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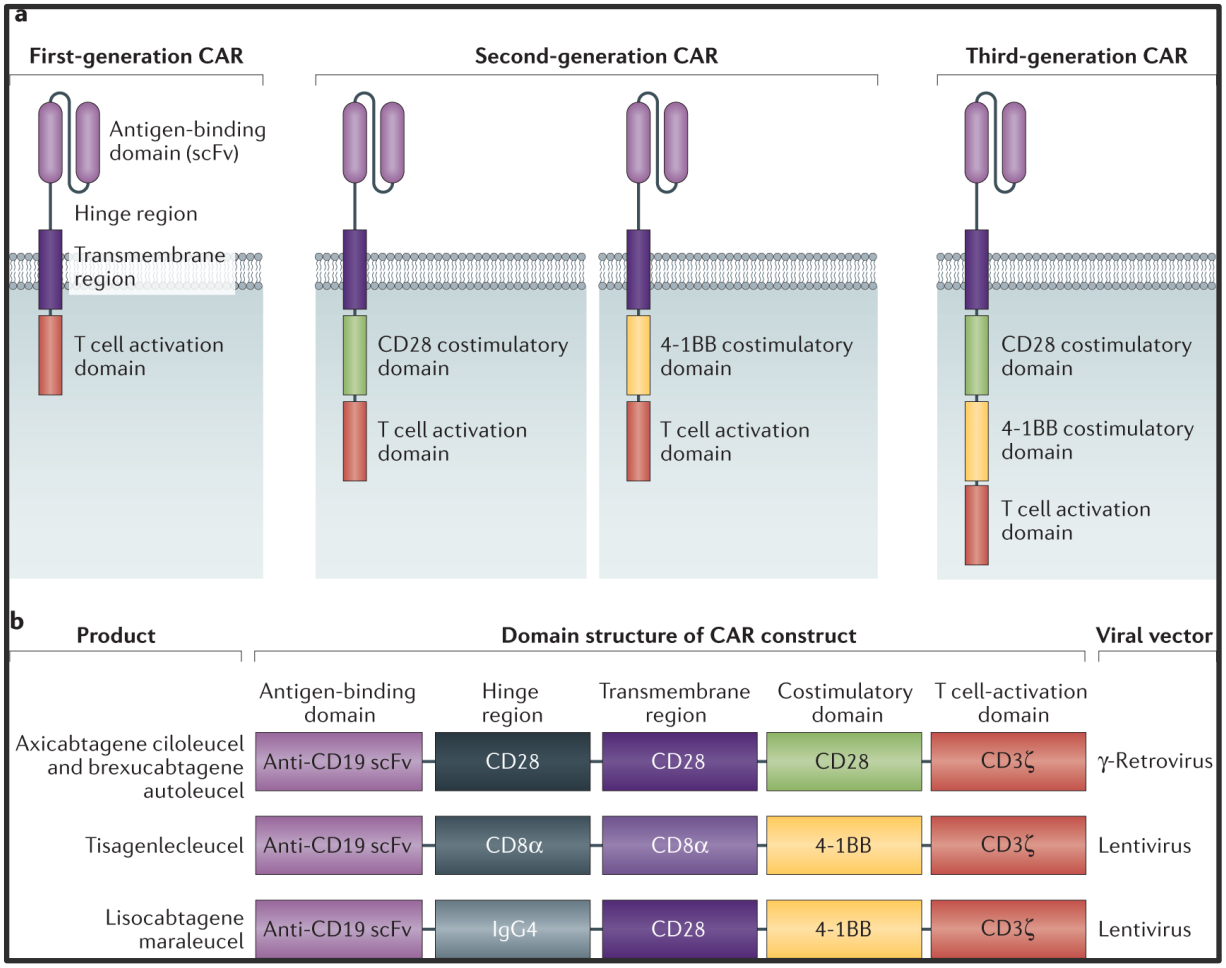
CAR T-Cell Therapy for Hematologic Malignancies ASH 2021

Current FDA-Approved Indication



Axi-cel

DLBCL 2nd Failure

FL 2nd Failure

Brexucabtagene

MCL 2nd Failure

ALL Relapsed

Tisagen

DLBCL 2nd Failure

ALL, Relapsed <23

Liso-cel

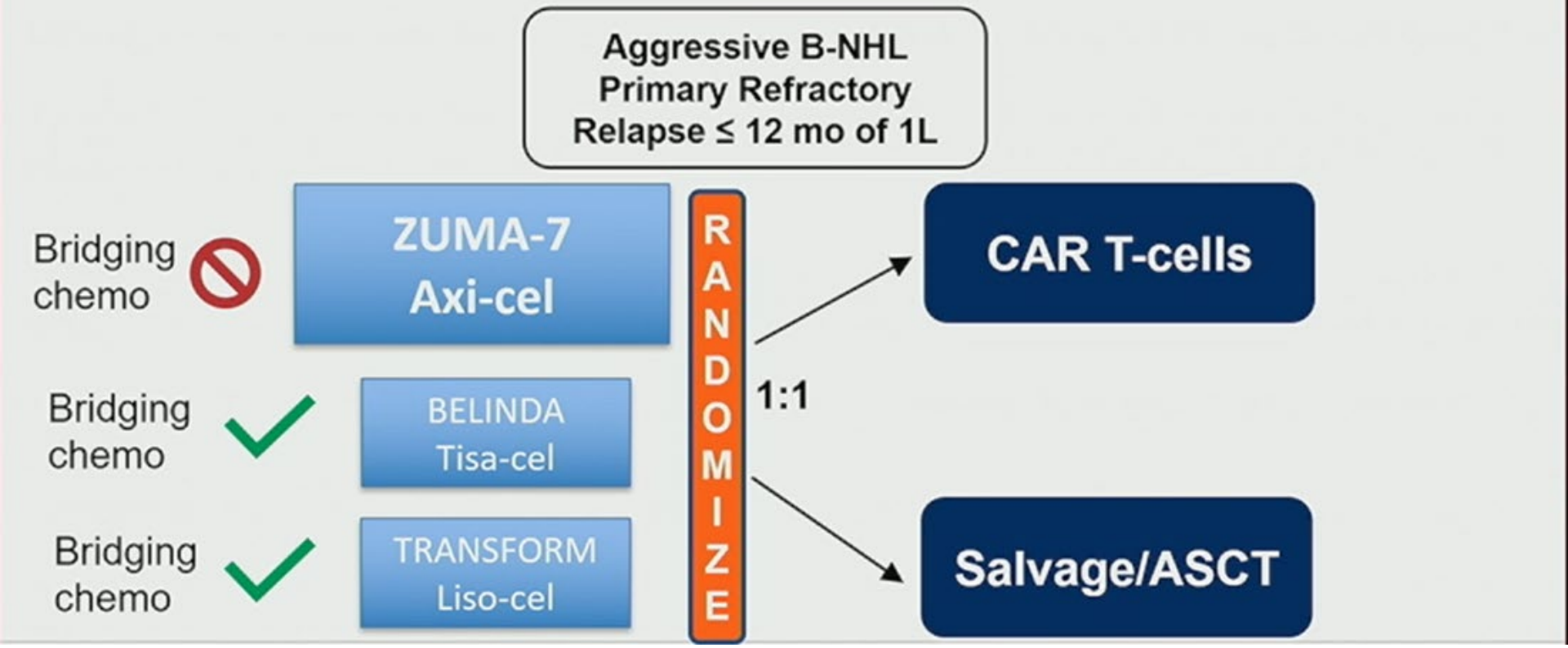
DLBCL 2nd Failure

Cappell KM and Kochenderfer JN. *Nat Rev Clin Oncol* 18, 715 (2021).

