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Comprehensive Cancer Center

FLASCO 2021: Updates in CAR-T therapies for DLBCL

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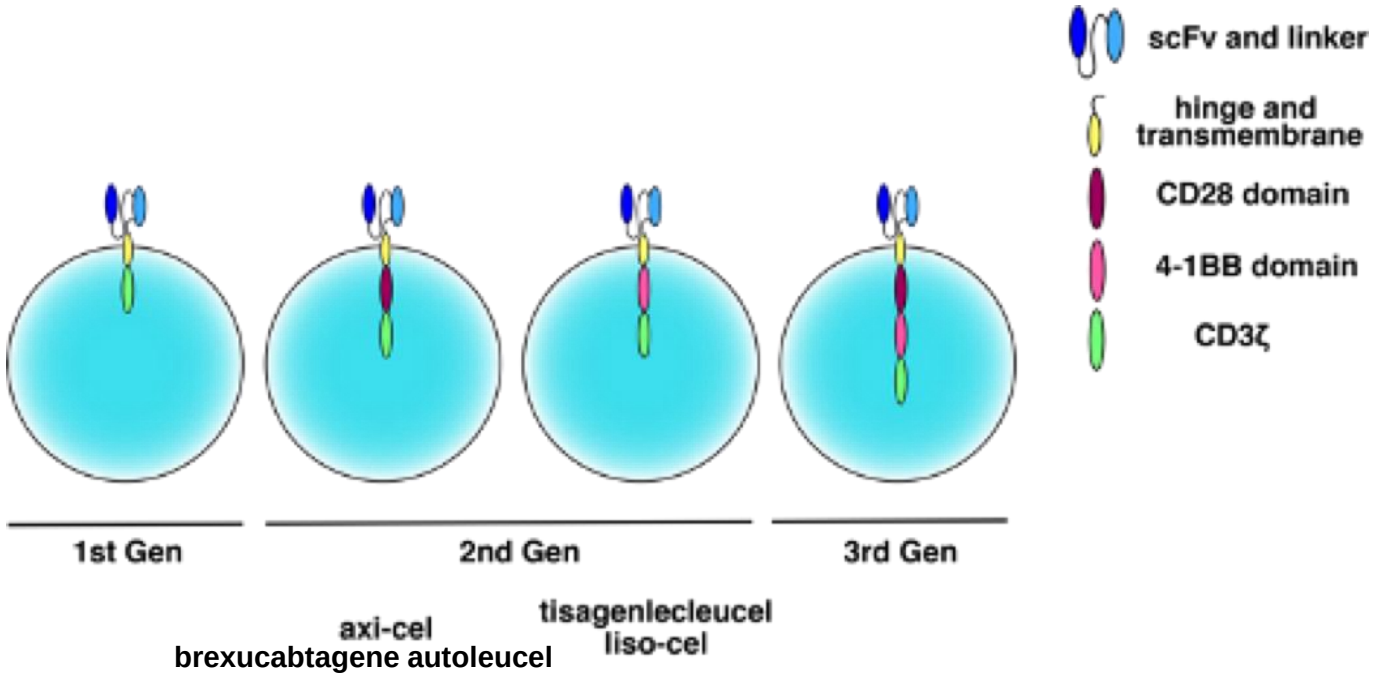
UNIVERSITY OF MIAMI HEALTH SYSTEM

Learning Objectives

At the conclusion of this CE activity, participants should be better able to:

- *Describe basic principles of chimeric antigen receptor T cell design and mechanism of action*
- *Recognize current and near-term future clinical indications for CAR-T therapy in adults*
- *Understand causes of treatment failure, including relapse, and emerging approaches to therapy*
- *Identify potential barriers to access and application of CAR-T therapies in practice*

Evolution of CAR-T construct design



Komanduri, *JCO, 2021*

ZUMA-1: Patient Characteristics

Characteristic	DLBCL (n=73)	TFL/PMBCL (n=20)	All Patients (n=93)
Median age (range), years	59 (25-76)	58 (28-76)	59 (25-76)
Age ≥60 years, n (%)	36 (49)	9 (45)	45 (48)
Male, n (%)	47 (64)	15 (75)	62 (67)
ECOG performance status 1, n (%)	48 (66)	8 (40)	56 (60)
Median number of prior therapies (#)	3 (1-7)	4 (2-12)	3 (1-12)
IPI 3-4, n (%)	32 (44)	9 (45)	41 (44)
Disease stage III/IV, n (%)	64 (88)	15 (75)	79 (85)
Refractory subgroup, n (%)*			
Refractory to 2nd or later-line therapy	56 (77)	16 (80)	72 (77)
Relapse post-ASCT	15 (21)	4 (20)	19 (20)

*2 patients had primary refractory status

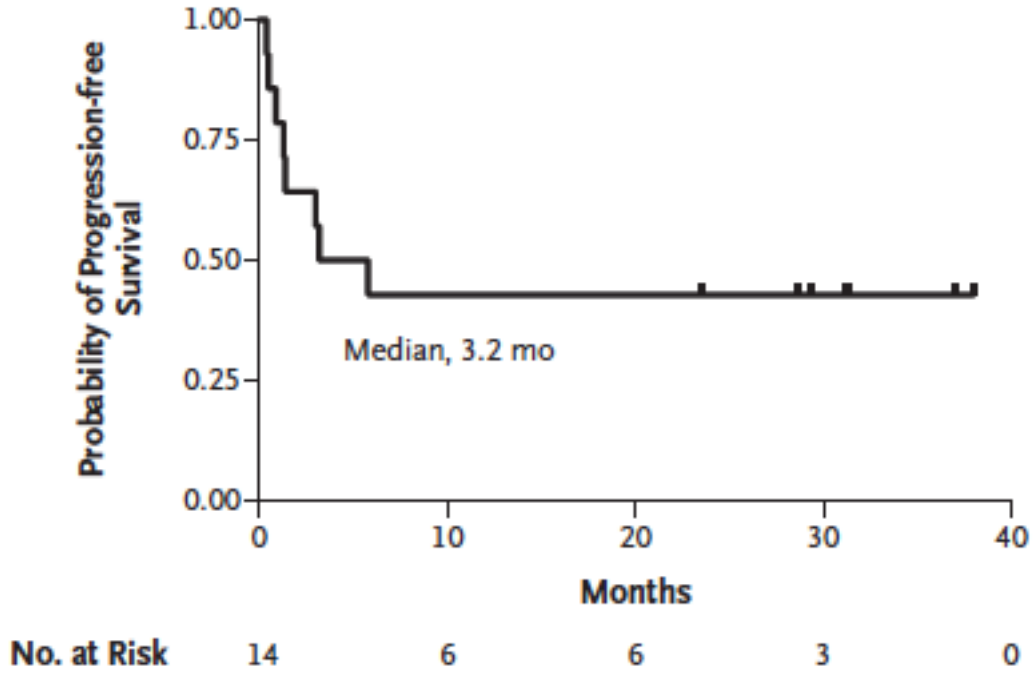
ZUMA-1 Met Primary Endpoint of ORR in Combined Group

Best Response	ZUMA-1 Phase 2					
	DLBCL		TFL/PMBCL		Combined	
	ORR (%)	CR (%)	ORR (%)	CR (%)	ORR (%)	CR (%)
mITT[b]	n = 77		n = 24		n = 101	
	82	49	83	71	82	54

[a]Inferential testing when 92 axi-cel–dosed patients had 6 mo of follow-up. ORR 82%, *P*<0.0001. [b]mITT (modified intention-to-treat) set of all patients dosed with axi-cel.
CR, complete response; DLBCL, diffuse large B cell lymphoma; ORR; objective response rate; PMBCL; primary mediastinal B cell lymphoma; TFL, transformed follicular lymphoma.

