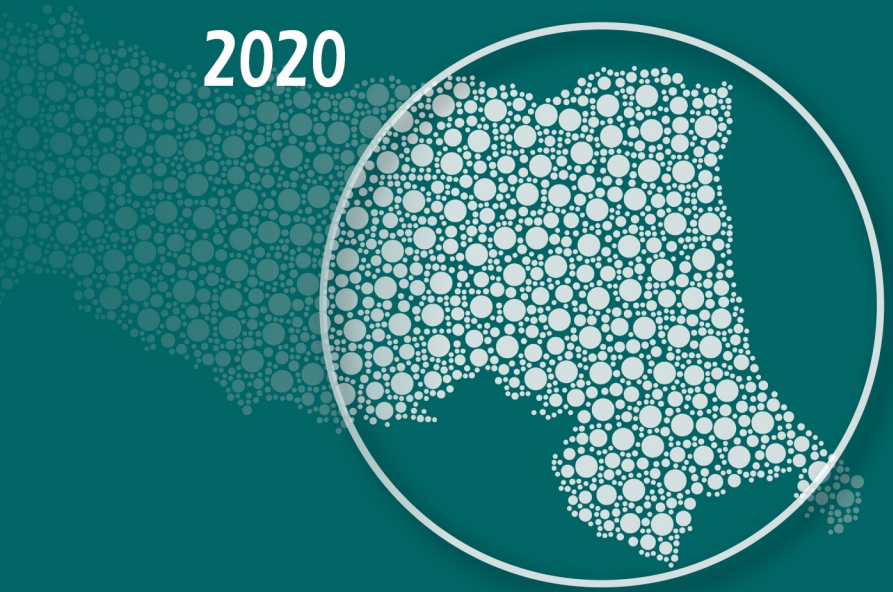


Progetto
Ematologia
Romagna

I risultati ottenuti

Cinzia Pellegrini

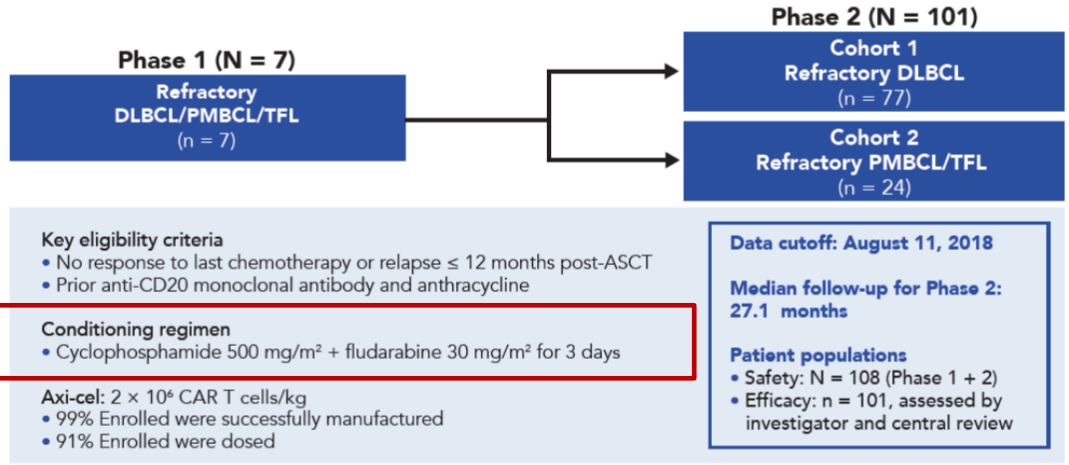
Relatore: Cinzia Pellegrini

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Consulenza ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazione ad Advisory Board (NIENTE DA DICHIARARE)
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario (NIENTE DA DICHIARARE)

AXI-CEL, ZUMA-1 Study

ZUMA-1 study design



Characteristic	Phase 1 and 2 N = 108
Median (range) age, y	58 (23 – 76)
≥ 65 y, n (%)	25%
Disease stage III/IV, n (%)	83%
IPI score 3-4, n (%)	44%
≥ 3 prior therapies, n (%)	70%
Chemorefractory (no response to prior therapy or relapse < 1 year from ASCT)	100%
Relapse post-ASCT, n (%)	23%

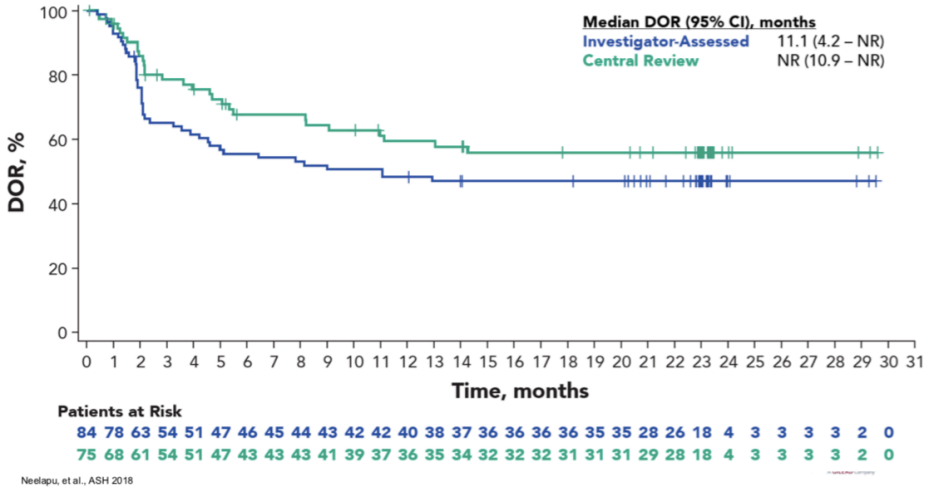
Neelapu S.S, ASH 2018

Objective Responce and DOR (ZUMA-1)

	Investigator-Assessed (n = 101)		Central Review (n = 101)	
	ORR	CR	ORR	CR
Best objective response, %	83	58	74	54
Ongoing, %[a]	39	37	36	35