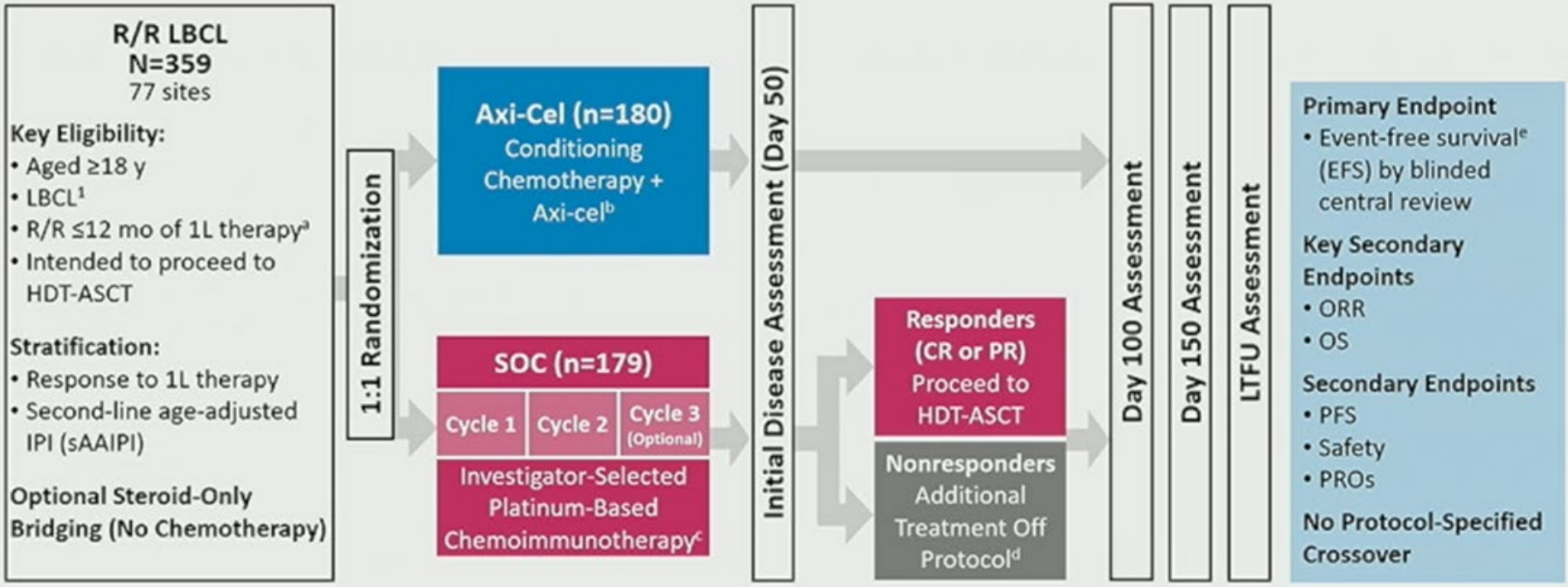
Updates

- Large B-Cell Lymphoma
  - CAR T Cell as Second-Line Therapy (ZUMA-7, TRANSFORM, BELINDA)
  - CAR T-Cell Therapy for Primary Refractory DLBCL (ZUMA-12)
- Follicular Lymphoma (ZUMA-5)
- Myeloma
  - Cilta-cel (CARTITUDE)
- New CAR T-Cell Products, Approaches, Indications
  - Novel Targets
  - AlloCAR T Therapy
  - iPSC-Derived NK CAR T Cells
  - AML MICA/MICB
  - Myeloma - Gamma Secretase Inhibitor

ZUMA-7: Uncharted Territory



ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL

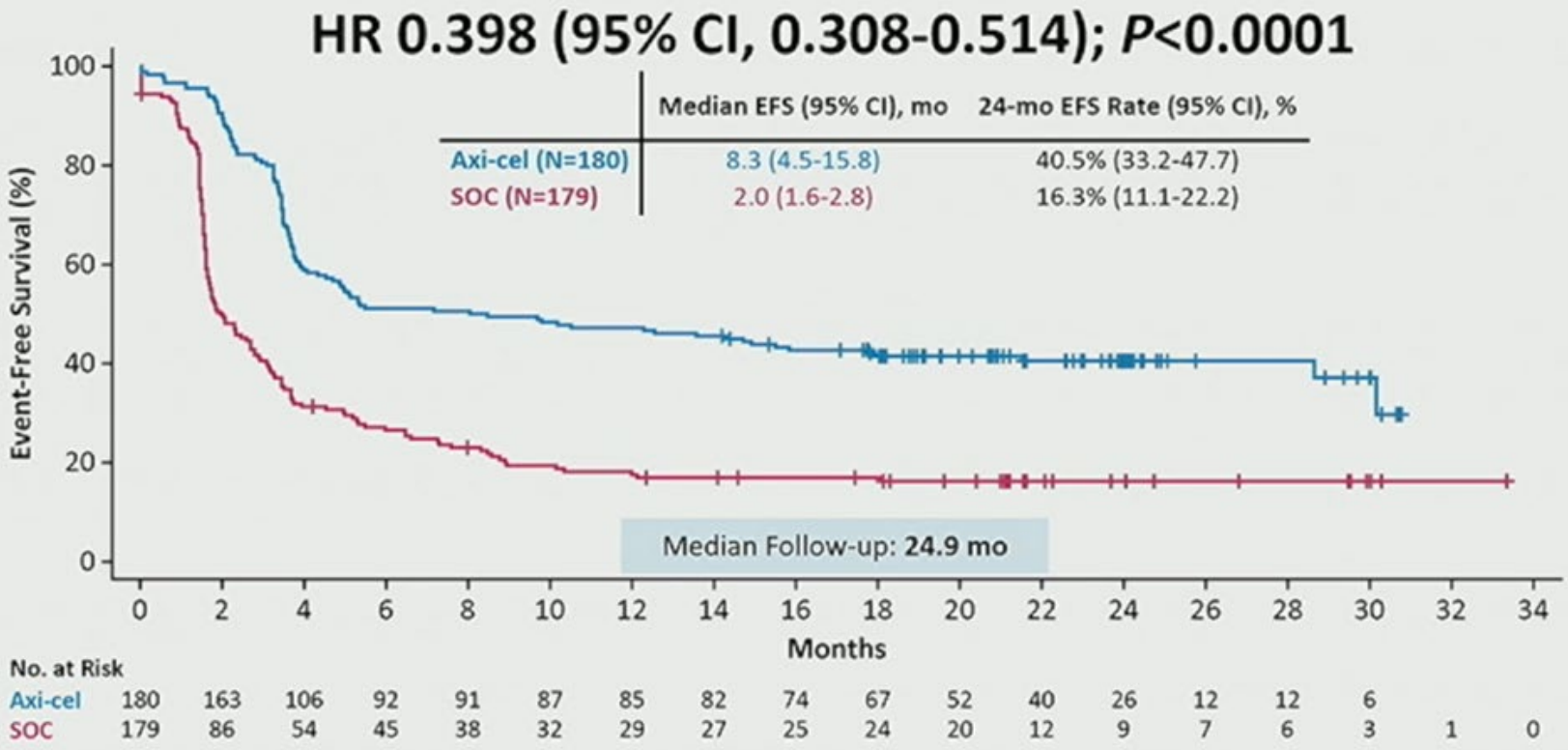


[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m²/day) and fludarabine (30 mg/m²/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10^6 CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood*. 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