CD19 CAR T therapy in r/r lymphoma

DLBCL

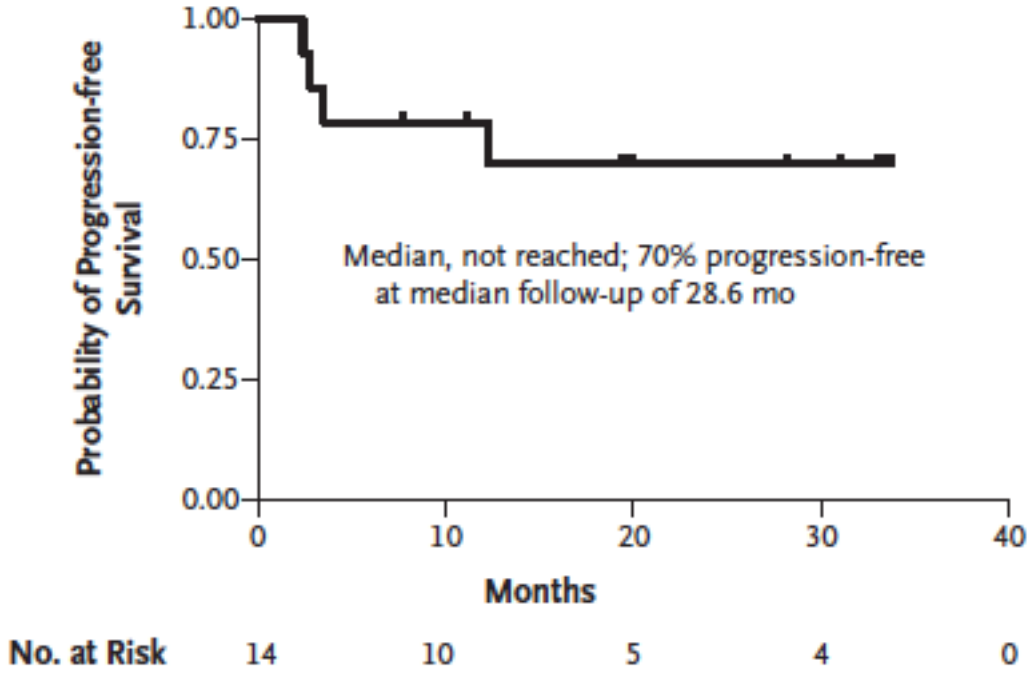


N = 14

ORR = 50%

CR rate = 43%

Follicular Lymphoma



N = 14

ORR = 79%

CR rate = 71%

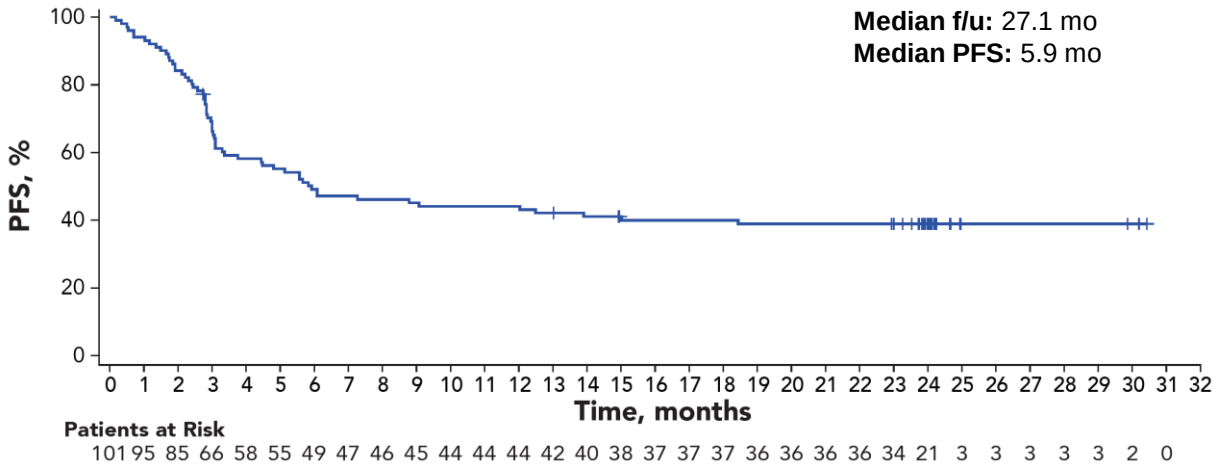
U Penn: CD19/CD3ζ/4-1BB

Schuster et al. *N Eng J Med* 2017

Durable responses with CAR T-cell therapy in r/r large B-cell lymphoma

ZUMA-1: PFS with axi-cel

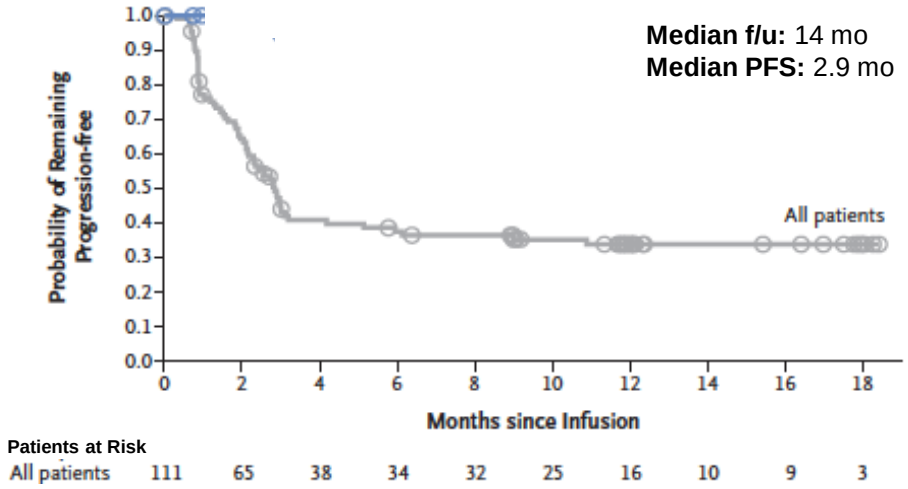
39% progression-free at 27.1 mo



Neelapu et al. *N Eng J Med* 2017
Locke et al. *Lancet Oncol* 2019

JULIET: PFS with tisagenlecleucel

34% progression-free at 14 mo[#]



[#]Calculated value from publication

Schuster et al. *N Eng J Med* 2019

Outcomes of Post-Marketing Use of an Anti-CD19 Chimeric Antigen Receptor (CAR) T Cell Therapy, Axicabtagene Ciloleucel (Axi-Cel), for the Treatment of Large B Cell Lymphoma in the United States

Marcelo C. Pasquini, Frederick Locke , Alex Herrera, Tanya Siddiqi, Armin Ghobadi, Krishna Komanduri, Zhen-Huan Hu, Hua Dong, Peiman Hematti, Sarah Nikiforow, Patricia Steinert, Anna G. Purdum, Mary M. Horowitz, Michele Hooper, Jun Kawashima, Caron Jacobson

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Objectives

- To describe early safety & efficacy outcomes of commercial axi-cel as part of a post-approval safety study (PASS).
- Analyze treatment patterns of axi-cel and outcomes of patients younger and older than 65 years

Demographics Compared to ZUMA-1

Characteristic	CIBMTR	ZUMA-1[1]
No. of Patients	533	108
Median Age, y (range)	61(19-86)	58 (23-76)
≥ 65 y	37%	25%
Male	66%	68%
ECOG performance status 0-1	80%	100%
>3 prior lines of therapy	66%	70%
Double/Triple Hit Lymphoma	36%	11%
Prior Auto-HCT	32%	25%
Prior Allo-HCT	2%	0
History of CNS lymphoma	1%	0
Prior CAR T-cell	0.9%	0

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[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544

