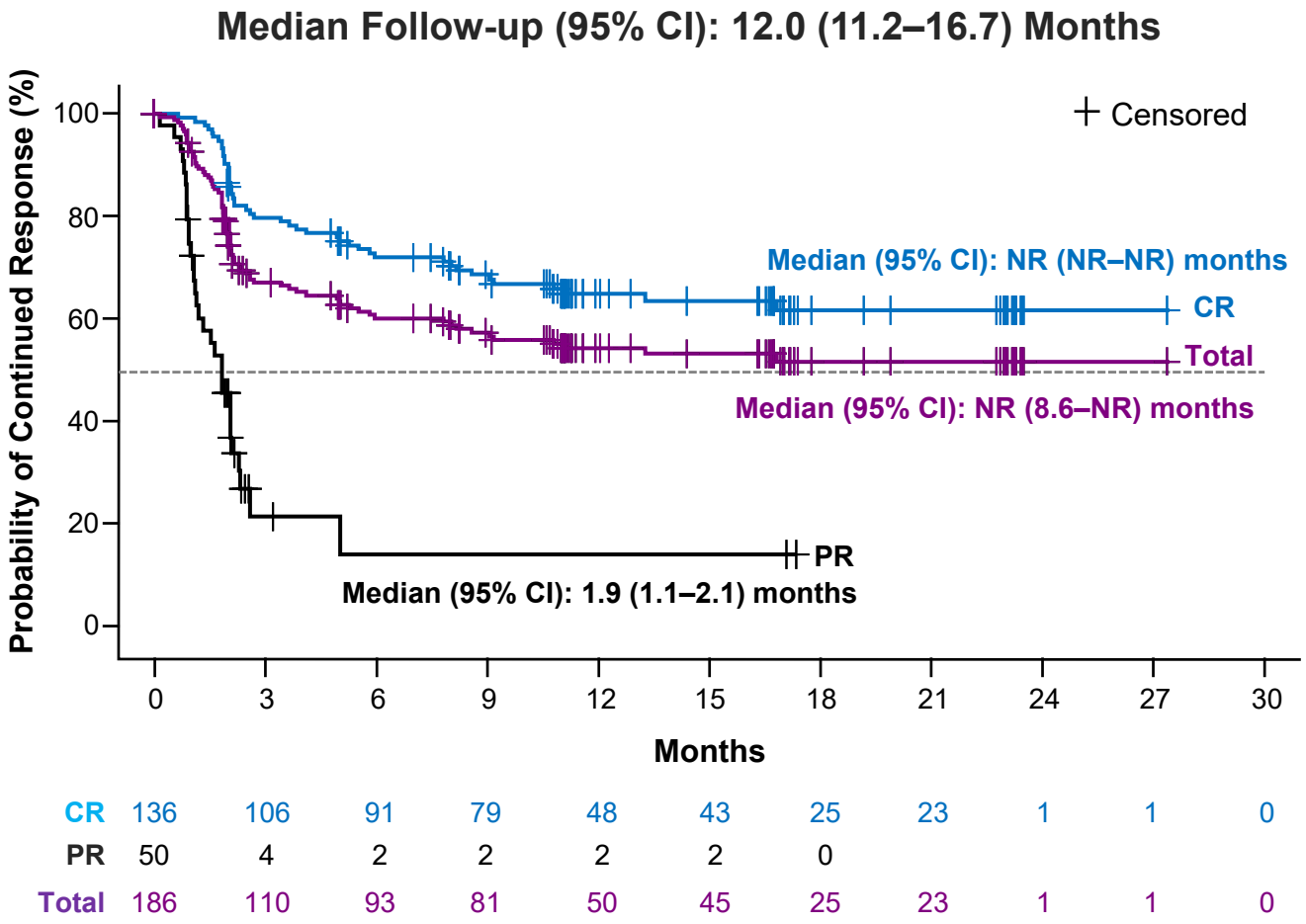
CRS and NE were reversible

- 1 patient had an unresolved NE (grade 1 tremor) at data cutoff
- 8 patients had ongoing CRS/NE at time of death from other reasons

t and graded per National Cancer Institute Common Terminology Criteria for Adverse Events v4.03.
ological event; toci, tocilizumab.