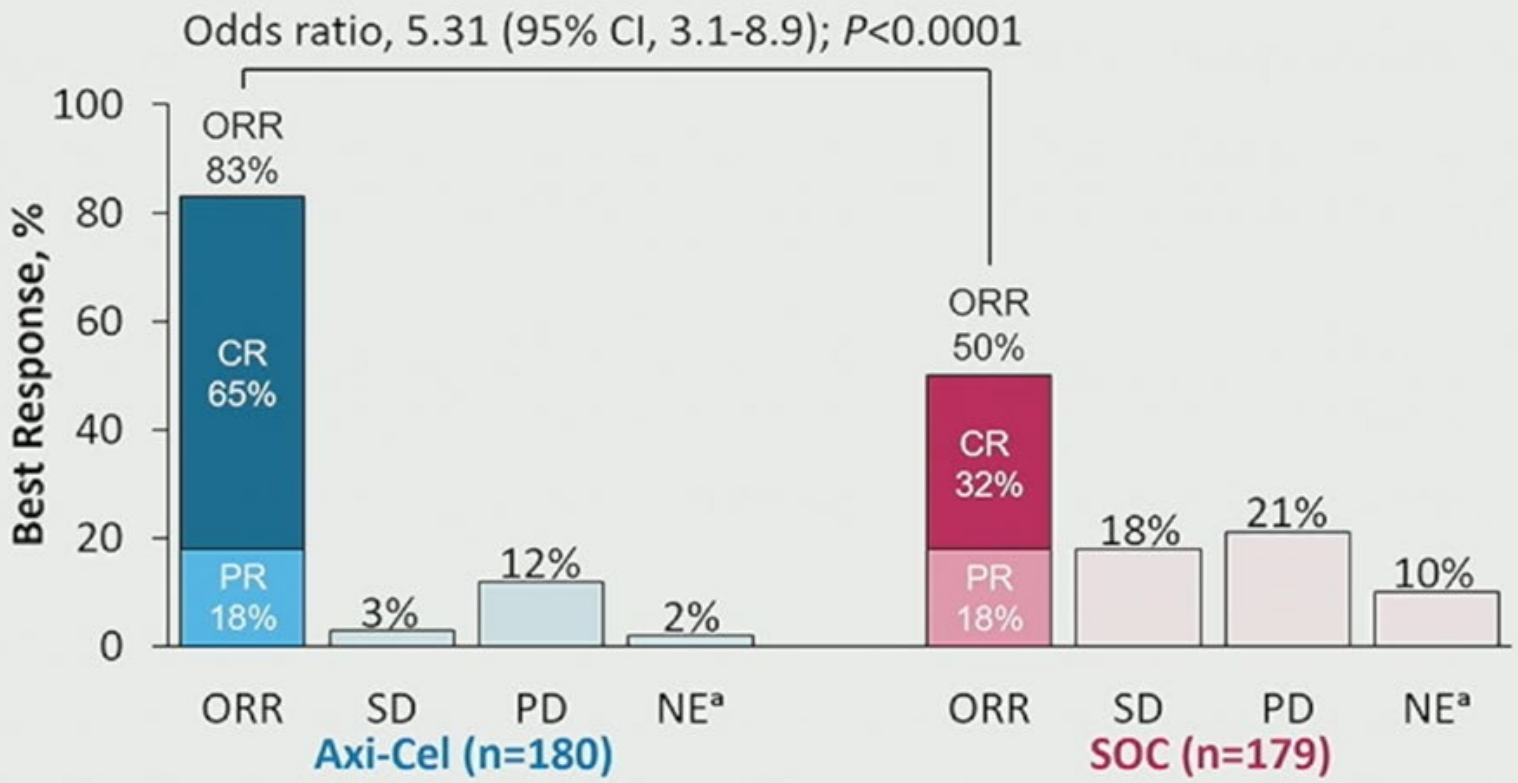
Locke et al ASH 2021 Plenary Abstract 2

Primary EFS Endpoint: Axi-Cel Is Superior to SOC



Locke et al ASH 2021 Plenary Abstract 2

ORR Was Significantly Higher in Axi-Cel Versus SOC Patients

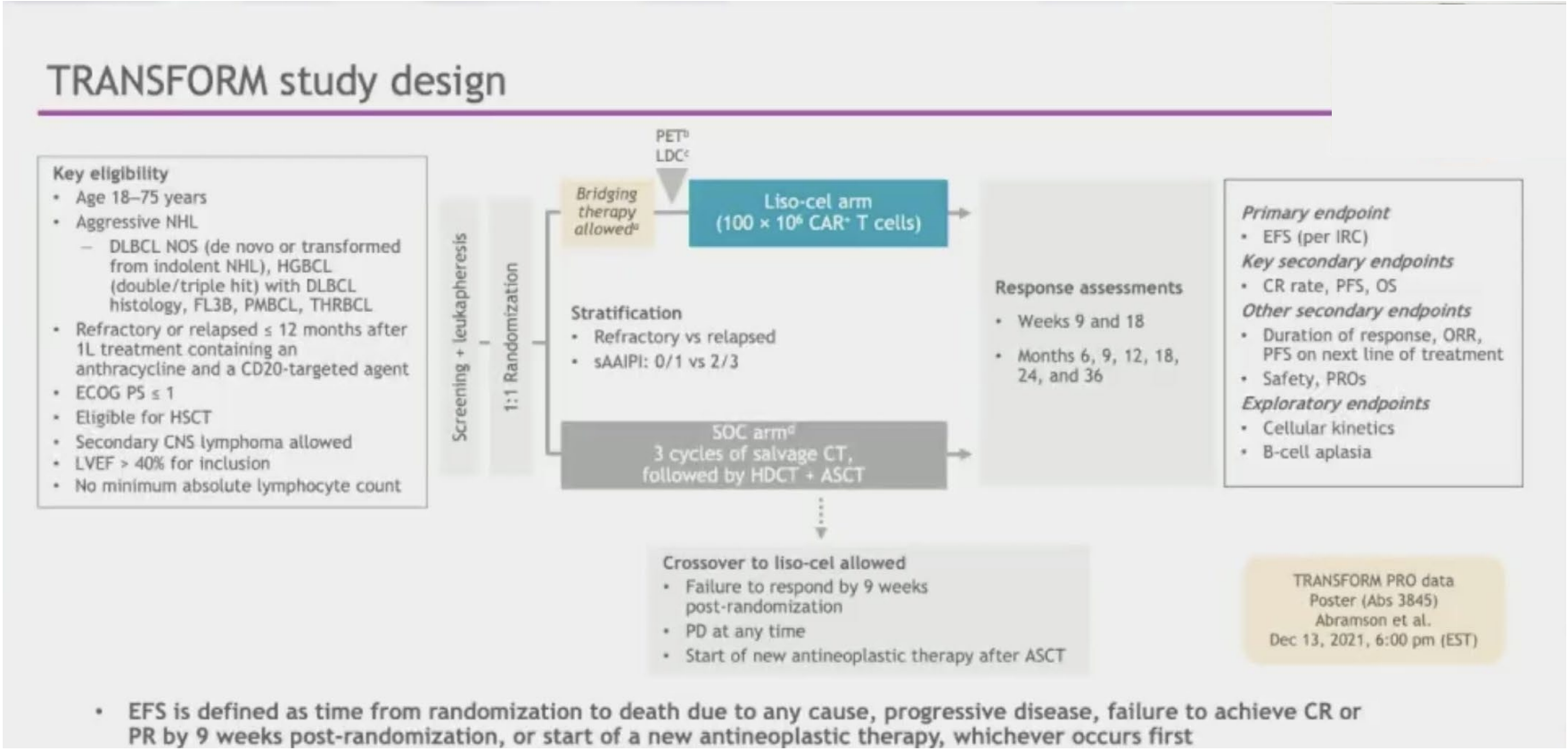


[a] Not evaluable (NE): In the axi-cel arm, response assessments were not done for 4 patients. In the SOC arm, there were 4 patients with undefined disease and 14 who did not have response assessments done.

Locke et al ASH 2021 Plenary Abstract 2

Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

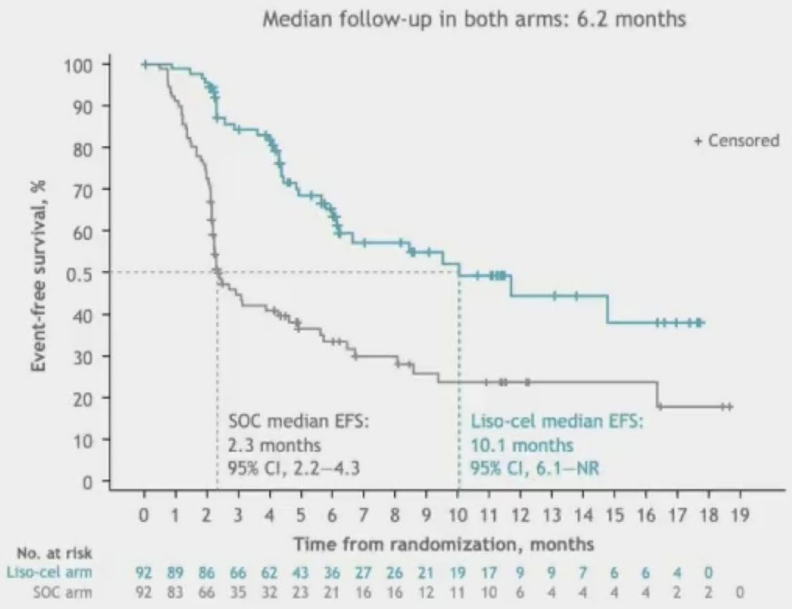
Kamdar et al, ASH 2021



Lisocabtagene maraleucel for 2nd line (<12m) relapsed DLBCL

Kamdar et al, ASH 2021

TRANSFORM: Event-free survival per IRC (ITT set; primary endpoint)



	Liso-cel arm (n = 92)	SOC arm (n = 92)
Patients with events, n	35	63
Stratified HR (95% CI)	0.349 (0.229–0.530)	
	$P < 0.0001$	
6-month EFS rate, % (SE)	63.3 (5.77)	33.4 (5.30)
Two-sided 95% CI	52.0–74.7	23.0–43.8
12-month EFS rate, % (SE)	44.5 (7.72)	23.7 (5.28)
Two-sided 95% CI	29.4–59.6	13.4–34.1

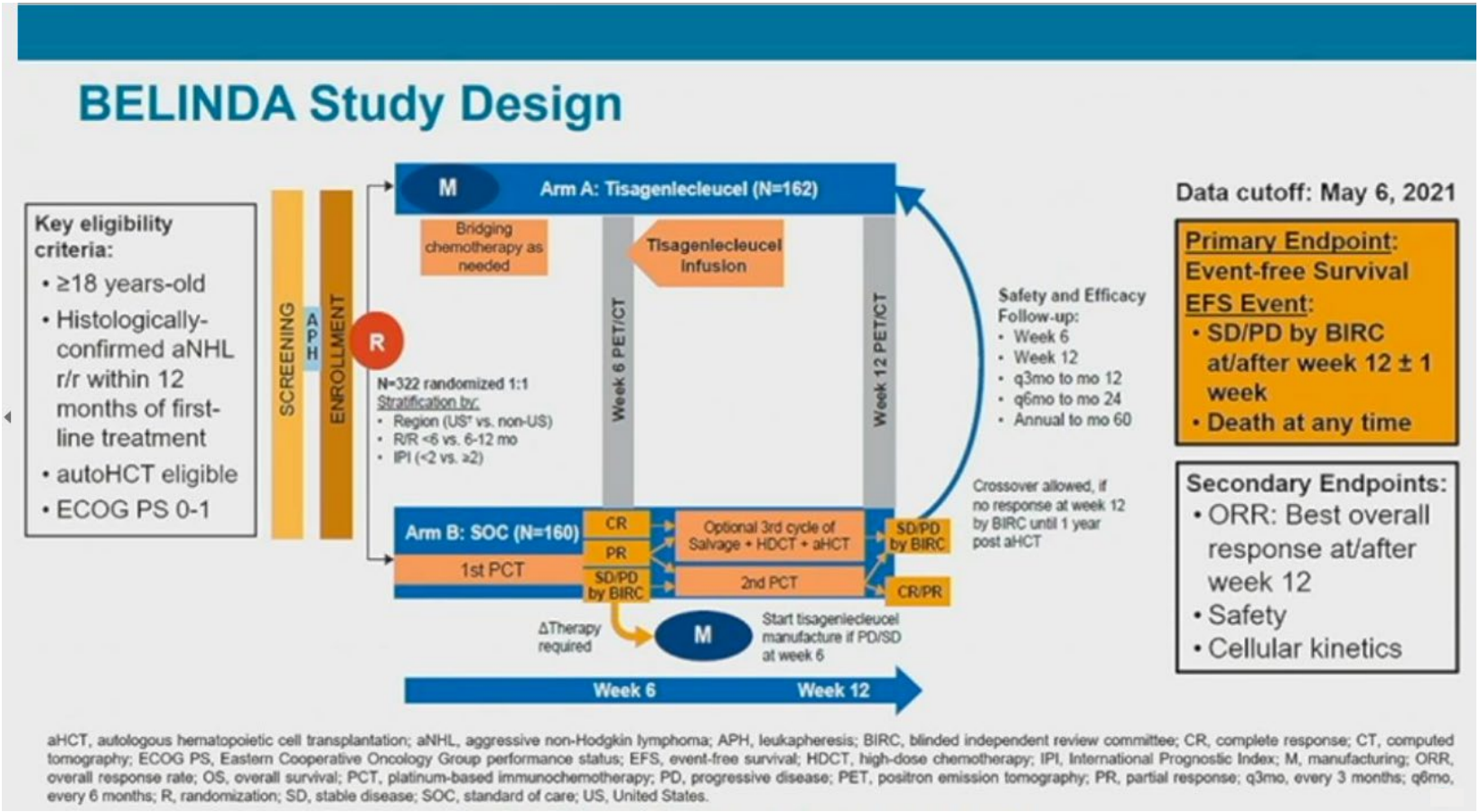
One-sided *P* value significance threshold to reject the null hypothesis was < 0.012