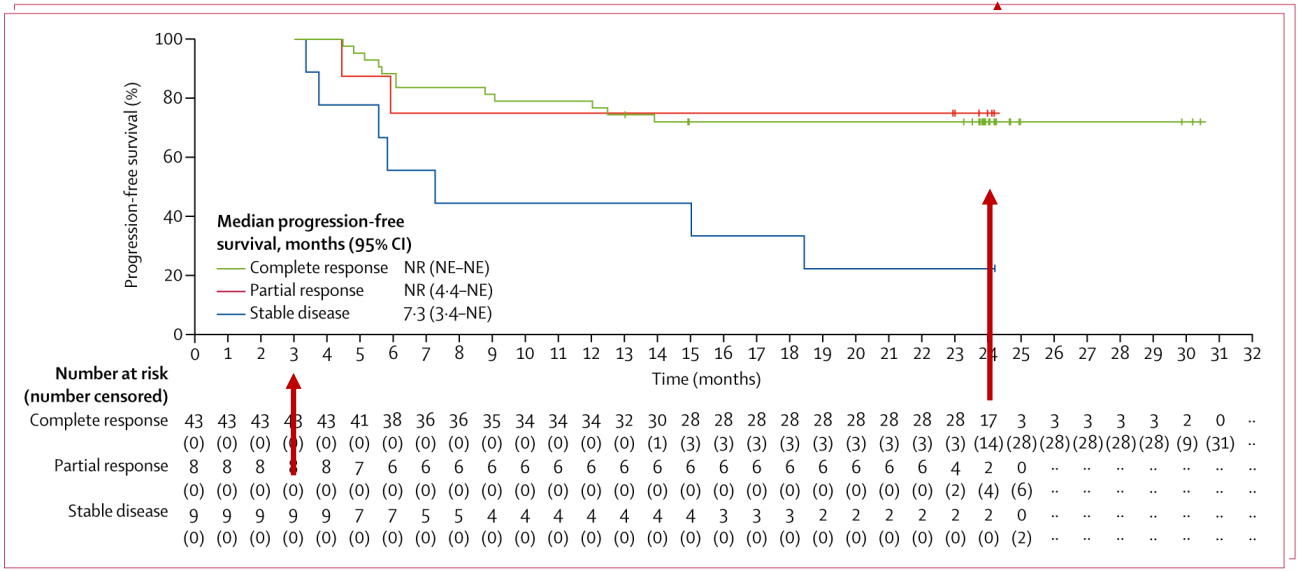
[a]Three patients with ongoing response per investigator review were not ongoing responders per central review. Two of these patients underwent SCT prior to documented progression, which was considered a censor event per central review but not per investigator assessment. The third patient was deemed to have PD per central review after 10.9 months but was assessed to be in ongoing response at 23.4 mo per investigator.
CR, complete response; ORR, objective response rate; PD, progressive disease; SCT, stem cell transplantation.

- 93% of patients with ongoing response at 12 months remained in response at 24 months
- 81% concordance of ORR between investigator assessment and central review
- 91% ORR and 70% CR rate for the 33 Phase 2 patients with DE/HGBCL
  - 48% in ongoing response (all ongoing CR)
- Only 5% (2/39) ongoing responders underwent allogeneic stem cell transplant, and none received autologous stem cell transplant



Neelapu, et al., ASH 2018

CR or PR at 3 Months and Long Term Response

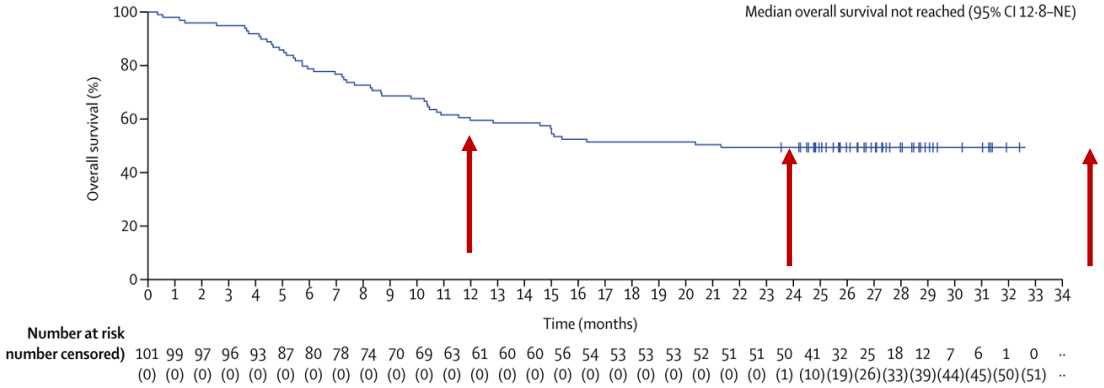


In a post-hoc analysis, the estimated proportion of patients with PFS at 24 months

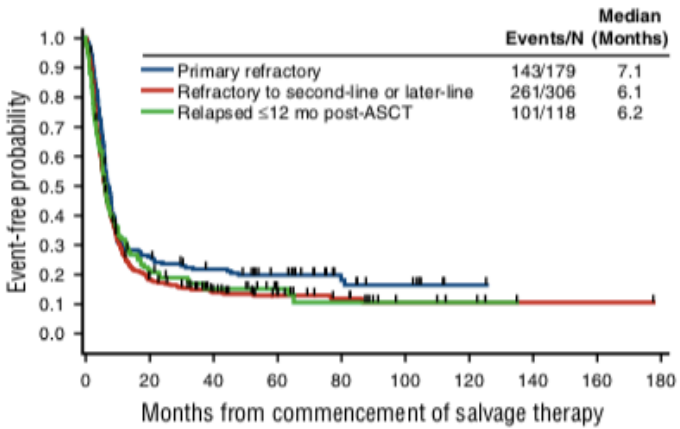
72% among those in CR at 3 months
75% among those with PR at 3 months
22.2% among those with SD at 3 months

Locke F. et al Lancet Oncology 2019

Overall Survival (ZUMA-1 vs SCHOLAR-1)



SCHOLAR-1 study - OS



Zuma -1: Axi-cell:

60% of patients alive at 1 years

51% of patients alive at 2 years

47% of patients alive at 3 years

Crump M. et al; Blood 2017

Locke F. et al Lancet Oncology 2019/ Neelapu SS, et al. ASH 2019 Abstract 203 oral

Standard-of-Care Axicabtagene Ciloleucel for Relapsed or Refractory Large B-Cell Lymphoma: Results From the US Lymphoma CAR T Consortium

Loretta J. Nastoupil, MD[1]; Michael D. Jain, MD, PhD[2]; Lei Feng, MD[1]; Jay Y. Spiegel, MD[3]; Armin Ghobadi, MD[4]; Yi Lin, MD, PhD[5]; Saurabh Dahiya, MD[6]; Matthew Lunning, DO[7]; Lazaros Lekakis, MD[8]; Patrick Reagan, MD[9]; Olalekan Oluwole, MBBS[10]; Joseph McGuirk, DO[11]; Abhinav Deol, MD[12]; Alison R. Sehgal, MD[13]; Andre Goy, MD[14]; Brian T. Hill, MD, PhD[15]; Khoan Vu, MD[16]; Charalambos Andreadis, MD, MSCE[16]; Javier Munoz, MD, MS[17]; Jason Westin, MD[1]; Julio C. Chavez, MD, MS[2]; Amanda Cashen, MD[4]; N. Nora Bennani, MD[5]; Aaron P. Rapoport, MD[6]; Julie M. Vose, MD[7]; David B. Miklos, MD, PhD[3]; Sattva S. Neelapu, MD[1]; and Frederick L. Locke, MD[2]