Response and Durability by IRC Assessment

Efficacy-Evaluable Patients (N=256)	
ORR (95% CI)	73% (67–78)
CR rate (95% CI)	53% (47–59)
Time to first CR or PR, median (range), months	1.0 (0.7–8.9)
DOR at 6 months (95% CI), %	60.4 (52.6–67.3)
DOR at 12 months (95% CI), %	54.7 (46.7–62.0)

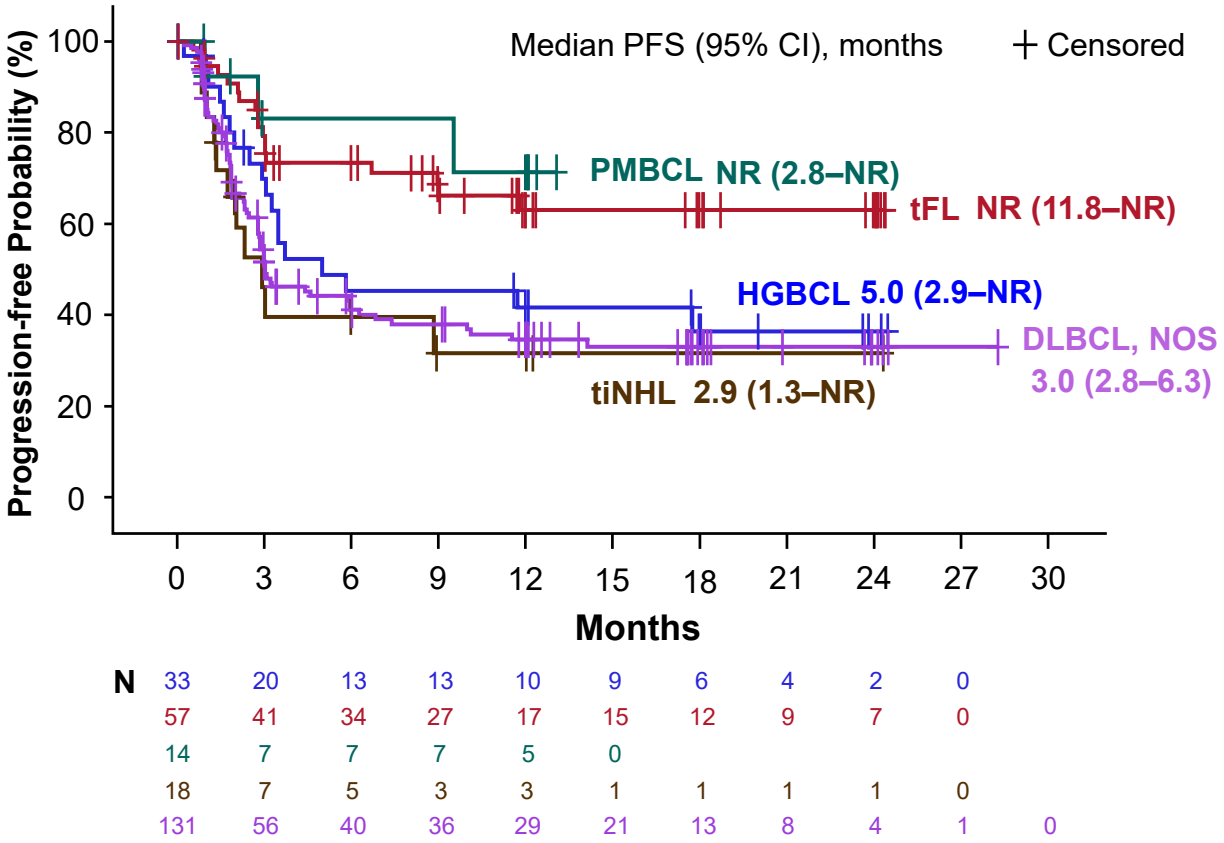