EFS is defined as the time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization or start of a new antineoplastic therapy due to efficacy concerns, whichever occurs first.
CI, confidence interval; HR, hazard ratio; NR, not reached; SE, standard error.

Kamdar M, et al. ASH 2021 [Abstract #91]

Tisagenlecleucel for 2nd line (<12m) relapsed DLBCL

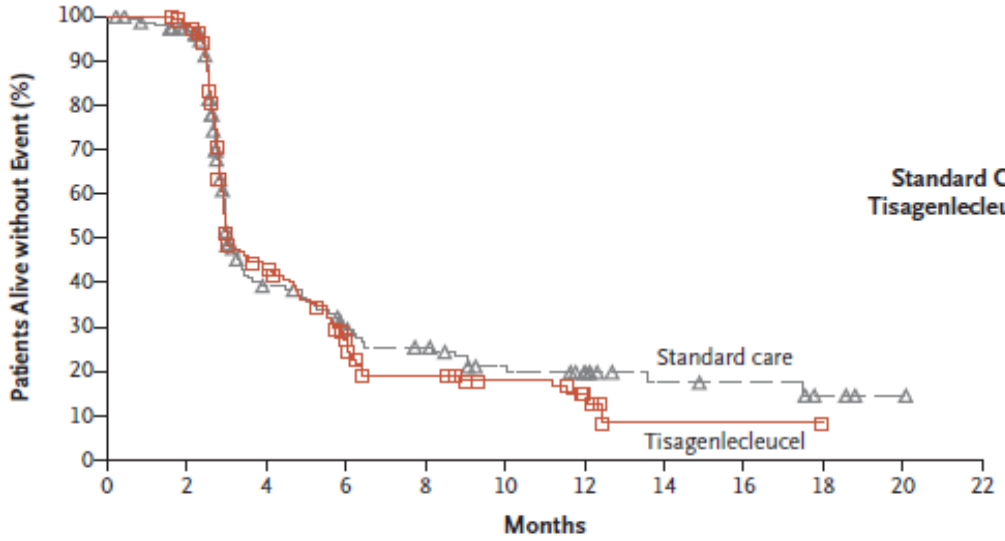
Bishop et al, NEJM 2021



aHCT, autologous hematopoietic cell transplantation; aNHL, aggressive non-Hodgkin lymphoma; APH, leukapheresis; BIRC, blinded independent review committee; CR, complete response; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDCT, high-dose chemotherapy; IPI, International Prognostic Index; M, manufacturing; ORR, overall response rate; OS, overall survival; PCT, platinum-based immunochemotherapy; PD, progressive disease; PET, positron emission tomography; PR, partial response; q3mo, every 3 months; q6mo, every 6 months; R, randomization; SD, stable disease; SOC, standard of care; US, United States.

Tisagenlecleucel for 2nd line (<12m) relapsed DLBCL

Bishop et al, NEJM 2021



No. at Risk												
Standard care	160	148	45	31	25	17	12	7	6	3	1	0
Tisagenlecleucel	162	156	57	32	19	13	6	1	1	0	0	0

	No. of Patients	No. of Events	Median Event-free Survival (95% CI)
			mo
Standard Care	160	104	3.0 (3.0–3.5)
Tisagenlecleucel	162	117	3.0 (2.9–4.2)

Hazard ratio for event or death (tisagenlecleucel vs. standard care), 1.07 (95% CI, 0.82–1.40)
P=0.61

Figure 2. Kaplan–Meier Plot of Event-free Survival.

An event was defined as progressive disease or stable disease on or after day 71 or death at any time (i.e., event-free survival at a given time point represents the estimated percentage of patients who had a complete or partial response at this time point among all ran-

Summary of second line CAR T studies

Randomized trials of CAR T-cells vs. SOC in 2nd line transplant-eligible DLBCL with primary refractory disease or relapse within 1 year of 1st line therapy

	ZUMA-7	TRANSFORM	BELINDA
CAR T-cell	Axicabtagene Ciloleucel	Lisocabtagene Maraleucel	Tisagenlecleucel
n	359	184	322
% infused in CAR arm	94%	98%	96%
Median EFS	8.3 mo vs. 2 mo	10.1 mo vs. 2.3 mo	3 mo vs. 3 mo
Hazard ratio	0.398 (*P*<*0*.0001)	0.349; (*P* < 0.0001)	1.07 (*P*=0.69)
Median follow-up	25 months	6 months	10 months
CR rate	65% vs 32%	66% vs 39%	28% vs 28%
Grade ≥3 CRS/NT	6% / 21%	1% / 4%	5% / 3%
	Locke, et al. Abstract 2	Kamdar, et al. Abstract 91	Bishop, et al. Abstract LBA-6

Implications of second line CAR T studies

- In patients with chemoresistant disease (short first remission), more chemo (and AutoSCT) is not effective
- Why different outcome in BELINDA study with tisagenlecleucel?
  - Chemotherapy bridging (sicker patients)
  - Additional chemo cycles for standard group
  - Longer time (52d) to get CAR T (and 25.9% pre-infusion PD)
  - Different agent
  - Less lymphodepletion
  - Event definitions
- CAR T will be SOC for those with PD < 1 year
- AutoSCT remains SOC for those with later relapses

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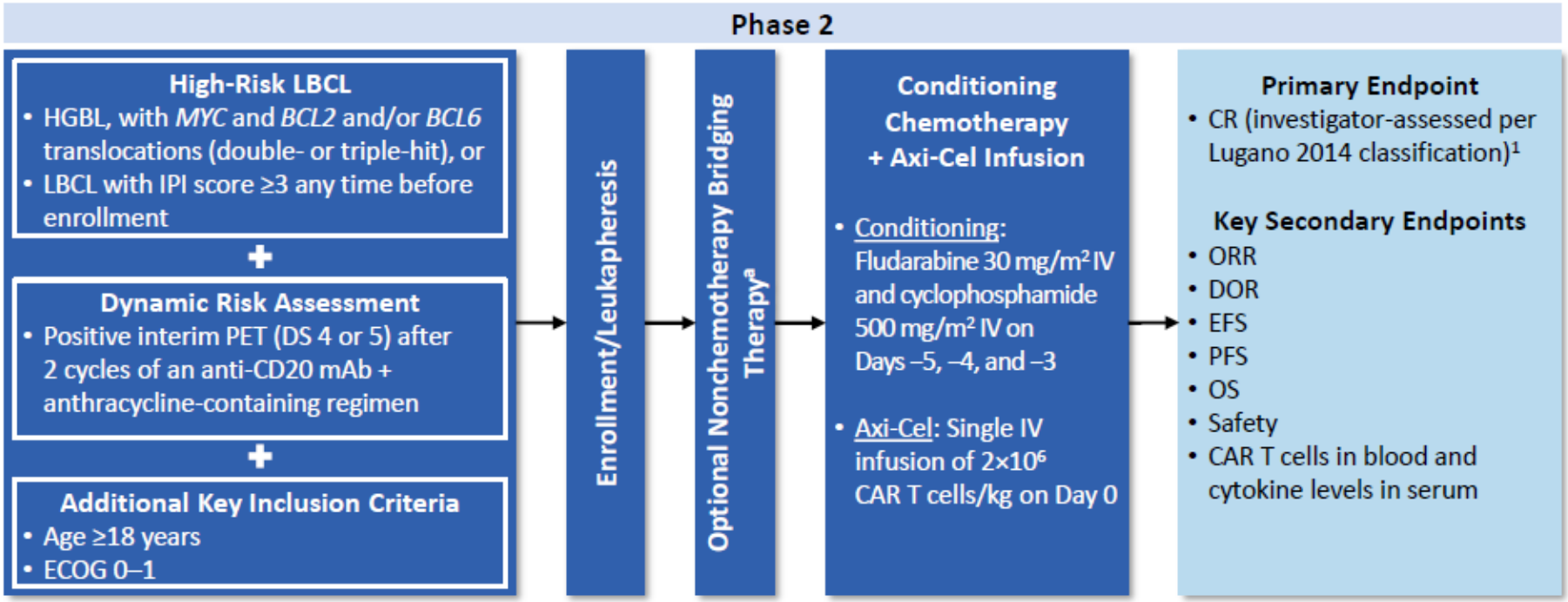
Primary Analysis of ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel as First-Line Therapy in Patients With High-Risk Large B-Cell Lymphoma