CONTEXT

Key Objective

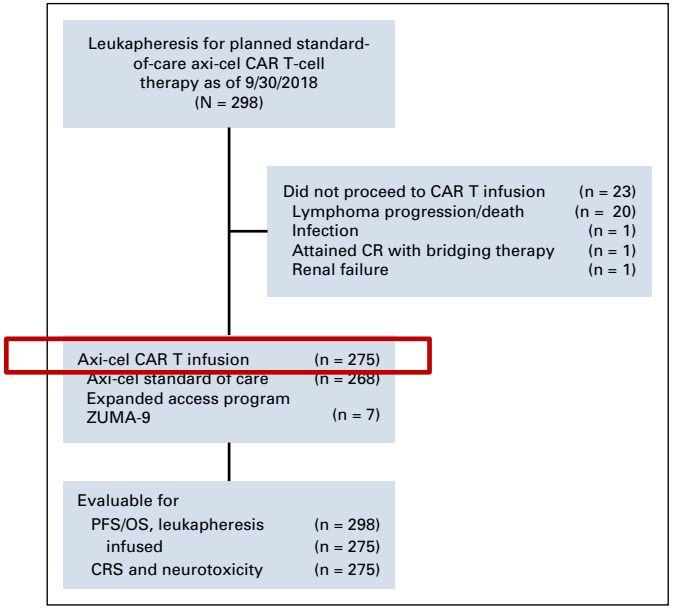
Seventeen US centers set out to delineate the characteristics and outcomes of 298 patients apheresed with intention to be treated with commercially available axicabtagene ciloleucel, an autologous anti-CD19 CAR T-cell.

Knowledge Generated

Practice patterns varied from the registrational ZUMA-1 trial. 43% of patients had comorbidities or characteristics that would have deemed them ineligible. Despite this, safety and efficacy outcomes were comparable to ZUMA-1. We identified patient and disease characteristics associated with outcomes.

Relevance

Our findings suggest favorable outcomes reported in prospective trials with axicabtagene ciloleucel can be achieved across multiple centers in the United States using commercial product as a standard of care.



Nastoupil L.J. et al. JCO 2020

Baseline Characteristics

Characteristic	No. (%)
No. of patients	298
Age, years	
< 60	144 (48.3)
≥ 60	154 (51.7)
Median (range)	60 (21-83)
Sex (male)	192 (64.0)
ECOG PS	
0	76 (25.5)
1	164 (55.0)
2	46 (15.4)
3	11 (3.7)
4	1 (< 1.0)
Disease stage	
I or II	52 (17.6)
III or IV	244 (82.4)
International Prognostic Index score[a]	
0-2	136 (45.6)
3-5	162 (54.4)
Disease type	
DLBCL	203 (68.1)
PMBCL	19 (6.4)
TFL	76 (25.5)
GCB-like[b]	158 (59.8)
Non-GCB[b]	106 (40.1)
Double/triple-hit[c]	64 (22.8)
Double expressor[c]	98 (37.4)
CD19 status[d]	
Positive by flow cytometry	137 (92.6)
Positive by IHC	57 (87.7)
LDH > ULN at leukapheresis[e]	157 (60.6)
LDH > ULN at conditioning[e] chemotherapy	155 (59.4)
Bulky disease (≥ 10 cm)	68 (22.7)
Prior therapies	
≥ 3 prior lines of therapy	222 (74.5)
Median No. of prior lines (range)	3 (2-11)
History of primary refractory disease	101 (33.9)
Refractory to most recent therapy	125 (42.0)
Relapsed	72 (24.0)
Prior ASCT	98 (32.9)
Prior allogeneic SCT	7 (2.4)
Prior CD-19–directed therapy[f]	5 (1.7)

Characteristics Differentiating Patients in the Real World from ZUMA-1

Characteristic	No. (%)
1 criterion	76 (58.9)
≥ 2 criteria	53 (41.1)
ECOG PS > 1	58 (19.0)
Platelets < 75,000/μL	34 (11.4)
DVT/PE within 6 months	31 (10.4)
History of CNS disease	21 (7.0)
Renal insufficiency (GFR < 60 mL/min/1.73 m^2)	21 (7.0)
Prior checkpoint inhibitor therapy	17 (5.7)
LVEF < 50%	10 (3.4)
Symptomatic pleural effusion	10 (3.4)
Bilirubin > 1.5 g/dL	7 (2.4)
Prior CD19-directed therapy	5 (1.7)

129 (43%) patients with exclusion criteria

Nastoupil L.J. et al. JCO 2020

Safety of Axi-Cel in the Real World

	SOC Axi-cel N = 275 (mITT)	ZUMA-1[1] N = 108
All Grades of CRS*, N (%)	251 (91.2%)	100 (93%)
Grade ≥ 3 CRS, N (%)	18 (7%)	14 (13%)
Median time to onset of CRS	3 days	2 days
All Grades of NT, N (%)**	189 (68.7%)	70 (65%)
Grade ≥ 3 NT, N (%)	85 (31%)	33 (31%)
Median time to onset of NT	6 days	5 days

* Lee criteria used for grading CRS

** CTCAE or CARTOX criteria used for grading neurotoxicity

[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544
Nastoupil L.J. et al. JCO 2020

Efficacy of Axi-Cel in the Real World

	SOC Axi-cel Evaluable	SOC Axi-Cel	ZUMA-1[1] N=108
Median follow up, months		3.9	15.4
Best ORR at Day 90, N (%)	275	201 (82)	89 (82)
Best CR at Day 90, N (%)		142 (64)	63 (58)