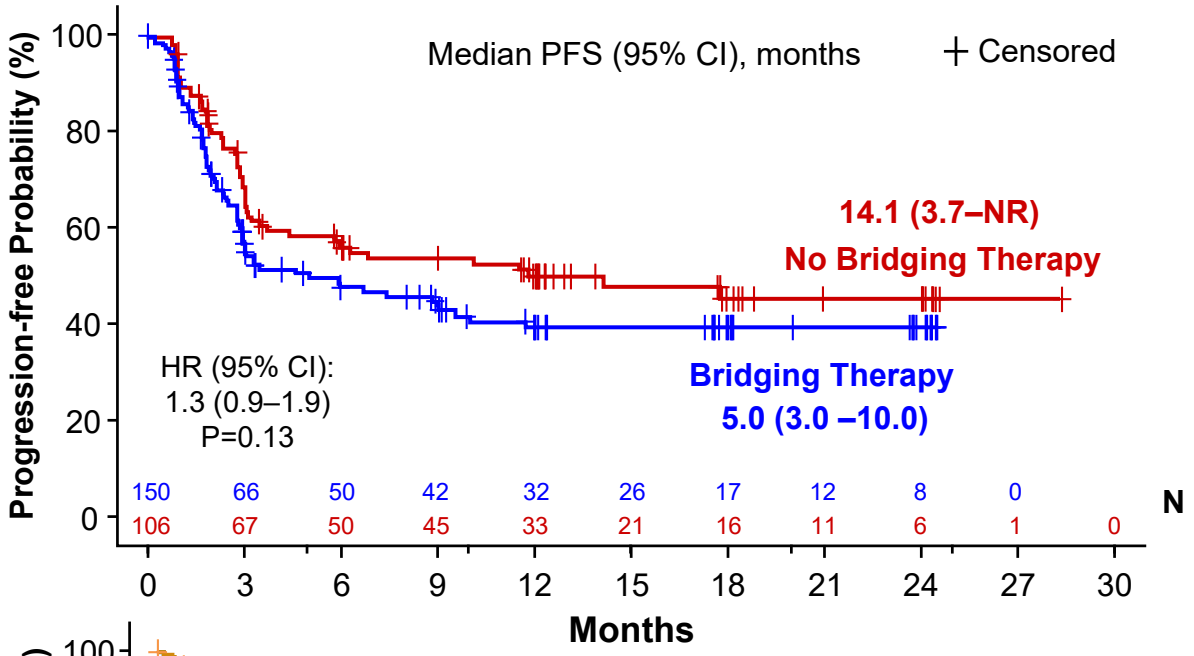
Efficacy among patients who received nonconforming product (n=25) was similar to those who received liso-cel

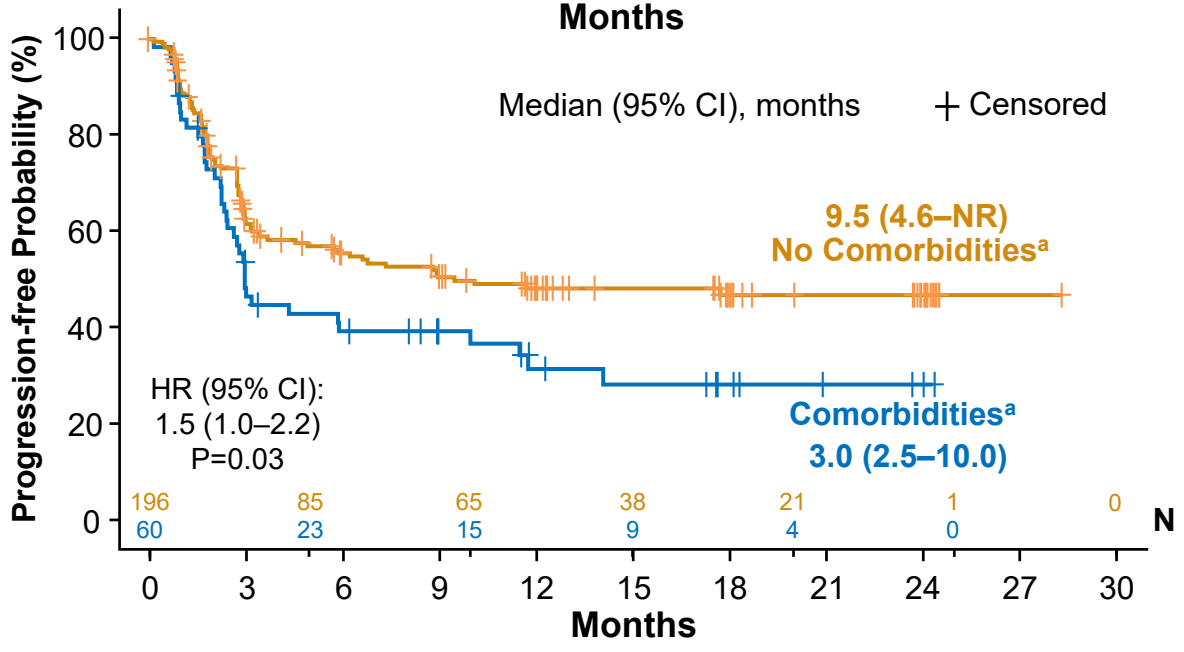
Abramson JS, Lancet 2020

CI, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PR, partial response.