Sattva S. Neelapu, MD[1]; Michael Dickinson, MBBS, D Med Sci, FRACP, FRCPA[2]; Javier L. Munoz, MD, MS, MBA, FACP[3]; Matthew L. Ulrickson, MD[3]; Catherine Thieblemont, MD, PhD[4]; Olalekan O. Oluwole, MD, MBBS, MPH[5]; Alex F. Herrera, MD[6]; Chaitra S. Ujjani, MD[7]; Yi Lin, MD, PhD[8]; Peter A. Riedell, MD[9]; Natasha Kekre, MD, MPH, FRCPC[10]; Sven de Vos, MD, PhD[11]; Christine Lui, MS[12]; Francesca Milletti, PhD[12]; Jinghui Dong, PhD[12]; Hairong Xu, MD, PhD[12]; and Julio C. Chavez, MD[13]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Peter MacCallum Cancer Centre, Royal Melbourne Hospital and the University of Melbourne, Melbourne, Victoria, Australia; [3]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [4]Hôpital Saint Louis, Paris, France; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [6]City of Hope National Medical Center, Duarte, CA, USA; [7]Seattle Cancer Care Alliance, Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]University of Chicago Medicine, Chicago, IL, USA; [10]The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; [11]David Geffen School of Medicine at UCLA, Santa Monica, CA, USA; [12]Kite, a Gilead Company, Santa Monica, CA, USA; and [13]Moffitt Cancer Center, Tampa, FL, USA

ZUMA-12 Study Design



[a] Administered after leukapheresis and completed prior to initiating conditioning chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

Neelapu et al ASH 2021 Abstract 739

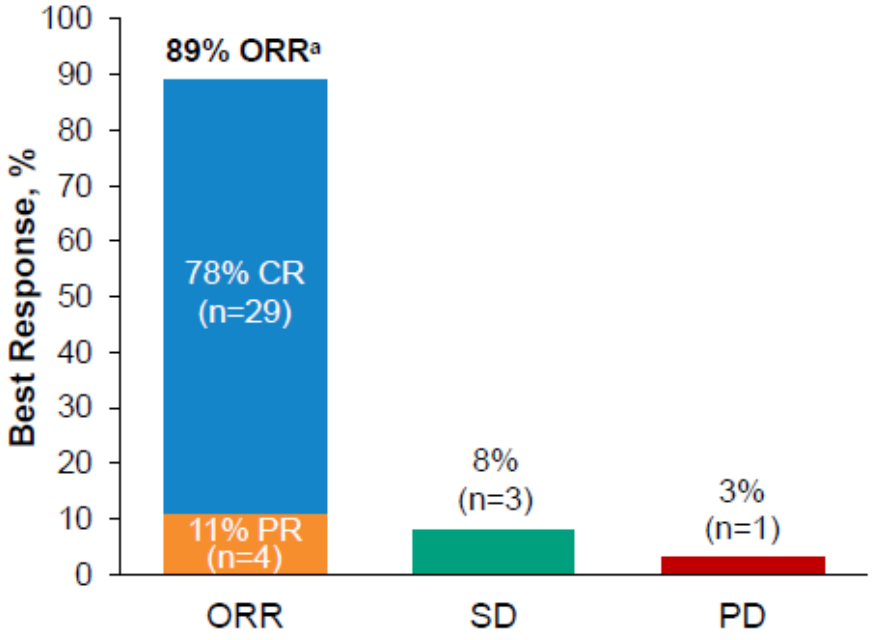
Baseline Patient Characteristics

Characteristic	All Treated (N=40)
Median age (range), years	61 (23–86)
≥65 years, n (%)	15 (38)
Male, n (%)	27 (68)
Disease stage III/IV, n (%)	38 (95)
ECOG 1, n (%)	25 (63)
1 Prior line of systemic therapy (2 cycles), n (%)	40 (100)
Best response of PR/SD to prior therapy[a]	23 (58)
Best response of PD to prior therapy[a]	16 (40)
Double- or triple-hit as determined by FISH per investigator, n (%)[b]	16 (40)
Double- or triple-hit as determined by FISH per central laboratory, n (%)[b]	10 (25)
IPI score ≥3, n (%)[c]	31 (78)
Deauville score 4, n (%)	19 (48)
Deauville score 5, n (%)	21 (53)

[a] One patient was not estimable for response to prior therapy. [b] Of 6 patients reported to be double- or triple-hit per investigator, 3 remained inconclusive, 1 was determined not to be double- or triple-hit, and 2 were not tested by the central laboratory. A total of 8 treated patients did not have central laboratory testing. [c] IPI score for eligibility was at the time of diagnosis or any time between diagnosis and enrollment.
ECOG, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; IPI, International Prognostic Index; PD, progressive disease; PR, partial response; SD, stable disease.

Neelapu et al ASH 2021 Abstract 739

ORR Was 89% (95% CI, 75–97) and CR Rate Was 78% (95% CI, 62–90) Among Efficacy-Evaluable Patients



	Efficacy Evaluable N=37[b]
Median follow-up (range), months	15.9 (6.0–26.7)
Patients with ≥12-month follow-up, n (%)	23 (62)
Patients with ongoing response as of data cutoff, n (%)	27 (73)
Median time to response (range), months	
Initial objective response	1.0 (0.9–6.8)
Initial CR	1.0 (0.9–6.8)
Patients converted from PR/SD to CR, n (%)[c]	7 (19)
PR to CR	6 (16)
SD to CR	1 (3)

- Among all treated patients (N=40), ORR was 90% (95% CI, 76–97); CR rate was 80% (95% CI, 64–91)

[a] Response assessments are based on best overall response. [b] Includes all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10^6 CAR T cells/kg. [c] All 7 patients converted to a CR by Month 6 postinfusion.
CR, complete response; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Neelapu et al ASH 2021 Abstract 739

Updates

- Large B-Cell Lymphoma
  - CAR T Cell as Second-Line Therapy (ZUMA-7, TRANSFORM, BELINDA)
  - CAR T for Primary Refractory DLBCL (ZUMA-12)
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Updated Analysis

- The updated efficacy analysis occurred when ≥80 treated patients with FL had ≥24 months of follow-up, per protocol[a]
- Efficacy analyses are reported in the 110 efficacy-eligible patients (86 with FL; 24 with MZL)[a]
  - The median follow-up for patients with FL was 30.9 months (range, 24.7–44.3)
  - The median follow-up for patients with MZL was 23.8 months (range, 7.4–39.4)
- Safety data are reported for all 149 patients treated with axi-cel (124 with FL; 25 with MZL)
- Data cutoff date: March 31, 2021

[a] Efficacy-eligible patients (inferential analysis set) included ≥80 treated patients with FL who had ≥24 months of follow-up after axi-cel infusion and treated patients with MZL who had ≥4 weeks of follow-up after axi-cel infusion as of the data cutoff date.
Axi-cel, axicabtagene ciloleucel; FL, follicular lymphoma; MZL, marginal zone lymphoma.

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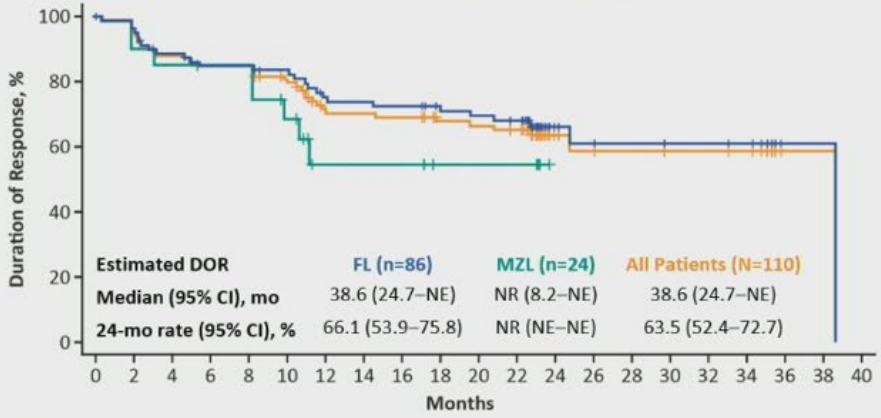
DOR and TTNT