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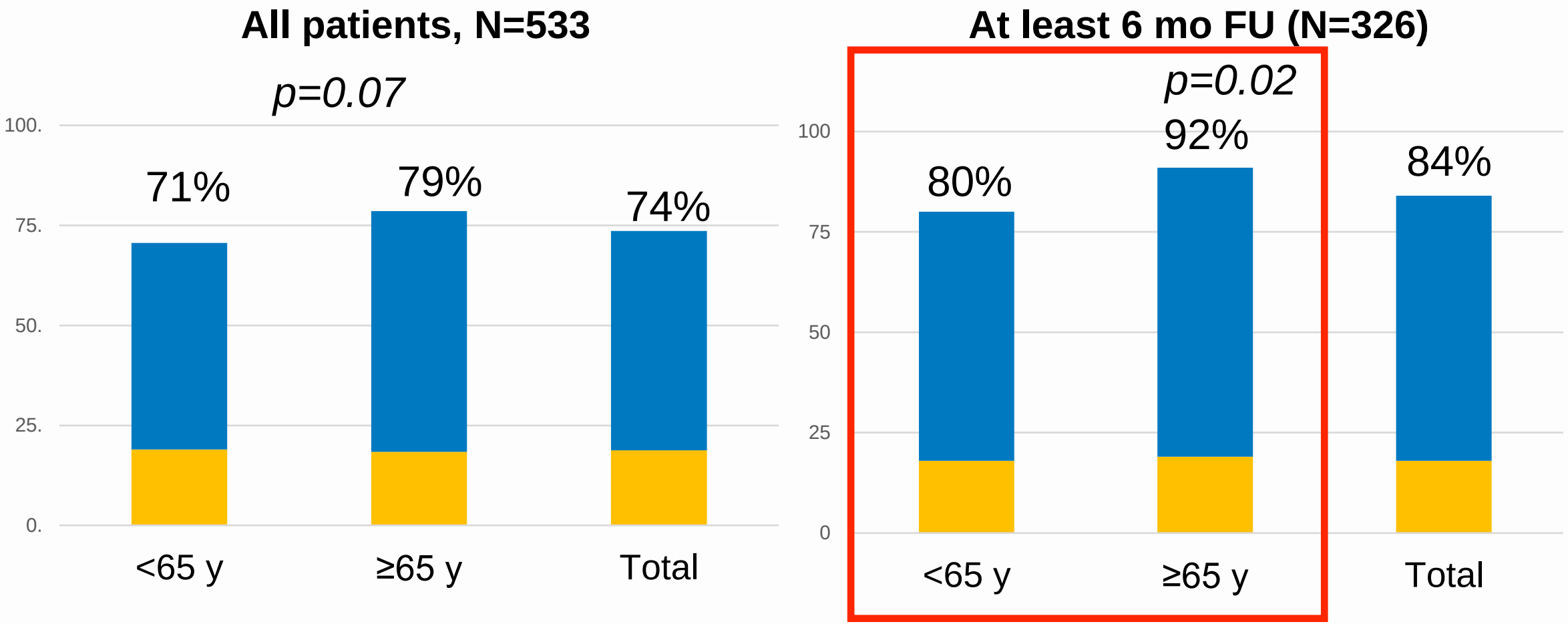
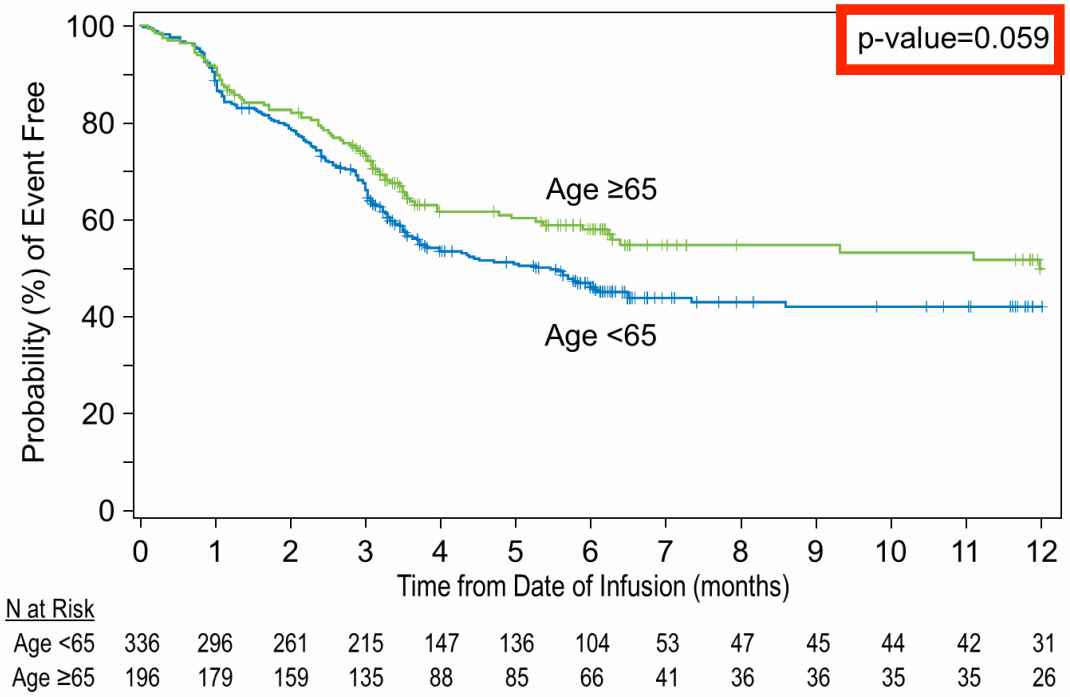
Disease Response after Axi-cel for LBCL



Age and Survival Outcomes after Axi-Cel for LBCL

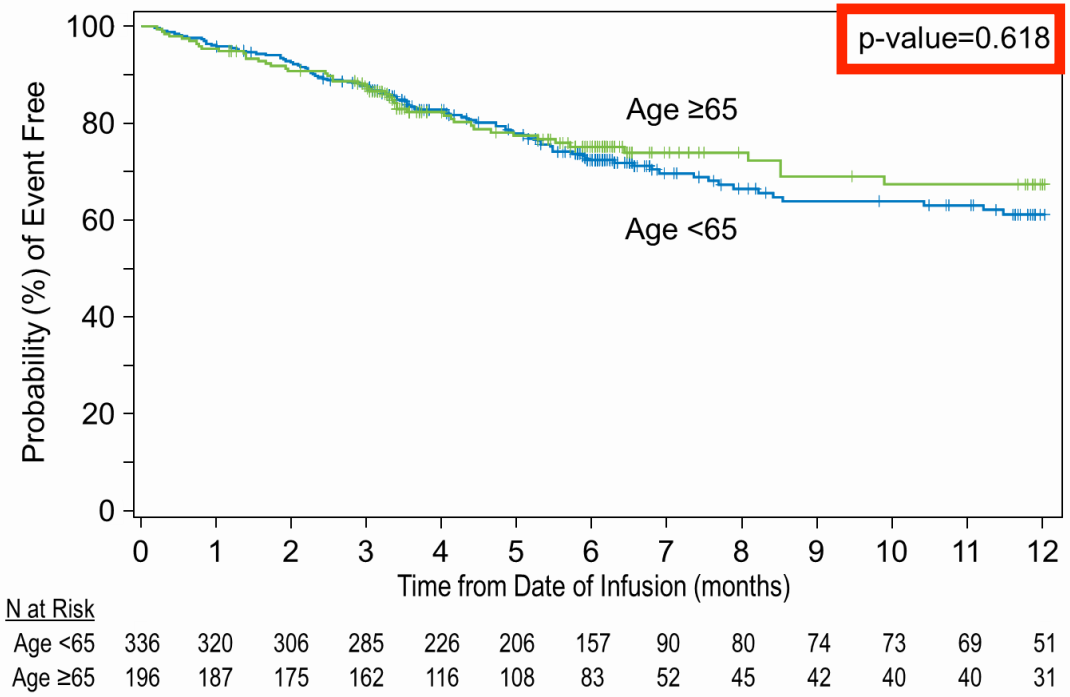
Progression-Free Survival



N at Risk

Age <65	336	296	261	215	147	136	104	53	47	45	44	42	31
Age ≥65	196	179	159	135	88	85	66	41	36	36	35	35	26

Overall Survival



N at Risk

Age <65	336	320	306	285	226	206	157	90	80	74	73	69	51
Age ≥65	196	187	175	162	116	108	83	52	45	42	40	40	31

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Conclusion

- This analysis demonstrates the successful implementation of an outcomes database for capturing data on recipients of commercial CAR T-cells.
- Axi-cel in the real-world setting is used in older patients and with a greater proportion of high-risk disease (double/triple hit lymphoma) yet results are similar to ZUMA-1 trial.
- Older patients (≥65 years) have similar early safety and efficacy outcomes as younger patients.