Progression-Free Survival by Subgroup







Abramson JS, Lancet 2020, supplemental materials

Cross Trial Comparisons: CD19 CAR-T Cell Therapy for Aggressive Lymphoma

	Axicabtagene ciloleucel	Tisagenlecleucel	Lisocabtagene maraleucel
LD chemo	Cy/Flu 500/30 x 3d	Cy/Flu 250/25 x 3d Benda 90 x 2d	Cy/Flu 300/30 x 3d
Bridging Therapy	Not allowed	92%	59%
Indication	DLBCL, High grade, PMBCL, tFL	DLBCL, High grade, tFL	DLBCL, High grade, PMBCL, tFL, tIND
ORR	82%	53%	73%
CR	54%	40%	53%
CRS overall, 3/4	94%, 13%	58%, 23%*	42%, 2%
NT overall, 3/4	87%, 28%	21%, 12%	30%, 10%
Outpatient Rx	No	Yes (26%)	Yes
Reference	S. Neelapu NEJM 2017	S. Schuster NEJM 2018	J. Abramson Lancet 2020

* Penn grading scale,

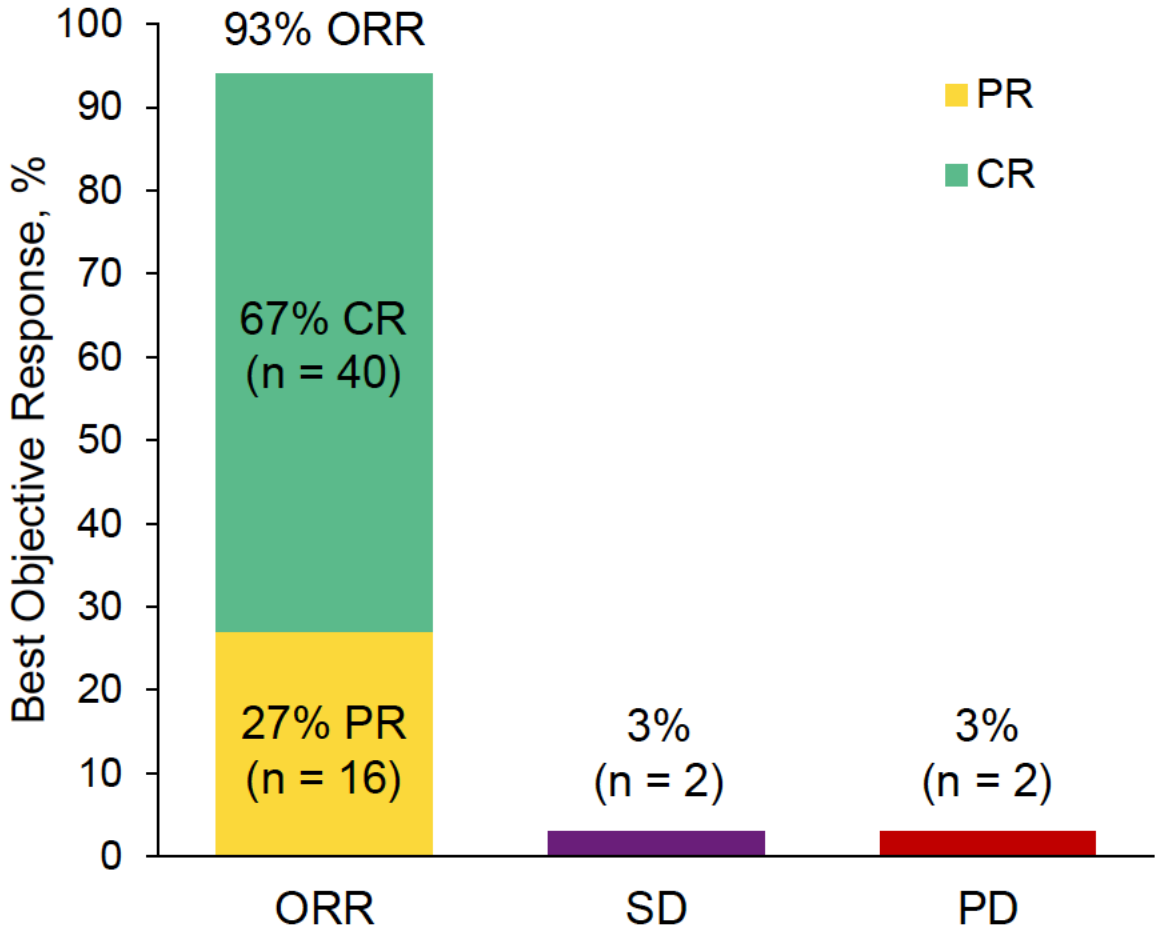
KTE-X19 (Brexucabtagene autoleucel) for Relapsed/Refractory Mantle cell NHL