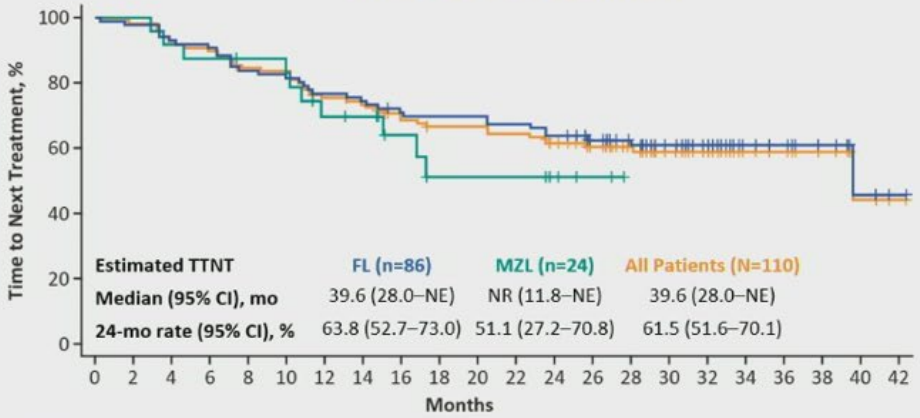
Duration of Response



No. at Risk

FL	81	77	69	64	64	61	54	53	52	48	47	45	14	12	11	10	10	9	1	1	0
MZL	20	18	17	16	16	12	6	6	6	4	4	4	0								
All Patients	101	95	86	80	80	73	60	59	58	52	51	49	14	12	11	10	10	9	1	1	0

Time to Next Treatment[a]



No. at Risk

FL	86	84	80	78	72	70	66	64	60	59	59	57	54	47	41	31	24	14	12	8	3	1
MZL	24	24	22	21	20	19	15	14	10	7	7	7	5	3	0							
All Patients	110	108	102	99	92	89	81	78	70	66	66	64	59	50	41	31	24	14	12	8	3	1

- At data cutoff, 57% of efficacy-eligible patients with FL (49 of 86) and 50% of patients with MZL (12 of 24) had ongoing responses
  - Of patients who achieved a CR, 68% of patients with FL (46 of 68) and 73% of patients with MZL (11 of 15) had ongoing responses

[a] A total of 28 efficacy-eligible patients received subsequent treatment, including 18 with new anti-cancer therapy and 10 with axi-cel retreatment. No patients received subsequent SCT.
Axi-cel, axicabtagene ciloleucel; CR, complete response; DOR, duration of response; FL, follicular lymphoma; MZL, marginal zone lymphoma; NE, not estimable; NR, not reached, SCT, stem-cell transplantation; TTNT, time to next treatment.

Neelapu et al ASH 2021 Abstract 93

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Updated Results From CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma

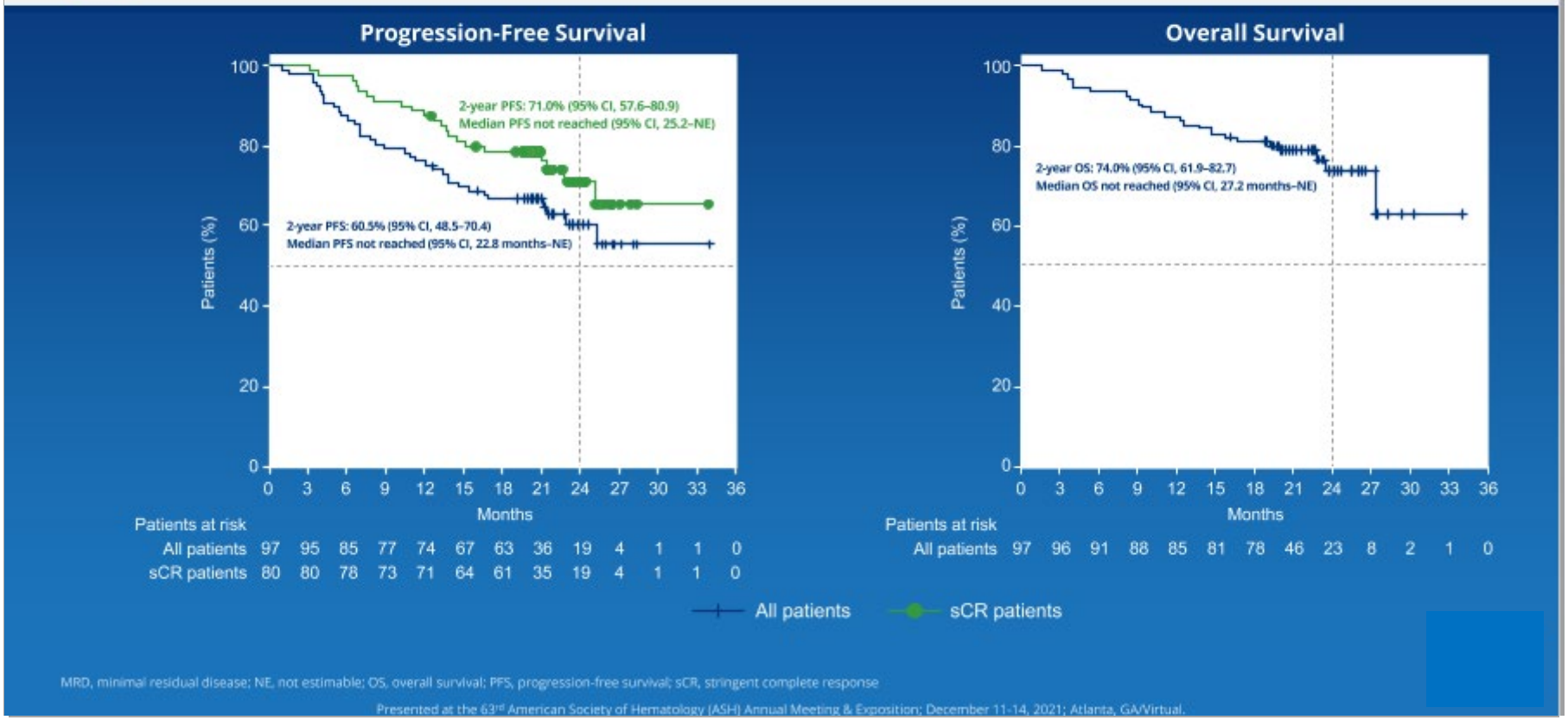
Thomas Martin[1*], Saad Z Usmani[2], Jesus G Berdeja[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], Parameswaran Hari[7], David Avigan[8], Abhinav Deol[9], Myo Htut[10], Alexander Lesokhin[11], Nikhil C Munshi[12], Elizabeth O'Donnell[13], A Keith Stewart[14], Jordan M Schecter[15], Jenna D Goldberg[15], Carolyn C Jackson[15], Tzu-Min Yeh[15], Arnob Banerjee[16], Alicia Allred[16], Enrique Zudaire[16], William Deraedt[17], Deepu Madduri[15], Yunsi Olyslager[17], Changwei Zhou[18], Lida Pacaud[18], Yi Lin[19], Sundar Jagannath[20]

[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]Levine Cancer Institute, Charlotte, NC, USA; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]University of Chicago, Chicago, IL, USA; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [9]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [10]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [13]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [14]University Health Network and the Princess Margaret Cancer Centre, Toronto, ON, Canada; [15]Janssen R&D, Raritan, NJ, USA; [16]Janssen R&D, Spring House, PA, USA; [17]Janssen R&D, Beerse, Belgium; [18]Legend Biotech USA, Piscataway, NJ, USA; [19]Mayo Clinic, Rochester, MN, USA; [20]Mount Sinai Medical Center, New York, NY, USA