Tisagenlecleucel Chimeric Antigen Receptor (CAR) T-Cell Therapy for Adults with Diffuse Large B-Cell Lymphoma (DLBCL): Real World Experience from the Center for International Blood & Marrow Transplant Research (CIBMTR) Cellular Therapy Registry

Samantha Jaglowski, Zhen-Huan, Yiyun Zhang, Hu, Manali Kamdar, Monalisa Ghosh, Premal D Lulla, Joshua P Sasine, Miguel-Angel Perales, Peiman Hematti, Sarah Nikiforow, Patricia Steinert, Lan Yi, Raghav Chawla, Lida Pacaud, Mary M Horowitz, Eric Bleickardt, Marcelo C. Pasquini

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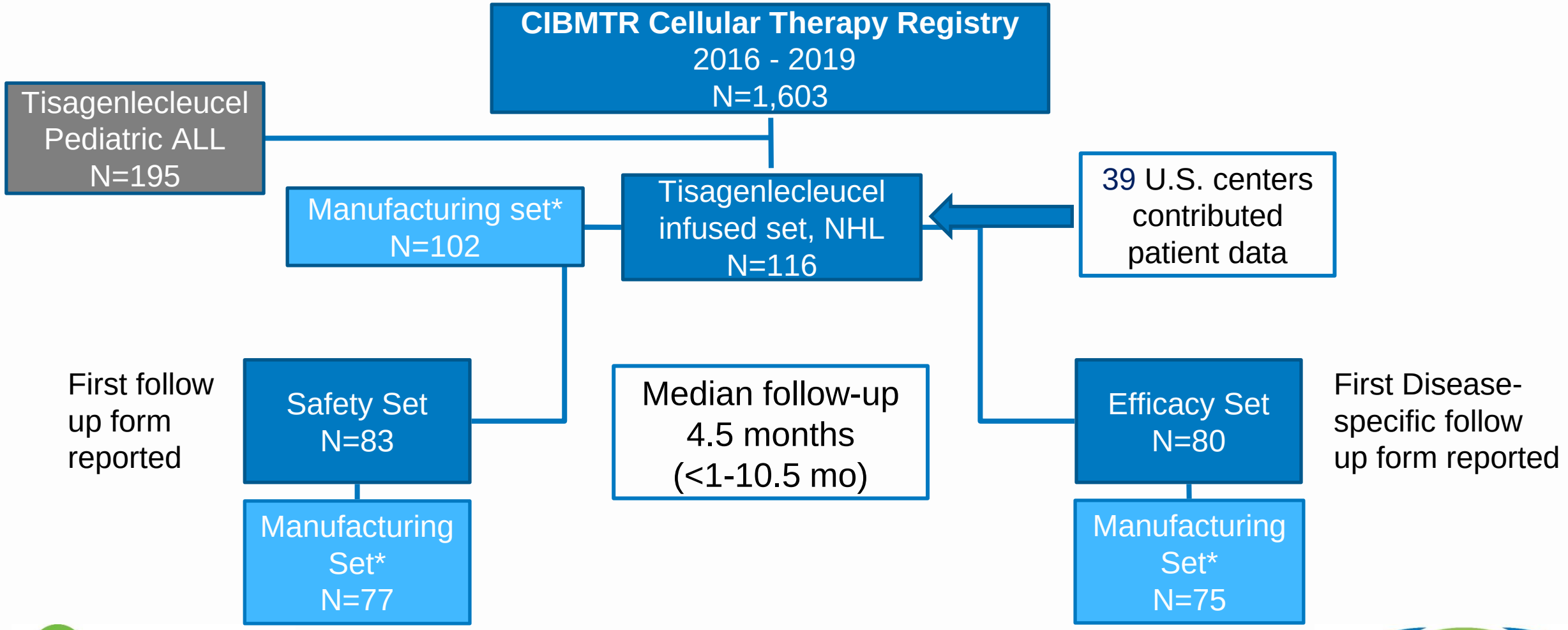
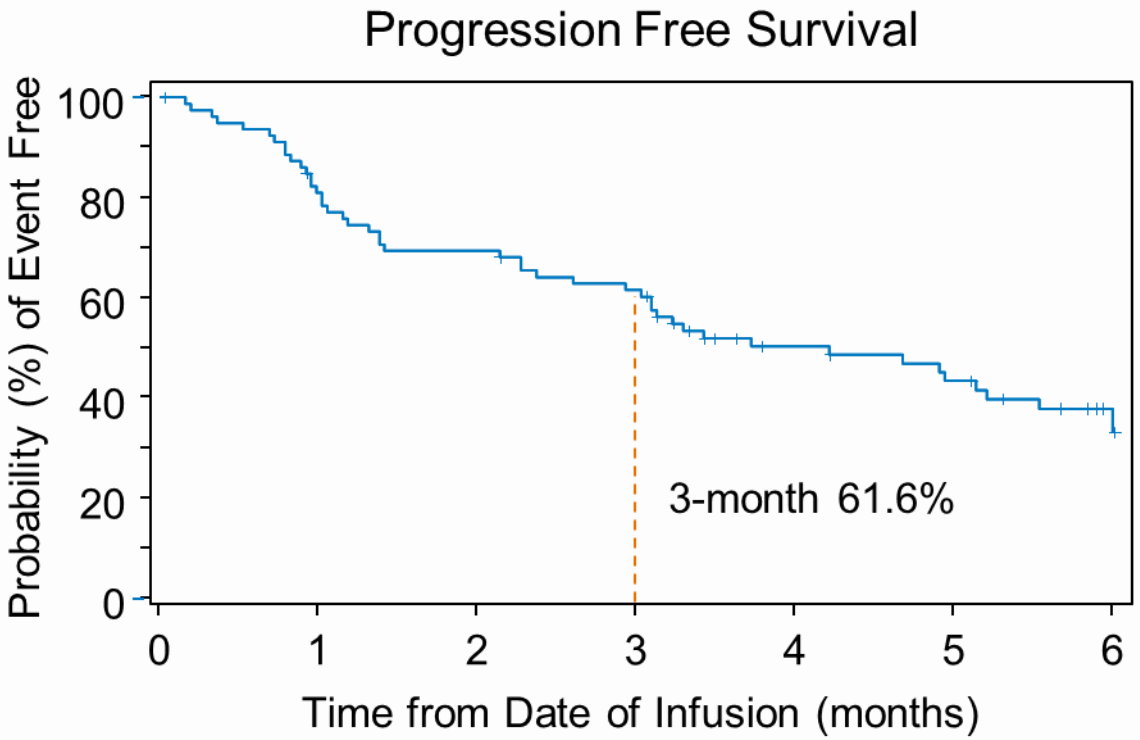
Overview of Patient Data