- ZUMA-2 trial, N=68
- Product similar to axicabtagene ciloleucel with different cell processing to eliminate B cells from the starting product
- FDA approved July, 2020

- Flu/Cy lymphodepletion (500/30 x 3d)
- 2 x 10^6 CAR-T cells/kg

Wang, M et al NEJM 2020

ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)

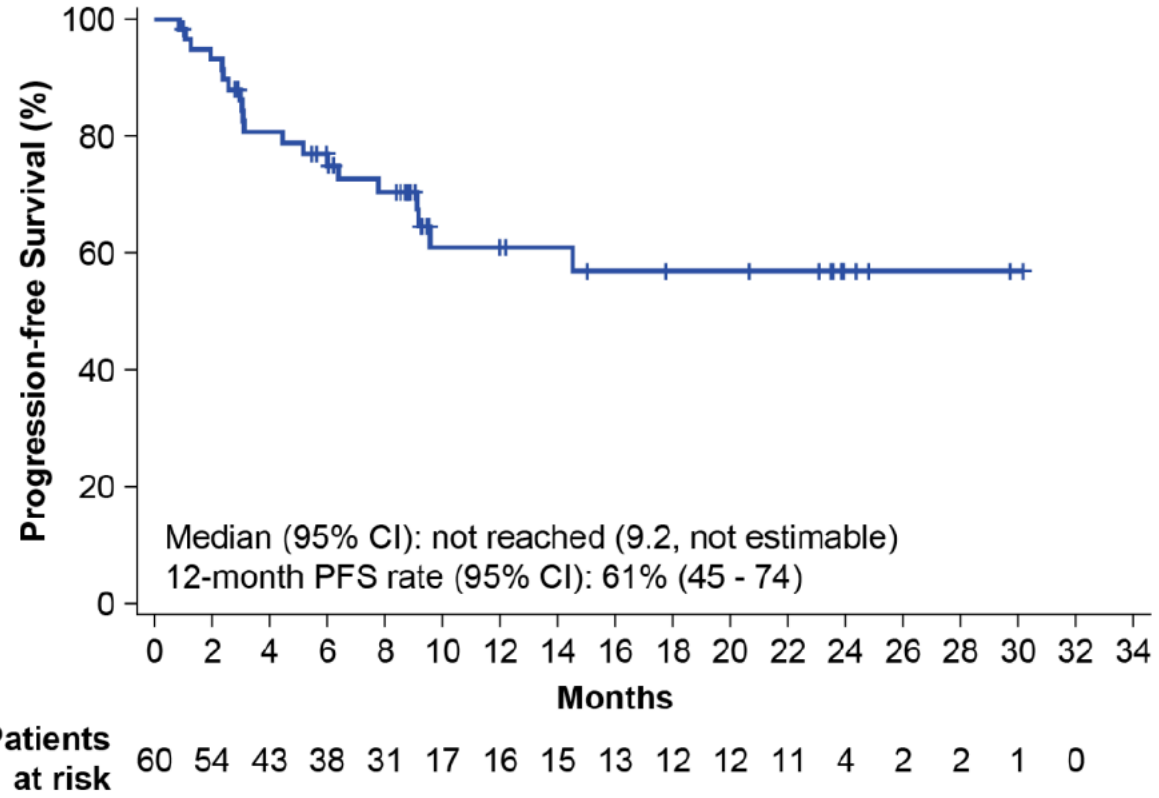


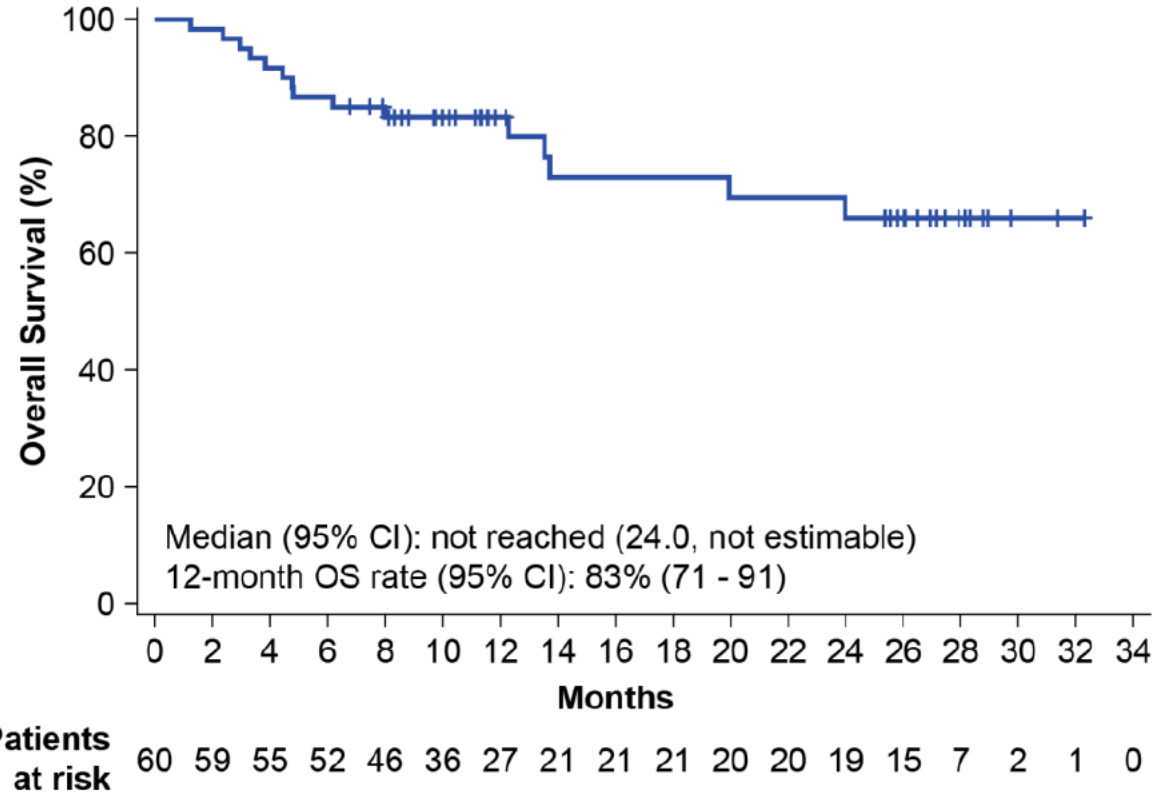
	Efficacy-Evaluable N = 60
Median follow-up (range), mo	12.3 (7.0 – 32.3)
Patients with ≥ 24 mo follow-up, n (%)	28 (47)
Median time to response (range), mo	
Initial response	1.0 (0.8 – 3.1)
CR	3.0 (0.9 – 9.3)
Patients converted from PR/SD to CR, n (%)	24 (40)
PR to CR	21 (35)
SD to CR	3 (5)

Investigator-assessed ORR in N = 60 was 88% (CR rate 70%), with 95% and 90% concordance between IRRC- and investigator-assessed ORR and CR rate, respectively. IRRC-assessed ORR in ITT (N = 74) was 85% (CR Rate 59%).
CR, complete response; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Progression-Free Survival and Overall Survival

- Median PFS and median OS were not reached after a median follow-up of 12.3 months





OS, overall survival; PFS, progression-free survival.