[1]Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544
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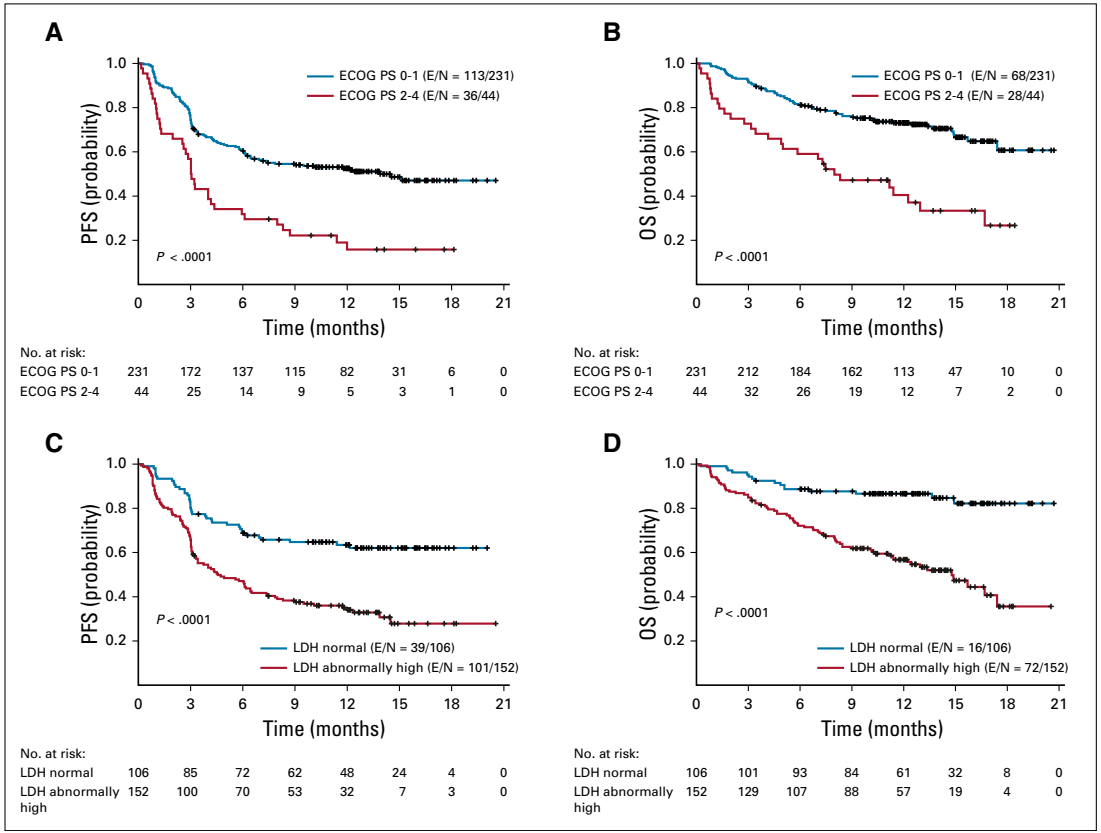
Predictors of response, resistance and toxicity



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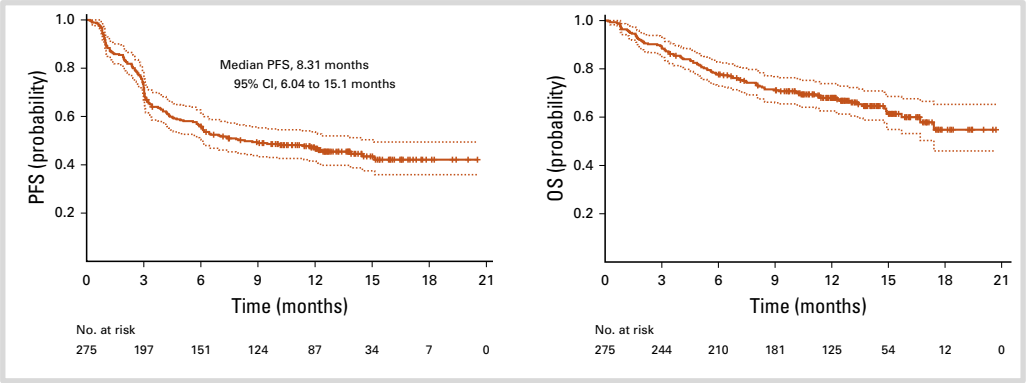
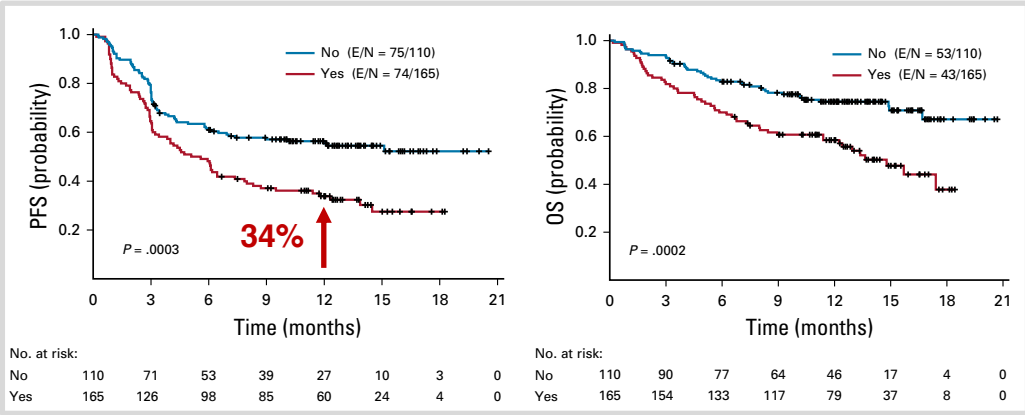
Standard of care Axi-cell: Outcome





Nastoupil L.J. et al. JCO 2020

Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance & Toxicity

Caron A. Jacobson, MD [1], *Bradley Hunter, MD, MPH[1], Philippe Armand, MD, PhD[1], Yusuke Kamihara, MD, PhD[1], Jerome Ritz, MD, PhD[1], Scott J Rodig, MD[2], Kyle Wright, M.D., Ph.D.[2], Mikel Lipschitz, M.S.[2], Robert A. Redd, MS[1], Joseph Maakaron, MD[3], Samantha Jaglowski, MD, MPH[3], Marcela V. Maus, MD, PhD[4], Yi-Bin Chen, MD[4], Jeremy S. Abramson, MD, MMSc[4], Justin Kline, MD[5], Jonathon B. Cohen, MD, MS[6], Stephen D. Smith, MD[7], David G. Maloney, MD, PhD[8], Ajay K. Gopal, MD[8], Matthew J. Frigault, MD[4]* and Utkarsh H. Acharya, DO[7,8]**

[1]*Dana Faber Cancer Institute, Boston, MA,* [2]*Brigham and Women's Hospital, Boston, MA,* [3]*Ohio State University, Columbus, OH,* [4]*Massachusetts General Hospital Cancer Center, Boston, MA,* [5]*University of Chicago, Chicago, IL,* [6]*Emory University, Atlanta, GA,* [7]*Seattle Cancer Care Alliance, University of Washington, Seattle, WA,* [8]*University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

**Contributed equally to this work*

Jacobson C.A. et al ASH 2018, Abstract 627

Univariate Analysis for Response

No correlation with:

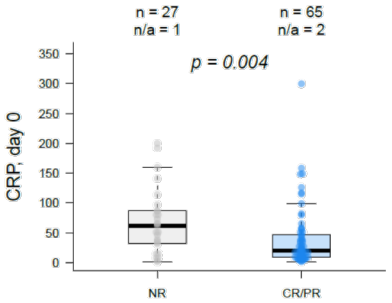
- IPI
- Cell of origin
- Double/triple hit cytogenetics
- Prior lines of therapy
- Bridging therapy
- Eligibility for ZUMA-1
- High grade CRS or NT
- Tociliuzumab or steroid use