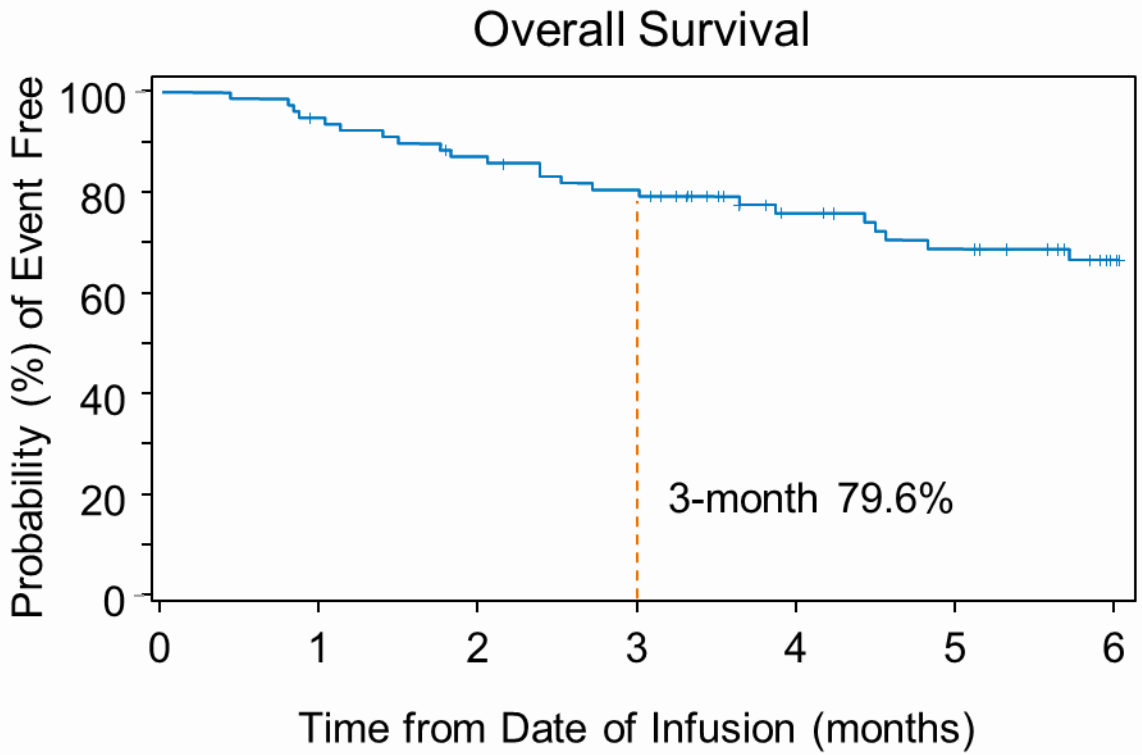
*Identifiable batches with available product characteristics

Progression-Free and Overall Survival



N at Risk

All subjects	80	63	54	47	30	25	14



N at Risk

All subjects	80	75	68	61	45	39	24

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Comparison to JULIET Pivotal Trial

	CIBMTR Registry N=83[a] (%)	JULIET[b] N=115 (%)
ORR	58	52
CR	40	38
DOR at 3 months	75	76
PFS at 3 and 6 months	62 / 33	46 / 39
OS at 3 and 6 months	80 / 67	83 / 61
CRS (Gr. ≥ 3)	4[c]	23[e]
Neurotoxicity (Gr. ≥ 3)	5[d]	11[f]

[a]Efficacy set N=80; safety set N=83
[b]Bachanova V, et. al. Clin Lymphoma Myeloma Leuk 2019 Sep. Vol 19; (Suppl 1); S251-S252
[c] ASTCT grading
[d] ICANS Grading
[e] UPenn grading
[f] MedDRA SMQ: non-infectious encephalopathy/delirium

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Conclusion (1)

- Tisagenlecleucel therapy real-world evidence confirms the efficacy data reported in the pivotal JULIET trial.
- Safety profile appears more favorable in the registry compared to the pivotal JULIET trial.
- Product with viability 60-79% demonstrates comparable outcome as product with ≥80% viability

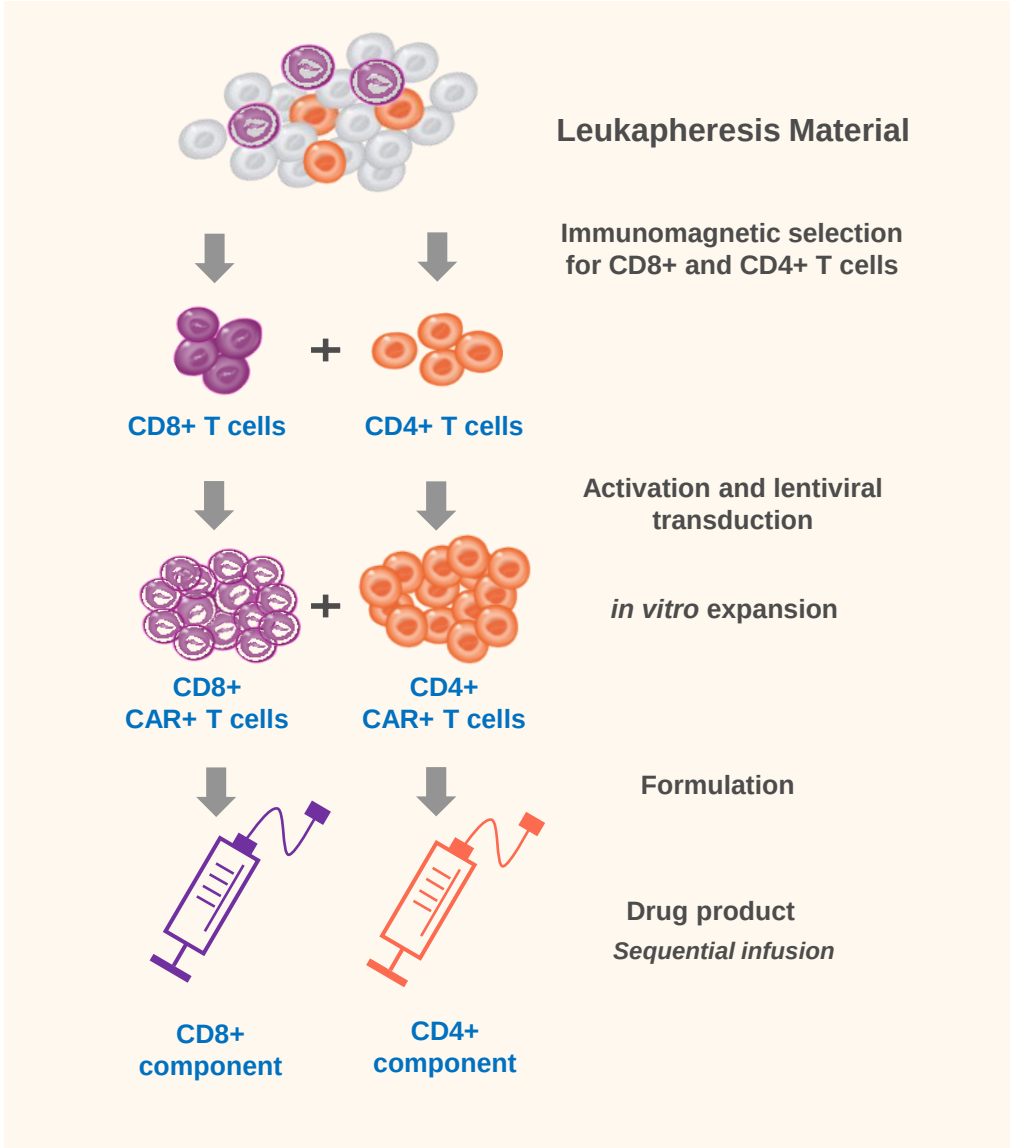
Pivotal Safety and Efficacy Results From TRANSCEND NHL 001, a Multicenter Phase 1 Study of lisocabtagene maraleucel (liso-cel) in Relapsed/Refractory (R/R) Large B-Cell Lymphomas

Jeremy S. Abramson,[1] M. Lia Palomba,[2] Leo I. Gordon,[3] Matthew Lunning,[4] Michael Wang,[5] Jon Arnason,[6] Amitkumar Mehta,[7] Enkhtsetseg Purev,[8] David G. Maloney,[9] Charalambos Andreadis,[10] Alison Sehgal,[11] Scott R. Solomon,[12] Nilanjan Ghosh,[13] Tina Albertson,[14] Jacob Garcia,[14] Ana Kostic,[14] Daniel Li,[14] Yeonhee Kim,[14] Tanya Siddiqi[15]

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Northwestern University Robert H. Lurie Comprehensive Cancer Center, Chicago, IL, USA; [4]University of Nebraska Medical Center, Omaha, NE, USA; [5]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [6]Beth Israel Deaconess Medical Center, Boston, MA, USA; [7]University of Alabama at Birmingham, Birmingham, AL, USA; [8]University of Colorado School of Medicine, Aurora, CO, USA; [9]Fred Hutchison Cancer Research Center, Seattle, WA, USA; [10]University of California, San Francisco, San Francisco, CA, USA; [11]University of Pittsburgh Medical Center, Pittsburgh, PA, USA; [12]Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA, USA; [13]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [14]Juno Therapeutics, a Bristol-Myers Squibb Company, Seattle, WA, USA; [15]City of Hope National Medical Center, Duarte, CA, USA

This study was funded by Bristol-Myers Squibb.