Axicabtagene ciloleucel for Relapsed/Refractory indolent NHL

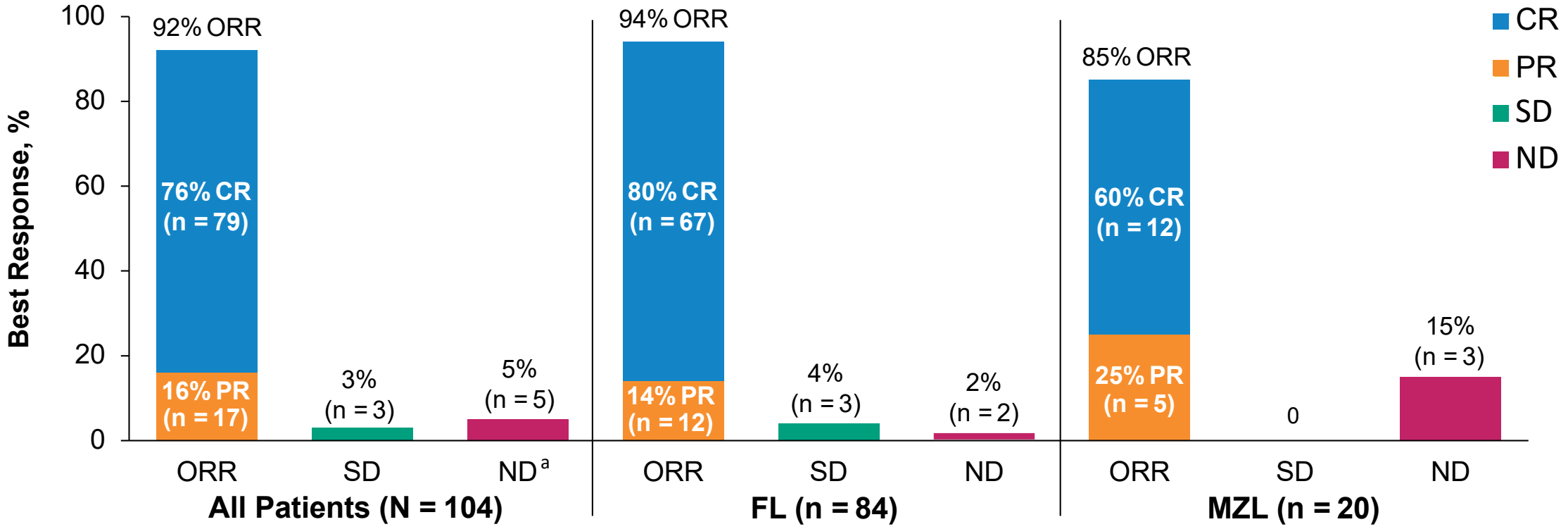
- ZUMA-5 trial, N=146 treated
- Follicular NHL = 124, Marginal zone NHL 22

- Flu/Cy lymphodepletion and 2 x 10^6 CAR-T cells/kg

- CRS $\geq$ grade 3 = 10 (7%)
- NT $\geq$ grade 3 = 28 (19%)

Jacobson, C et al ASH 2020

ORR by IRRC Assessment Was 92% (95% CI, 85 – 97); CR Rate Was 76% (95% CI, 67 – 84)



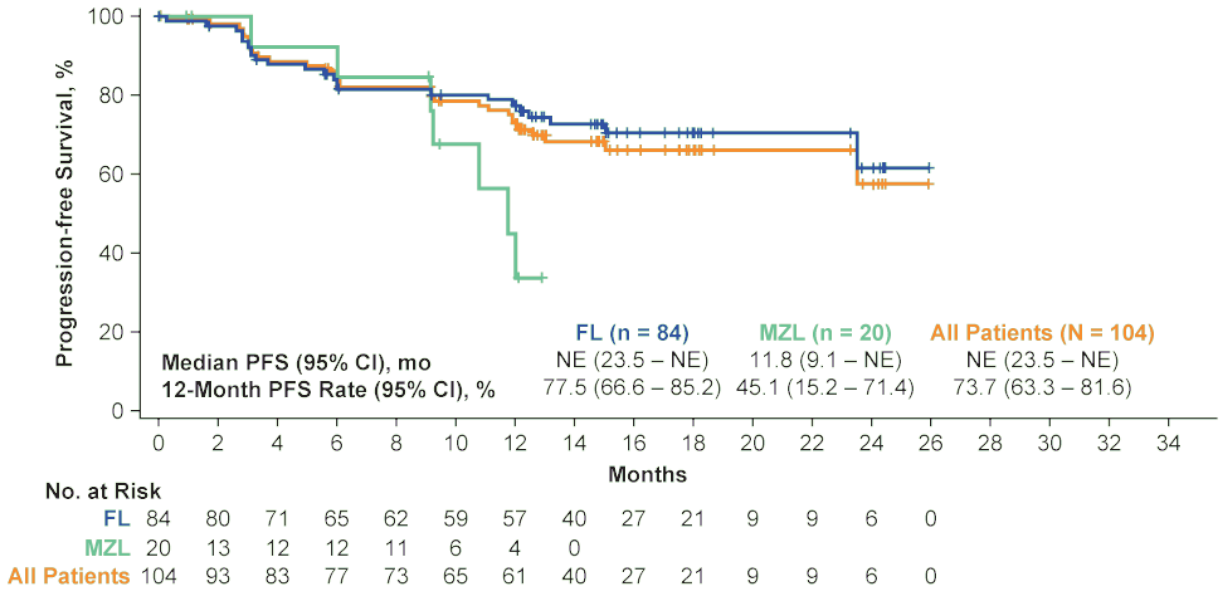
- The median time to first response was 1 month (range, 0.8 – 3.1)
- Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9 – 11.2)