Inferior outcomes in patients with:

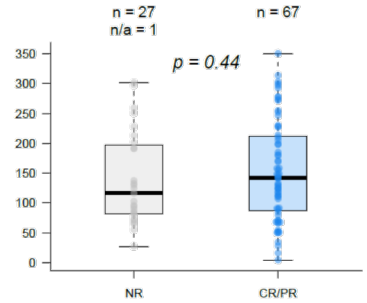
- Poor performance status (ECOG PS 2-4)*
- Increased tumor bulk

* Denotes statistical significance

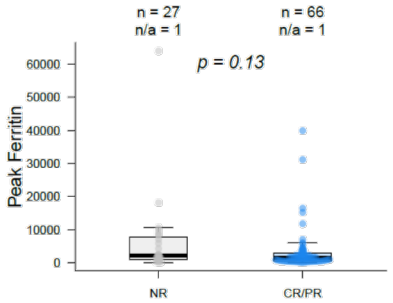
Day 0 CRP



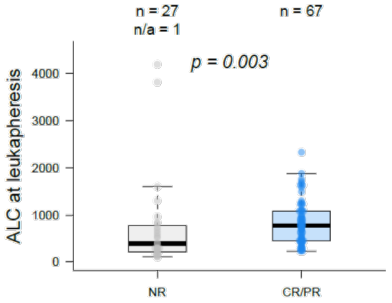
Peak CRP



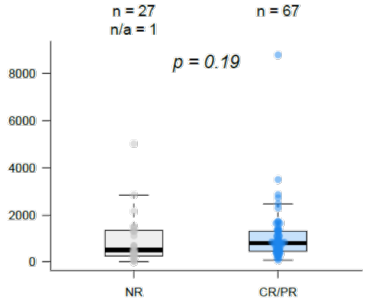
Peak Ferritin



ALC at apheresis



Peak ALC

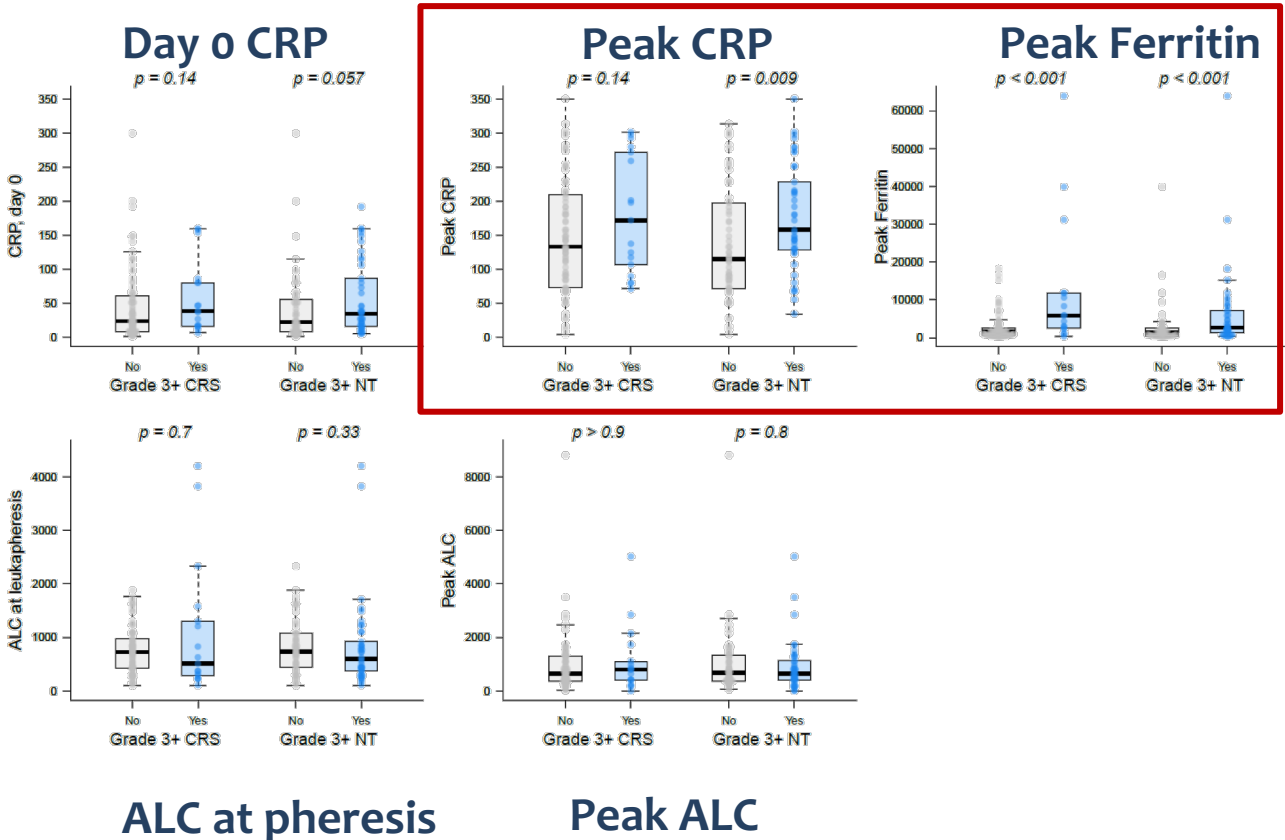


Jacobson C.A. et al ASH 2018, Abstract 627

Univariate Analysis for Toxicity: Grade 3+ CRS and NT

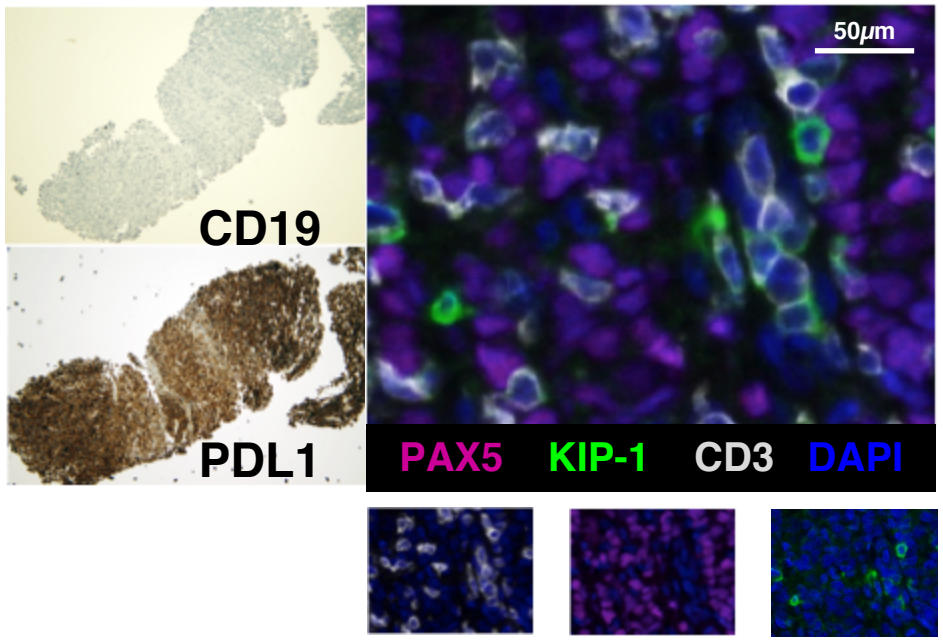
No correlation with:

- PS
- Tumor bulk
- IPI
- Prior lines of therapy
- Bridging therapy
- Eligibility for ZUMA-1

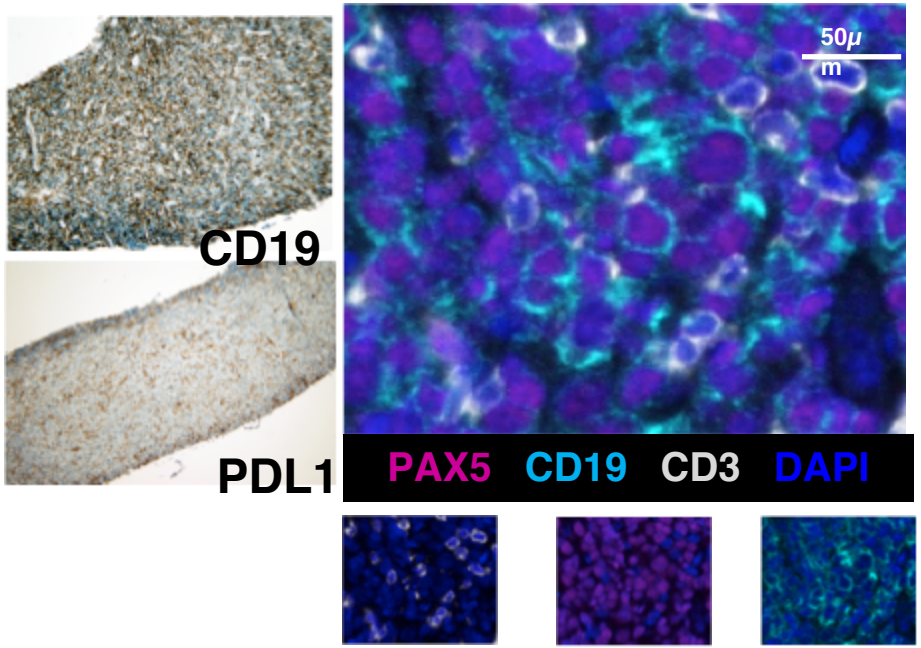


Jacobson C.A. et al ASH 2018, Abstract 627

Time of Progression Biopsies Highlight Different Mechanisms of Resistance



Patient 1, Primary refractory,
Day 37 post-treatment biopsy



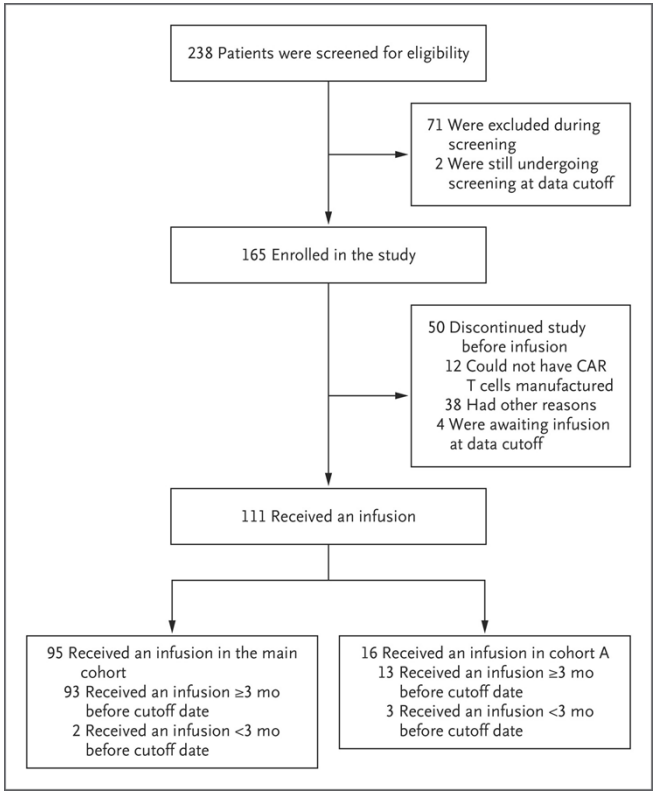
Patient 2, Primary refractory
Day 58 post-treatment biopsy

Courtesy of Mikel Lipschitz, Kyle Wright, and Scott Rodig

Conclusions: Axi-cell avaiable data

- Commercial axi-cel in a real world setting results in similar ORR, DOR, PFS, and OS compared to ZUMA-1, with a comparable toxicity profile
- Predictors of response: low day 0 CRP and high ALC at apheresis
- Associations with toxicity: high peak CRP (NT) and high peak ferritin (NT and CRS)
- Low day 0 CRP and low peak ferritin defined groups with significantly superior survival
- The use of bridging therapy for otherwise ZUMA-1 eligible patients did not appear to improve outcomes or impact high grade toxicity
- Results support the use of axi-cel outside of strict clinical trial criteria, although the outcomes may be slightly inferior
- Characterization of the tumor and peripheral blood immunophenotype highlights potential mechanisms and markers of response and resistance

JULIET STUDY:
Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma



Median time from enrollment to infusion: 54 days
92% of patients received bridging therapy

	Patients (N = 111)
Age, median (range), years	56 (22-76)
≥ 65 years, %	23
ECOG performance status 0/1, %	55/45
Central histology review	
Diffuse large B-cell lymphoma, %	79
Transformed follicular lymphoma, %	19
Double/triple hits in *CMYC/BCL2/BCL6* genes, %	17[a]
Cell of origin[b]	
Germinal/Nongerminal center B-cell type, %	57/41
Number of prior lines of antineoplastic therapy, %	
2/3/4-6	44/31/21
IPI ≥ 2 at study entry, %	72
Refractory/relapsed to last therapy, %	55/45
Prior auto-SCT, %	49
Bridging chemotherapy, n	**102**
Lymphodepleting chemotherapy, n	**103**

[a] *CMYC + BCL2*, n = 10; *CMYC + BCL2 + BCL6*, n = 5; *CMYC + BCL6*, n = 4.
[b] Determined by the Choi algorithm.