*Presenting author.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

CARTITUDE-1: Progression-Free Survival and Overall Survival

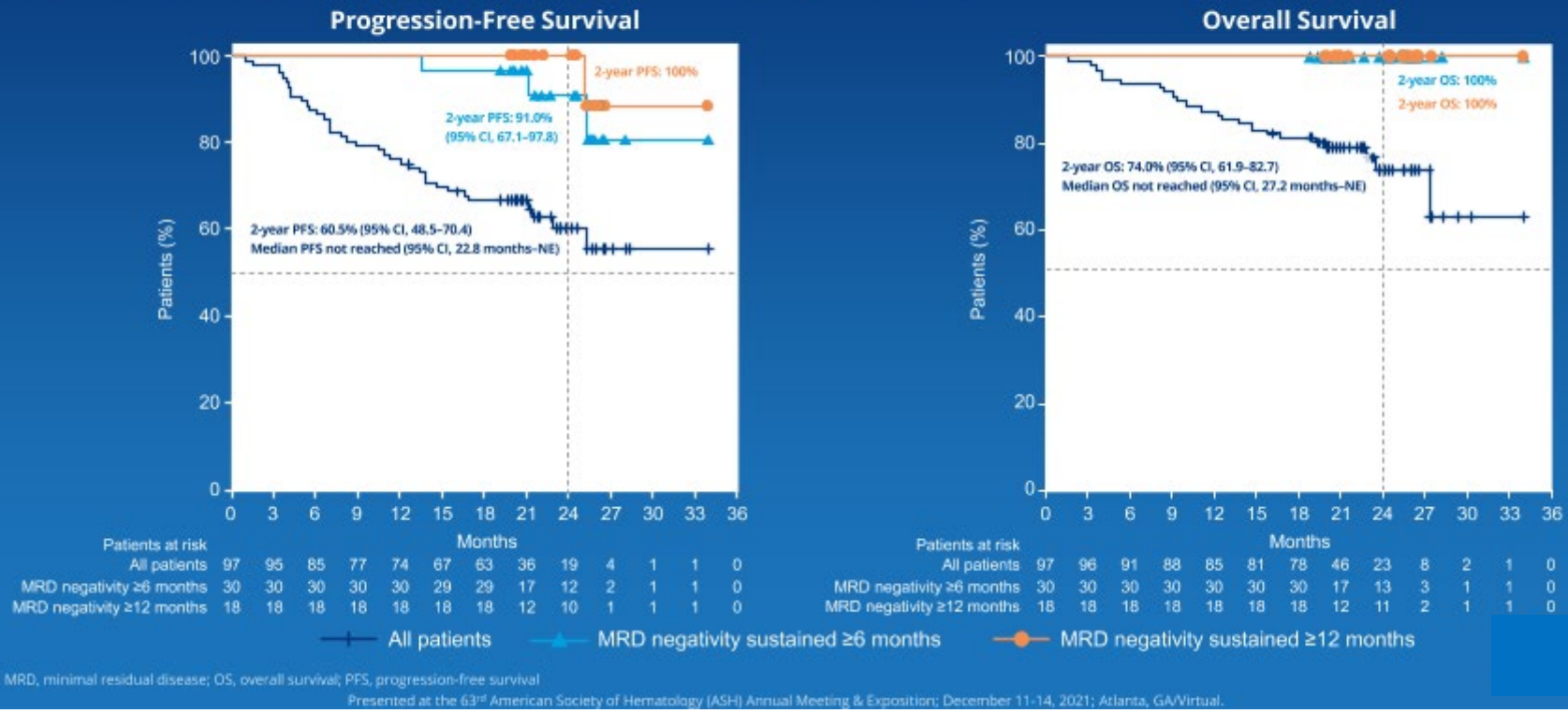


MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

CARTITUDE-1: Progression-Free Survival and Overall Survival by MRD Negativity (10^{-5}) sustained for ≥ 6 and 12 months

- Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})



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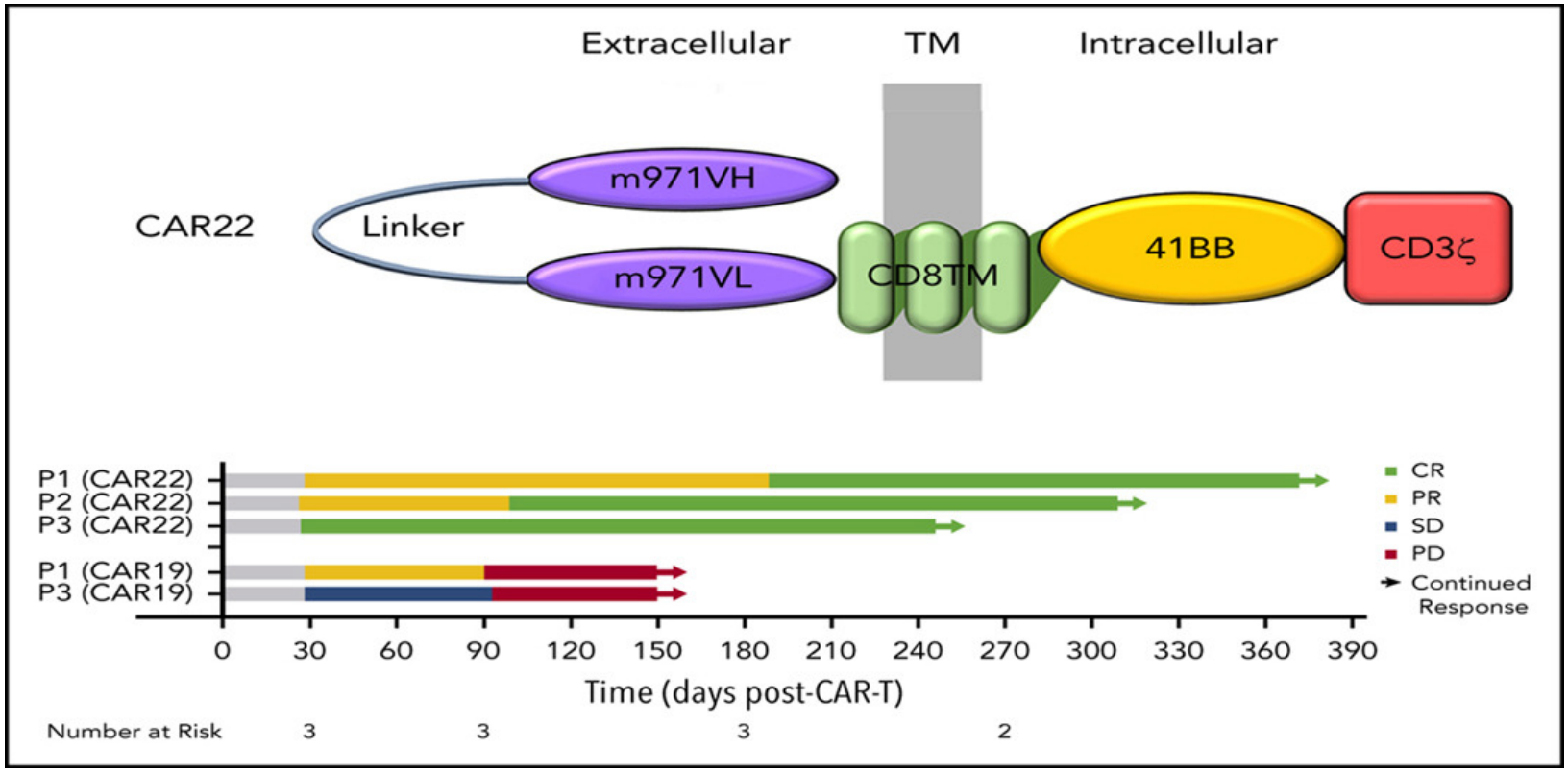
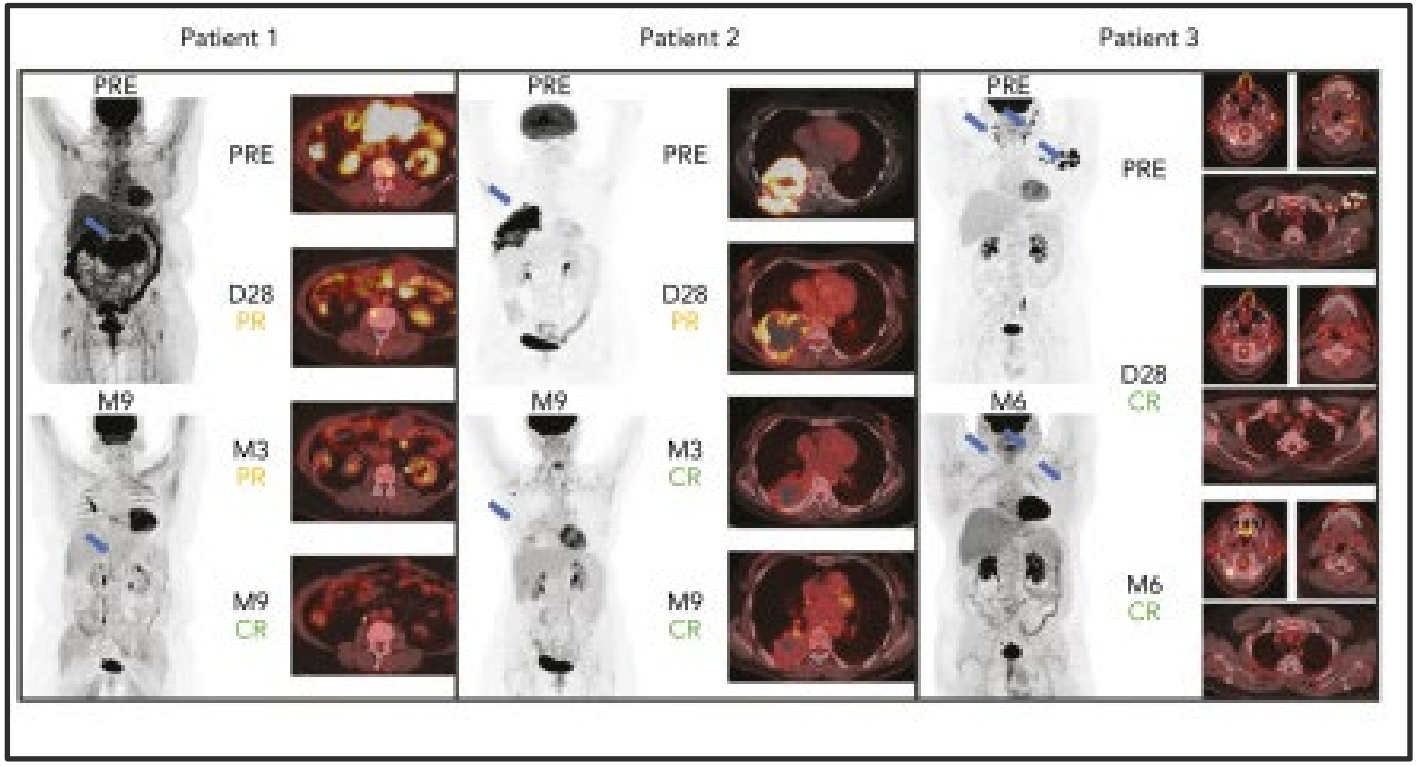
CD22-directed CAR T-cell therapy induces complete remissions in CD19-directed CAR-refractory large B-cell lymphoma



Baird, et al. *Blood.* 2021;137(17):2321-2325.