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]

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.

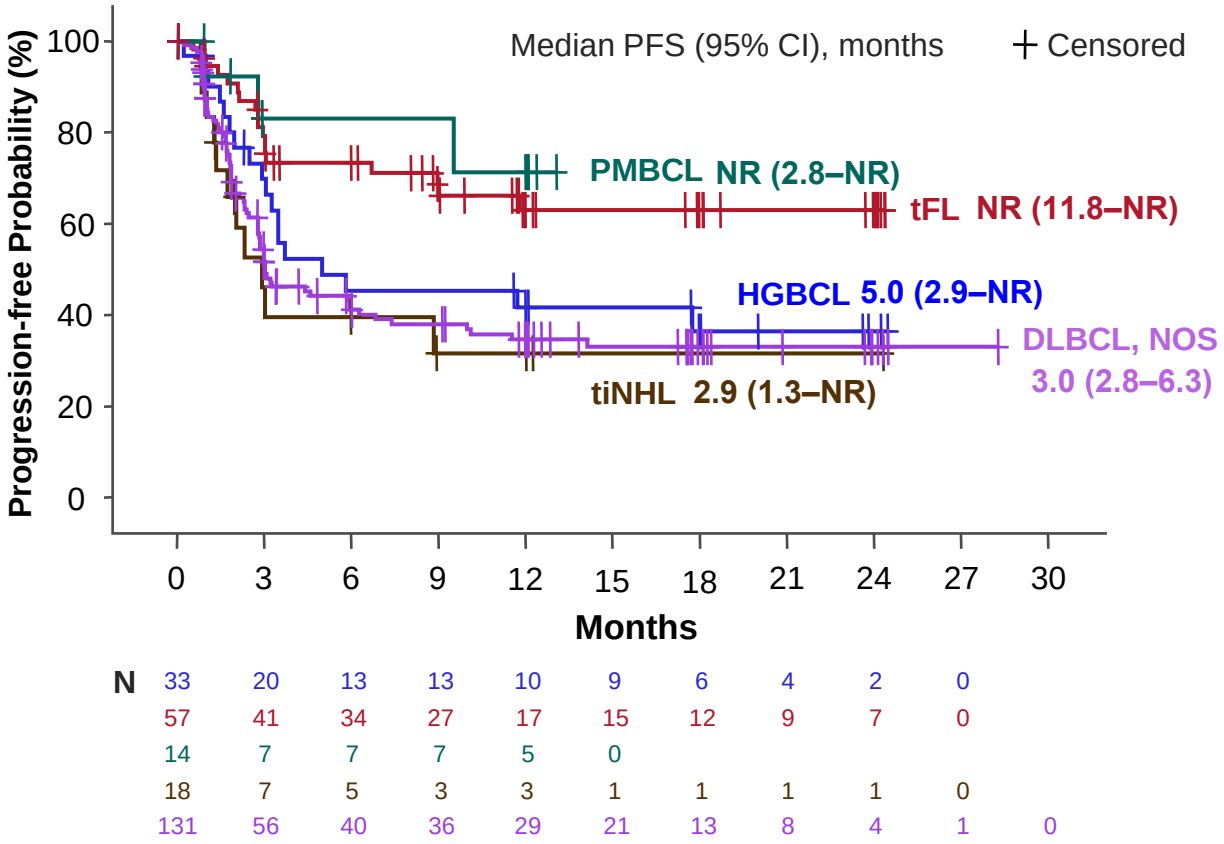
Treatment-Emergent Adverse Events[a] in ≥25% of Patients

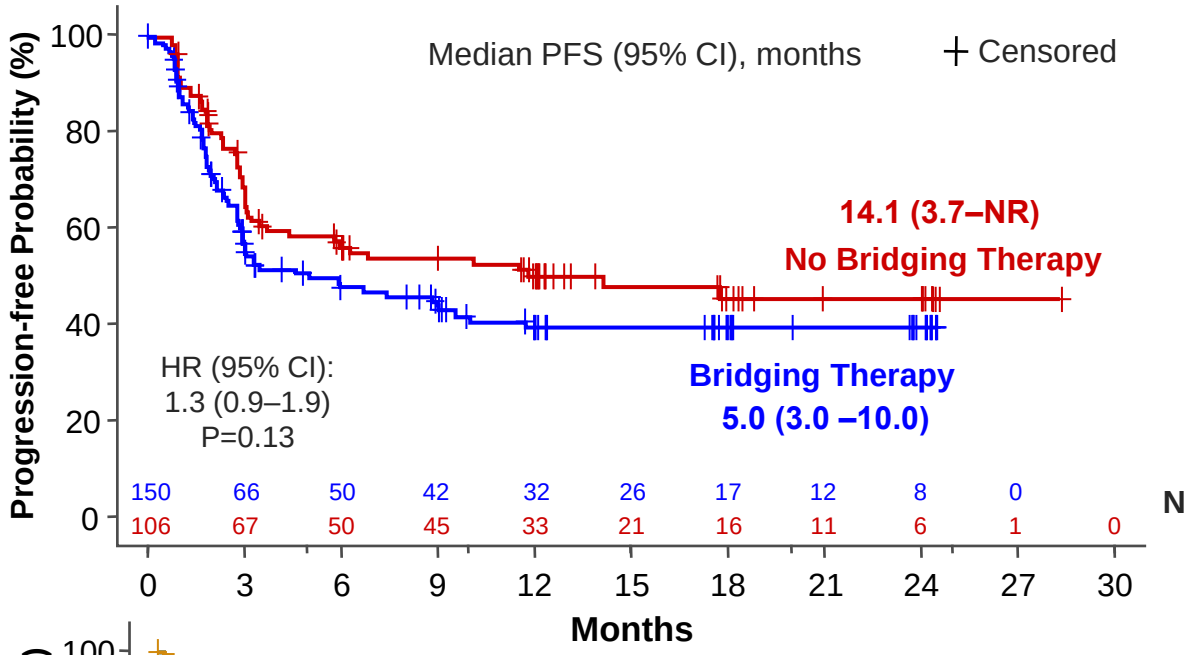
	All liso-cel–Treated Patients (N=269)	
	Any Grade	Grade ≥3
Any TEAEs,[a] n (%)	267 (99)	213 (79)
Neutropenia	169 (63)	161 (60)
Anemia	129 (48)	101 (38)
Fatigue	119 (44)	4 (1)
CRS	113 (42)	6 (2)
Nausea	90 (33)	4 (1)
Thrombocytopenia	84 (31)	72 (27)
Headache	80 (30)	3 (1)
Decreased appetite	76 (28)	7 (3)
Diarrhea	71 (26)	1 (<1)