The investigator-assessed ORR (N = 104) was 95%, with a CR rate of 77%. Concordance between investigator-assessed and IRRC-assessed ORR was 91%. [a] For the 5 patients reported as ND, 4 (1 FL; 3 MZL) had no disease at baseline and postbaseline per IRRC but were considered with disease by the investigator; 1 patient with FL died before the first disease assessment.

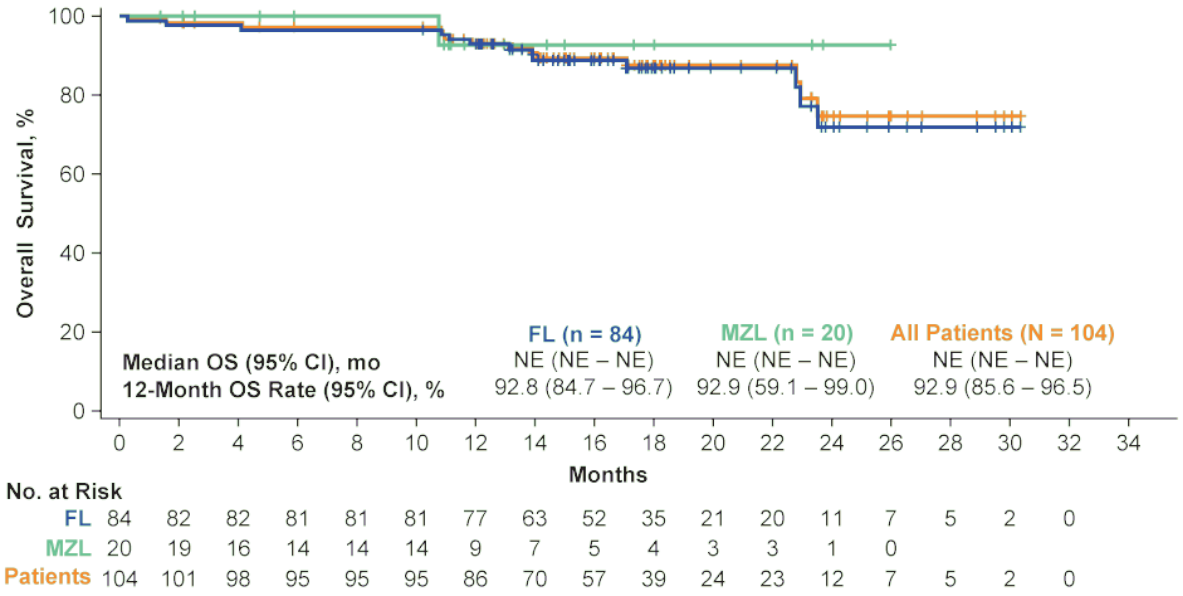
CR, complete response; FL, follicular lymphoma; IRRC, Independent Radiology Review Committee; MZL, marginal zone lymphoma; ND, undefined/not done; ORR, overall response rate; PR, partial response; SD, stable disease.

Progression-Free Survival and Overall Survival

Progression-Free Survival



Overall Survival



- With a median follow-up of 17.5 months, median PFS and median OS were not reached
  - The 12-month PFS rate was 73.7% (95% CI, 63.3 – 81.6) for all patients
  - The 12-month OS rate was 92.9% (95% CI, 85.6 – 96.5) for all patients

FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Conclusions and Future Directions

- Approval of 4 CD19 CAR-T cell products for Aggressive NHL, FL and MCL
- Treatments appear to lead to long lasting remissions for CR patients
- Await second line randomized trials against SOC autologous HCT
- Product selection needs to consider **efficacy**, **safety**, as well as **production reliability** and **cost**
- Many opportunities to improve outcome
  - Optimize patient selection for treatment (earlier in course, lower tumor burden)
  - Combine CAR-T cells + additional agents (ibrutinib, PD-1 or PD-L1 antibodies)
  - Target multiple antigens to decrease antigen negative escape
  - Universal CAR-T cells: “Off the shelf” allogeneic cell products

Immunotherapy is changing the way cancer is treated!

BEZOS FAMILY IMMUNOTHERAPY CLINIC