CD22-directed CAR T-cell therapy induces complete remissions in CD19-directed CAR-refractory large B-cell lymphoma

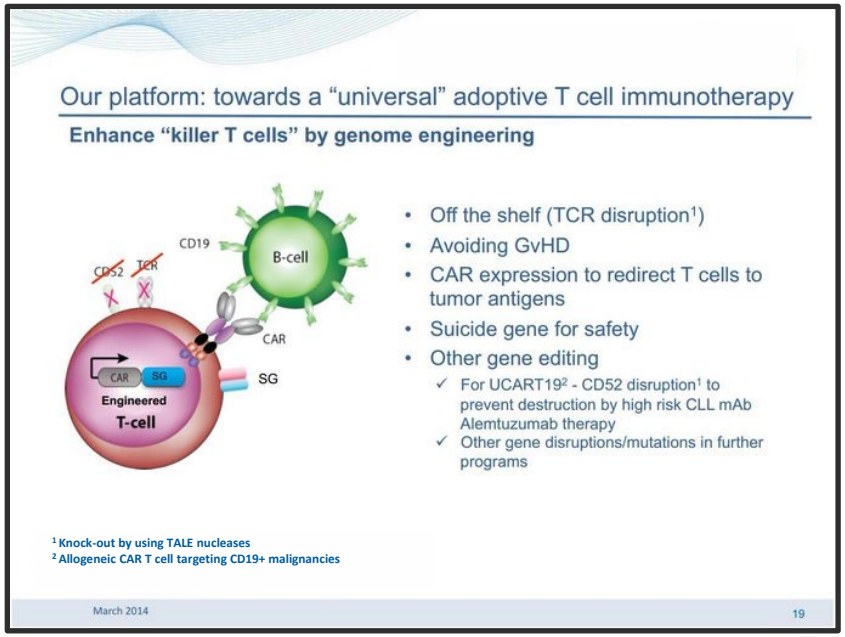


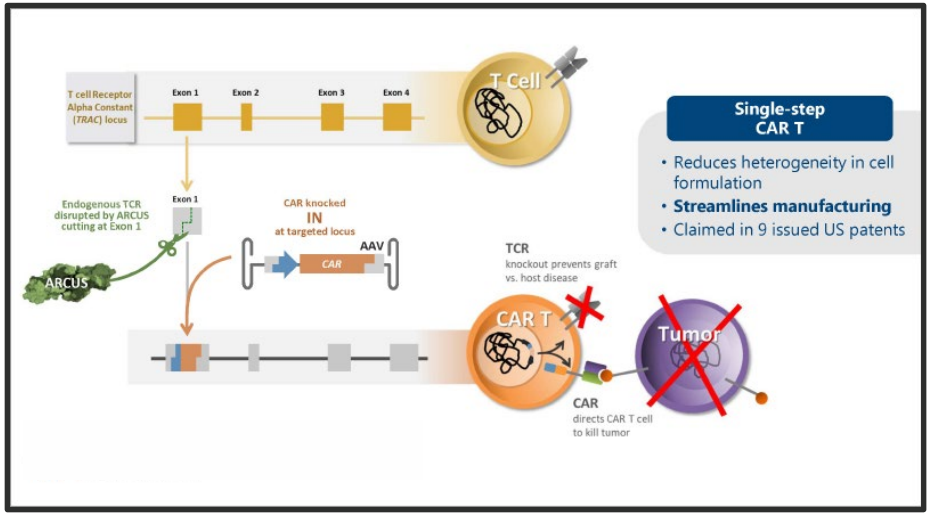
Baird, et al. *Blood.* 2021;137(17):2321-2325.

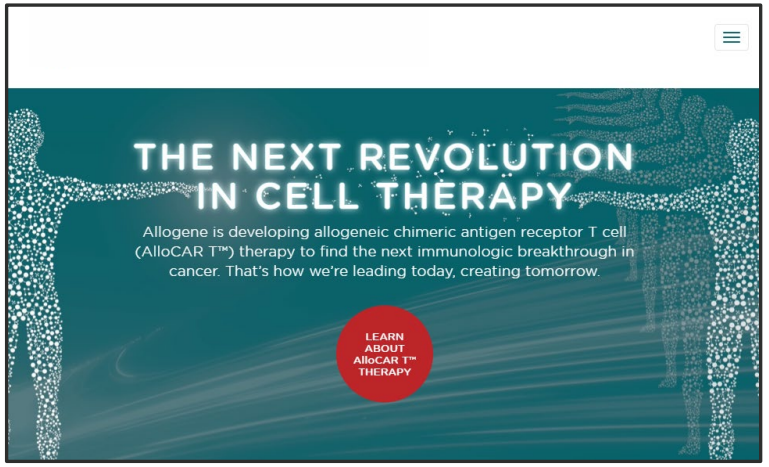
Updates

- Large B-Cell Lymphoma
  - CAR T Cell as Second-Line Therapy (ZUMA-7, TRANSFORM, BELINDA)
  - CAR T for Primary Refractory DLBCL (ZUMA-12)
- Follicular Lymphoma (ZUMA-5)
- Myeloma
  - Cilta-cel (CARTITUDE)
- New CAR T-Cell Products, Approaches, Indications
  - Novel Targets
  - AlloCAR T Therapy
  - iPSC-Derived NK CAR T Cells
  - AML MICA/MICB
  - Myeloma - Gamma Secretase Inhibitor

Allogeneic CAR T-Cell Therapy

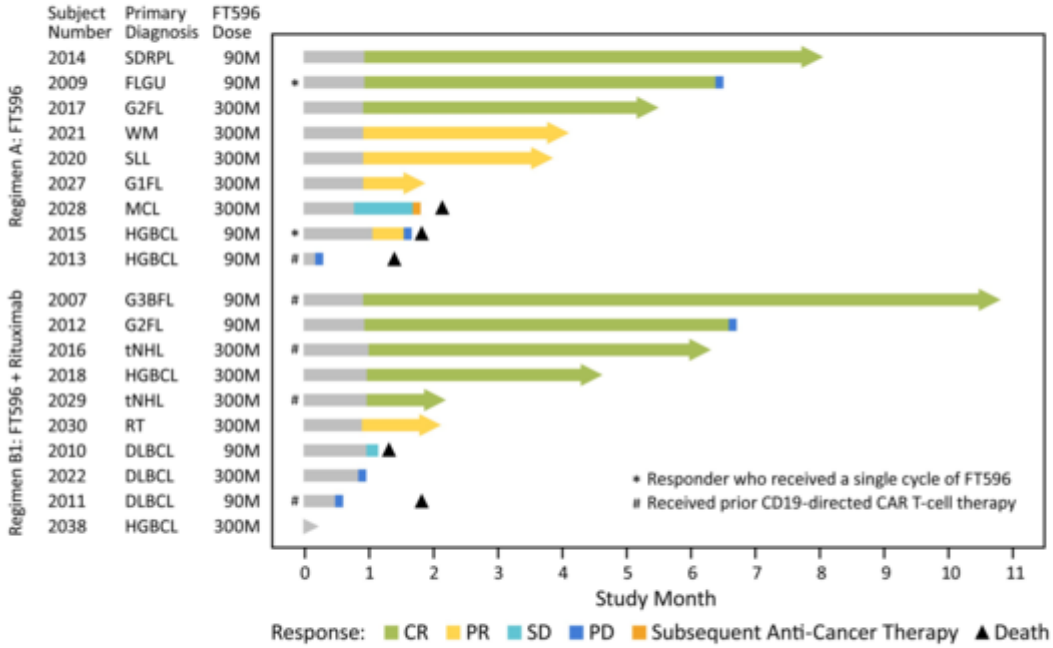






FT596-101: Patient Status and Time on Study

≥90M FT596 Cells



- Median study follow up time for patients treated at ≥90M FT596 cells is 4.2 months
- 10 of 13 responders remain in response at data cutoff between 1.9 and 10.8 months from initiation of treatment

CAR = Chimeric antigen receptor; CR = Complete response; DLBCL = Diffuse large B-cell lymphoma; FLGU = Follicular Lymphoma Grade Unknown; G2FL= Grade 2 follicular lymphoma; G3BFL = Grade 3B follicular lymphoma; HGBCL = High-grade B-cell lymphoma; M = Million; MCL = Mantle cell lymphoma; PD = Progressive disease; PR = Partial response; RT = Richter transformation; SD = Stable disease; SDRPL = Splenic diffuse red pulp small B-cell lymphoma; SLL = Small lymphocytic lymphoma; tNHL = Transformed indolent lymphoma; WM = Waldenstrom macroglobulinemia

Data cutoff date: 11 October 2021

Right arrow indicates subject is still in follow-up without documented disease progression or anti-cancer therapy at time of data cutoff
Patient 2038 pending response assessment; not included in efficacy-evaluable population

Conclusions

- CAR T (Axi-cel, Liso-cel) is established as second-line therapy for DLBCL with early disease progression (<12 months) **ZUMA-7, TRANSFORM, BELINDA**
- CAR T shows encouraging results in primary refractory lymphoma **ZUMA-12**
- Mature follow-up confirms a high proportion of durable remissions in FL, MZL. **ZUMA-5**
- Myeloma
  - Encouraging response rates and duration of response in heavily pretreated patients
- Many novel CAR T-cell innovations
  - Targets
  - Products
  - Indications
  - Combinations