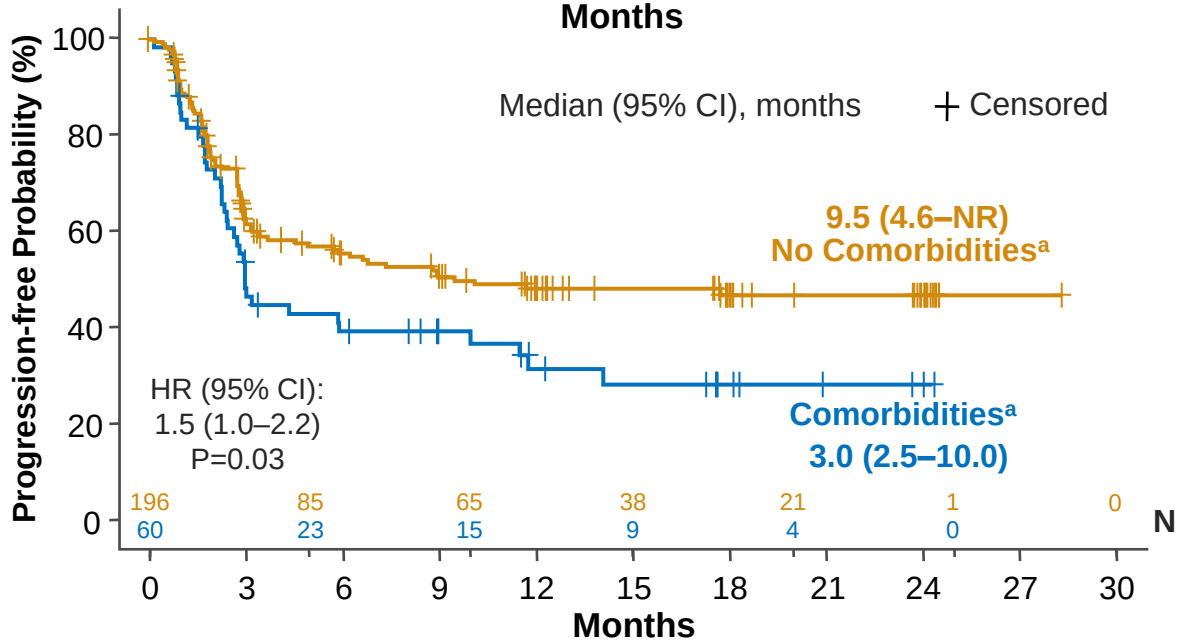
- Grade 5 TEAEs occurred in 7 patients (3%)
  - Considered related to liso-cel (n=4): diffuse alveolar damage (DLT), pulmonary hemorrhage, multiple organ dysfunction syndrome, cardiomyopathy
  - Considered unrelated to liso-cel (n=3): fludarabine leukoencephalopathy, septic shock, and progressive multifocal leukoencephalopathy
- No grade 5 CRS or NE occurred

[a]A TEAE was defined as an adverse event that started any time from initiation of liso-cel administration through and including 90 days following the final cycle of liso-cel. Any AE that occurred after the initiation of another anticancer treatment or liso-cel retreatment was not considered a liso-cel TEAE.
CRS, cytokine release syndrome; DLT, dose-limiting toxicity; NE, neurological event; TEAE, treatment-emergent adverse event.

Progression-Free Survival by Subgroup







[a]Comorbidities were defined as CrCl >30 but <60 mL/min or LVEF ≥40 to <50%.
CrCl, Creatinine clearance; DLBCL, diffuse large B-cell lymphoma; HGBCL, high-grade B-cell lymphoma; HR, hazard ratio; LVEF, left ventricular ejection fraction; NOS, not otherwise specified; NR, not reached; PMBCL, primary mediastinal large B-cell lymphoma; tFL, transformed from follicular lymphoma; tiNHL, transformed from indolent NHL

Multicenter CD19 CAR T-cell trials in aggressive NHL

Study	ZUMA-1	JULIET	TRANSCEND
Reference	Neelapu et al. NEJM 2017 Locke et al. Lancet Oncol 2019	Schuster et al. NEJM 2019	Abramson et al. ASH 2019
CAR T design	CD19/CD3ζ/CD28	CD19/CD3ζ/4-1BB	CD19/CD3ζ/4-1BB
CAR T dose	2 x 10^6/kg	Up to 0.6-6 x 10^8	0.5-1.5 x 10^8
Conditioning therapy	Cy/Flu	Cy/Flu or Bendamustine	Cy/Flu
Lymphoma subtypes Percentage	DLBCL / PMBCL / TFL 78 / 7 / 15	DLBCL / TFL / Other 79 / 19 / 2	DLBCL / PMBCL / TFL / Other 64 / 6 / 22 / 8
Relapsed/Refractory	Refractory	Relapsed or refractory	Relapsed or refractory
Relapse post-ASCT	23%	49%	35%
Bridging therapy	None	Allowed	Allowed
Manufacturing success	99%	94%	99%
Treated/Enrolled	108/120 (90%)	111/165 (67%)	269/344 (78%)*

*Additional 7% received nonconforming product

Design of trials comparing CAR-T to AutoSCT

Trial NCTID	Product	Vector	CAR-T Costim Domain	Defined CD4:CD8 Composition	Targeted Enrollment	Lymphodepletion Regimen (CAR-T ARM)	Inclusion Criteria	Study Start and Primary Completion Dates	Primary Outcome Measure	Other Selected Outcome Measures
ZUMA-7 NCT03391466	Axicabtagene ciloleucel	Retroviral	CD28	No	n=318	Fludarabine 30mg/m^2 Cyclophosphamide 500 mg/m^2 x3d	Age ≥18 ECOG 0-1 Plts >75K DLBCL, tFL, HGBL, T/HRBCL, Cutaneous DLBCL, EBV+ DLBCL	Dec 14, 2017 Jan 15, 2022	EFS at 5 years	ORR up to 5 years PFS up to 5 years OS up to 5 years mEFS up to 5 years DOR up to 5 years
BELINDA NCT03570892	Tisagenlecleucel	Lentiviral	4-1BB	No	n=359	Fludarabine 25mg/m^2 Cyclophosphamide 250 mg/m^2 x3d *OR* Bendamustine 90 mg/m2 x 2d	Age ≥18 ECOG 0-1 Plts >50K DLBCL, NOS FL Gr 3B PMBCL, T/HRBCL Intravascular LBCL ALK+ LBCL HGBCL HHV8+ DLBCL tFL, Cutaneous DLBCL	May 7, 2019 Dec 30, 2025	EFS at 5 years	OS at 5 years ORR at 5 years ORR at 5 years DOR at 5 years
TRANSFORM NCT03575351	Lisocabtagene maraleucel (JCAR017)	Lentiviral	4-1BB	Yes (1:1)	n=182	Fludarabine 30mg/m^2 Cyclophosphamide 300 mg/m^2 x3d	Age 18-75 ECOG 0-1 DLBCL (de novo or transformed) PMBCL T/HRBCL FL Gr3B	Oct 23, 2018 Sep 20, 2023	EFS at 3 years	CRR at 3 years PFS at 3 years OS at 4.5 years ORR at 3 years

Komanduri, *JCO, in press 2020*

Lessons from LBCL trials

- No prospective comparisons…trials comparing each product to AutoSCT will better help us compare efficacy and toxicity
- In each trial, the subset of patients with tFL and PMBCL did a bit better than DLBCL-NOS
- Use of a CD28 costimulatory domain appears to be associated with higher rates of CRS and ICANS as well as earlier onset of toxicity (axi-cel use in most centers is exclusively inpatient, while many centers have greater comfort with outpatient tisagenlecleucel and liso-cel)
- ORR rates may also be higher with axi-cel, while tisagenlecleucel may be better tolerated in elderly and infirm patients
- To date, in trial and commercial setting, axi-cel manufacturing success rates have been better, with shorter aphaeresis to infusion (“vein to vein”) times
- With all products, more than half of patients relapse and die of lymphoma, with antigen loss common
- Most patients, regardless of product, recover from B cell aplasia, suggesting a minority have long-term persistence of CAR-T cells

CAR-T therapies for NHL…caveats

- *We have no randomized control trials and critical elements of studies to date make comparisons across products…and studies (even of the same product) difficult, if not impossible:*
    - *Ability to administer bridging therapy*
    - *Dosing (e.g., fixed, weight-based dose), patient-to-patient variability in product composition*
    - *Likelihood of successful product manufacturing, achievement of release criteria, infusion*
    - *Varying criteria for assessment of toxicities (e.g., three conflicting scales in initial studies)*
- *"Real-world"* studies don't really reflect the REAL world, and this is even more true for patients who have indolent lymphomas, more likely to be managed entirely in the community than in academic centers. A large fraction of CAR-T patients are still treated in a small number of busy

Selective pressure of CAR-T therapy can lead to CD19 loss

Eliana Trial: Majority of relapsing patients had CD19 negative disease (N=15)

- Maude, S.L., Tisagenlecleucel in Children and Young Adults with B-Cell Lymphoblastic Leukemia. New England Journal of Medicine, 2018. 378(5): p. 439-448.