Schuster *et al*, N Engl J Med. 2019 Jan 3;380(1):45-56.

JULIET: Primary Endpoint Was Met, ORR 52%

Response Rate, %	Best Overall Response Rate (N = 93)	Response at 3 Months (N = 93)	Response at 6 Months (n = 93)
ORR (CR + PR)	52[a]	38	33
CR	40	32	29
PR	12	5	3

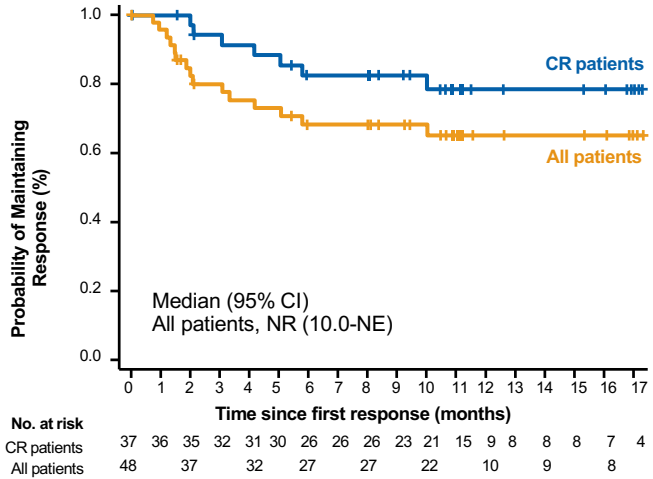
[a] *P* < .0001; (95% CI, 42%-64%). Null hypothesis of ORR ≤ 20%.

- Durability of responses is shown by the stability between 3 and 6 month response rates
- Response at 3 months is indicative of the long term benefit of this treatment
- No differences in outcomes based on lymphodepleting therapy used

CR, complete response;
ORR, overall response rate; PR, partial response.

Schuster *et al*, N Engl J Med. 2019 Jan 3;380(1):45-56.

JULIET: At 14 Months Median Follow-up, Median DOR Not Reached

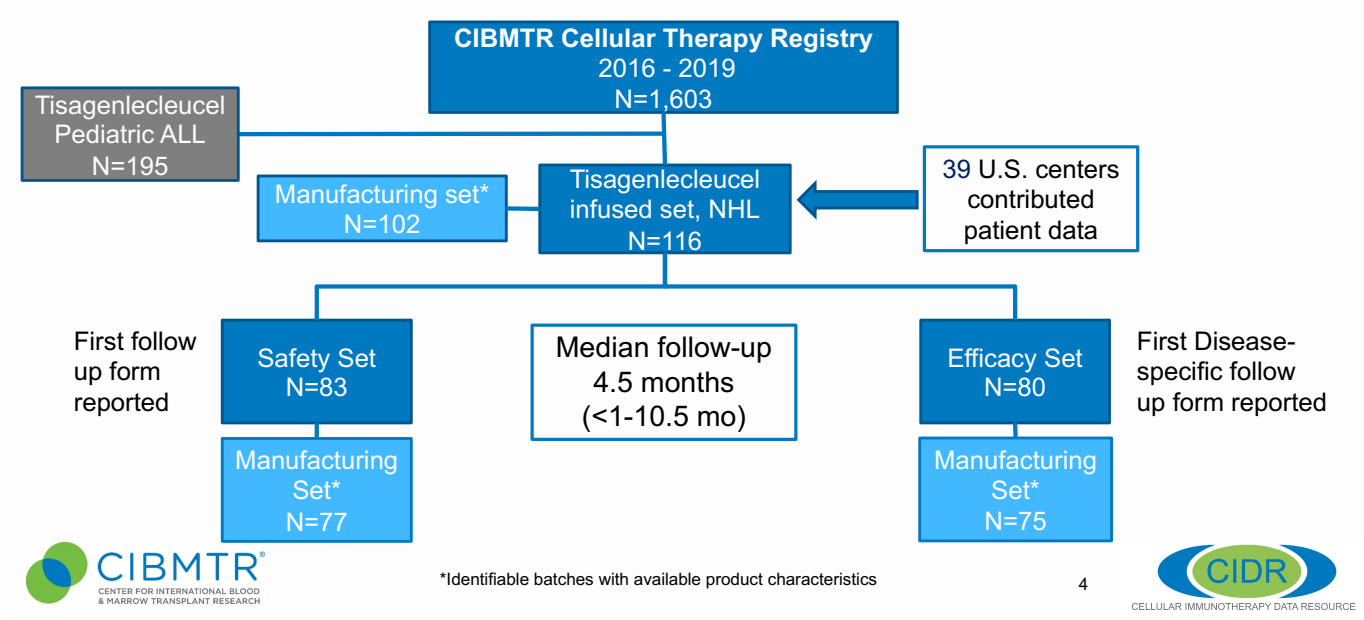


- **Median DOR has not been reached**
- **12-mo relapse-free survival rate**
  - **78.5% (95% CI, 60%-89%) among CR patients**
  - 65% (95% CI, 49%-78%) among all responders
- **54% (13/24) of patients converted from PR to CR**, including 2 patients 9-12 mo after initial response
- Tisagenlecleucel transgene was detected in peripheral blood for up to 2 years in responding patients
- No patients proceeded to transplant while in response

CR, complete response; DOR, duration of response; NE, not evaluable; NR, not reached; ORR, overall response rate; PR, partial response; SCT, stem cell transplant.

Schuster *et al*, N Engl J Med. 2019 Jan 3;380(1):45-56.

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



Jaglowsky S. et al C.A. et al ASH 2019, Abstract 614

Baseline Characteristics

Characteristic	NHL (N=116) n (%)
Median Age (range)	65 (15-89)
Male / Female	70 (60) / 46 (40)
Double/triple hit lymphoma	48 (41)
Transformed lymphoma	31 (27)
Disease status prior to tisagenlecleucel	
Refractory/Relapsed	37 (32) / 71 (61)
Prior autologous / allogeneic HCT	28 (24) / 5 (4)
Time from diagnosis to CAR T therapy (median)	15 months
Time from manufacturing start to infusion (median)	32 days

Jaglowsky S. et al C.A. et al ASH 2019, Abstract 614

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. $\geq$ 3)	4[c]	23[e]
Neurotoxicity (Gr. $\geq$ 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

Jaglowsky S. et al C.A. et al ASH 2019, Abstract 614

Conclusion Tisa-cell Therapy

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

The association between lower cell dose and lower overall response needs to be further studied with a larger number of patients.