Retrospective Review of 43 patients with relapsed DLBCL with CD19 assessed: 13/43 CD19 negative (~30%)

- Spiegel, J.Y., Outcomes in large B-cell lymphoma progressing after axicabtagene ciloleucel (Axi-cel): Results from the U.S. Lymphoma CAR-T Consortium. Journal of Clinical Oncology, 2019. 37(15_suppl): p. 7517-7517.

Potential strategies to mitigate relapse

Targeting multiple antigens with bicistronic or bi-allelic CAR-T constructs

- CD19/CD20 targeting

Shah, Hari, et al., MCW, Nat Med Oct 2020

- CD19/CD22 targeting

Spiegel, Muffly, Mackall, et al., Stanford, Nat Med, in press, 2020

Combination of CAR-T therapies (targeting single or dual targets) with checkpoint blockade (e.g., pembrolizumab)

VIRTUAL 2020 ESMO congress

Phase I Alexander study of AUTO3, the first CD19/22 dual targeting CAR T cell therapy, with pembrolizumab in patients with r/r DLBCL

Eleni Tholouli[1], Kirit Ardeshna[2], Aravind Ramakrishnan[3], Connie Batlevi[4], Maria Marzolini[2], Wendy Osborne[5], Carlos Bachier[6], Peter McSweeney[7], Elizabeth Budde[8], Nancy L. Bartlett[9], Yiyun Zhang[10], Muhammad Al-Hajj[10], Martin Pule[10], Simon Thomas[10], Maud Jonnaert[10], Vijay Peddareddigari[10], Nushmia Khokhar[10], Robert Chen[10], Lazaros Lekakis[11].

[1]Department of Haematology, Machester Royal Infirmary, Manchester, UK; [2]Department of Haematology, University College London Hospitals NHS Foundation Trust, London, UK; [3]Sarah Cannon Blood Cancer Center at St. David's South Austin Medical Center, Austin, TX; [4]Memorial Sloan Kettering Cancer Center, New York, NY; [5]Department of Haematology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle upon Tyne, UK; [6]Texas Transplant Institute, Nashville, TN; [7]Colorado Blood Cancer Institute at Presbyterian/St. Luke's Medical Center, Denver, CO; [8]T Cell Therapeutics Research Laboratory, Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA; [9]Washington University School of Medicine Siteman Cancer Center, St. Louis, MO; [10]Autolus Therapeutics, London, UK; [11]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL

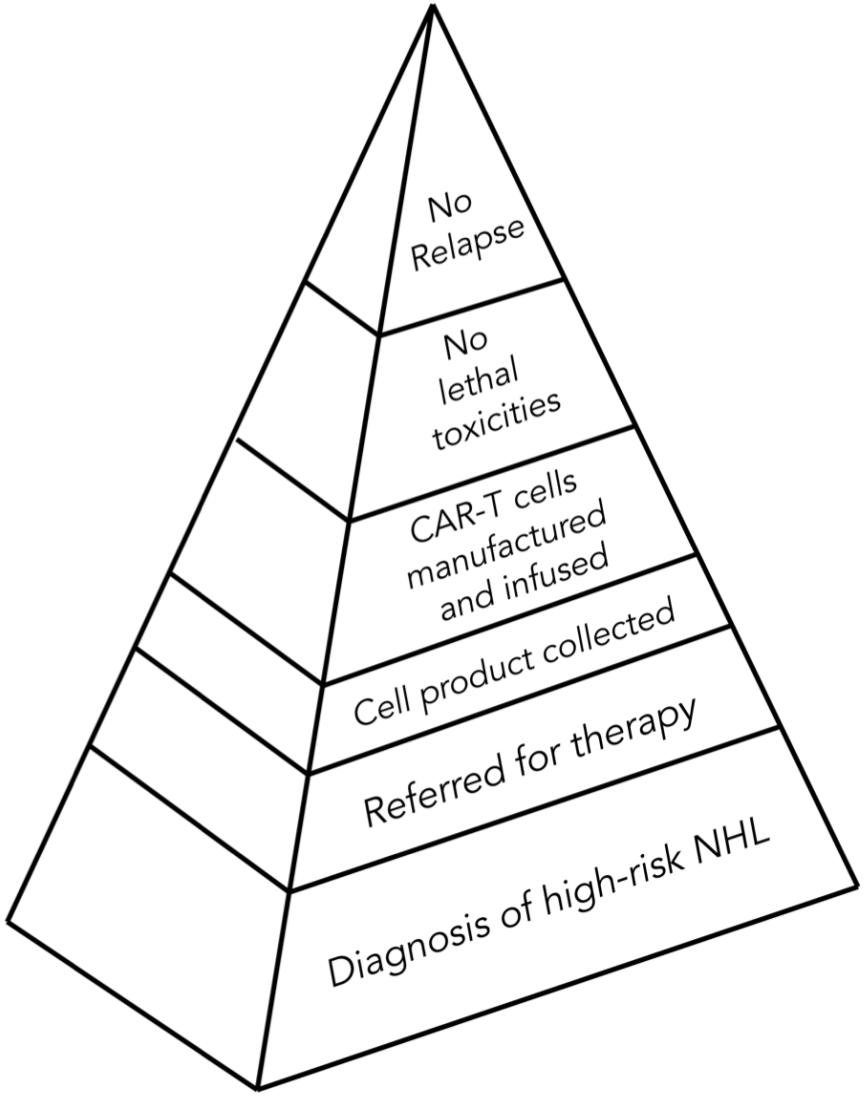
Summary
Phase I Cohorts, ALEXANDER Study

- AUTO3 has a tolerable and best-in-class safety profile
  - 0% ≥ Grade 3 CRS with primary infusion:
  - 6% ≥ Grade 3 (2/35) neurotoxicity
    - All cases of neurotoxicity in setting of disease progression, very minimal / undetectable CAR-T cells in peripheral blood and with confounding factors
    - Patients that achieved complete responses, where robust expansion was observed, no severe CRS or neurotoxicity of any grade was seen
- Completed RP2D cohort (150 - 450 x 10^6 CD19/CD22 CAR T cells with pembrolizumab D-1)
  - ORR 71% and CRR 64% (N=14)
- Complete responses are durable, 14/15 (93%) without progression (median f/u 6 months)
- Outpatient expansion cohort enrolling

Are CAR-T therapies reaching enough patients?

- Short answer is (for most)….NO!
- Estimate of DLBCL cases in the US is approximately 25K/year
- Probably 10K patients eligible per FDA label (~5K relapsed, 5K refractory)
- *Fewer than 4000 patients treated with both Yescarta and Kymriah since FDA approvals in October 2017!* ***<15% of patients who qualify***
- Likely similar underutilization rates to what we already see for both autologous and allogeneic transplantation

Between diagnosis to cure



Komanduri, *JCO, in press 2020*

Where is CAR-T therapy in mid-2020?

- CAR-T therapies have truly shifted our treatment paradigm with unprecedented success in relapsed and refractory CD19+ lymphoma/leukemia
- *However…*treatments are associated with significant relapse rates, non-relapse mortality and cost
- Novel therapies with improved efficacy, lower relapse rates and improved cost efficacy are still needed.
- Real success beyond CD19 targeting remains limited
- Next likely approvals will be for lisocabtagene ciloleucel for CD19+ NHL and BCMA-specific CAR therapy for myeloma
- Dual targeting in lymphoma appears promising but unproven
- With high costs (both for products and for care) access is limited even in the United States *a key challenge will be finding ways to sustainably provide access and develop new therapies*

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