The CIBMTR cellular therapy registry provides critical insights about CAR-T therapy

Registry participation is highly encouraged to further advance insights

Jaglowsky S. et al C.A. et al ASH 2019, Abstract 614

Zuma-2 Study: Axi-cell in R/R Mantle-cell Lymphoma

Phase 2

Enrollment/ Leukapheresis	Optional Bridging Therapy[a]	Conditioning Chemotherapy	CAR T Cell Dose	**Follow-Up Period**
R/R MCL	Dexamethasone 20 – 40 mg or equivalent PO or IV daily for 1 – 4 days, or ibrutinib 560 mg PO daily, or acalabrutinib 100 mg PO twice daily	Fludarabine 30 mg/m^2 IV and cyclophosphamide 500 mg/m^2 IV on Days −5, −4, −3	2×10^6 KTE-X19 cells/kg single IV infusion on Day 0	First tumor assessment on Day 28[b]

Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification[1])

Key Secondary Endpoints

- DOR
- PFS
- OS
- AEs
- ORR (Investigator-assessed per revised IWG criteria[2])
- EQ-5D
- Levels of CAR T cells in blood and cytokines in serum

[a] Administered after leukapheresis and completed ≤ 5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging.
[b] Bone marrow biopsy was done at screening and if positive, not done, or indeterminate, a biopsy was needed to confirm CR.
AE, adverse event; CAR, chimeric antigen receptor, DOR, duration of response; EQ-5D, European Quality of Life-5 Dimensions; IRRC, Independent Radiology Review Committee; IWG, International Working Group; MCL, mantle cell lymphoma; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, oral; R/R, relapsed/refractory.
1. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068. 2. Cheson BD, et al. *J Clin Oncol.* 2007;25:579-586.

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Zuma-2 Study: Patient Eligibility

Key Inclusion Criteria

- R/R MCL defined as
  - Disease progression after last regimen or
  - Failure to exhibit a CR or PR to the last regimen
- 1 – 5 Prior therapies that must have included
  - An anthracycline- or bendamustine-containing chemotherapy and
  - Anti-CD20 monoclonal antibody therapy and
  - Ibrutinib or acalabrutinib
- ≥ 1 Measurable lesion
- Age ≥ 18 years
- ECOG of 0 or 1
- Adequate bone marrow, renal, hepatic, pulmonary, and cardiac function
- ALC ≥ 100/µL

Key Exclusion Criteria

- Prior allogeneic SCT
- Prior CD19-targeted therapy
- Prior CAR T cell therapy
- Clinically significant infection
- History of or current CNS involvement by MCL or other CNS disorders

CAR, chimeric antigen receptor; CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; PR, partial response; R/R, relapsed/refractory; SCT, stem-cell transplant.

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Baseline Disease Characteristics

Characteristic	N = 68
Median age (range), years	65 (38 – 79)
≥ 65 years, n (%)	39 (57)
Male, n (%)	57 (84)
Stage IV disease, n (%)	58 (85)
ECOG 0/1, n (%)	100 (100)
Intermediate/high-risk MIPI, n (%)	38 (56)
Ki-67 proliferation index ≥ 50%, n/n (%)[a]	34/49 (69)
TP53 mutation, n/n (%)	6/36 (17)
Bone marrow involvement, n (%)	37 (54)
Extranodal disease, n (%)[b]	38 (56)
MCL morphology, n (%)[c]	
Classical	40 (59)
Pleomorphic	4 (6)
Blastoid	17 (25)

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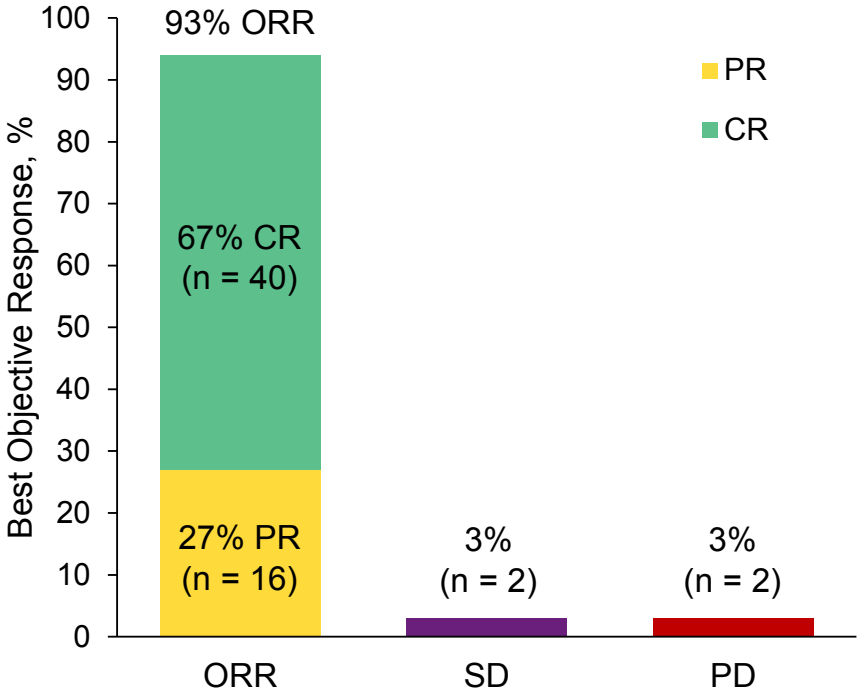
ORR by IRRC Assessment Was 93% (95% CI, 84 – 98) and CR Rate Was 67% (95% CI, 53 – 78)



	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.

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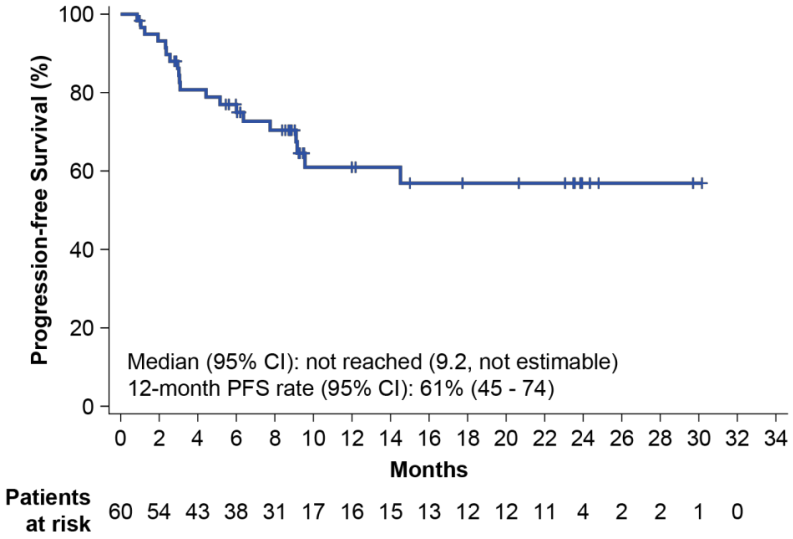
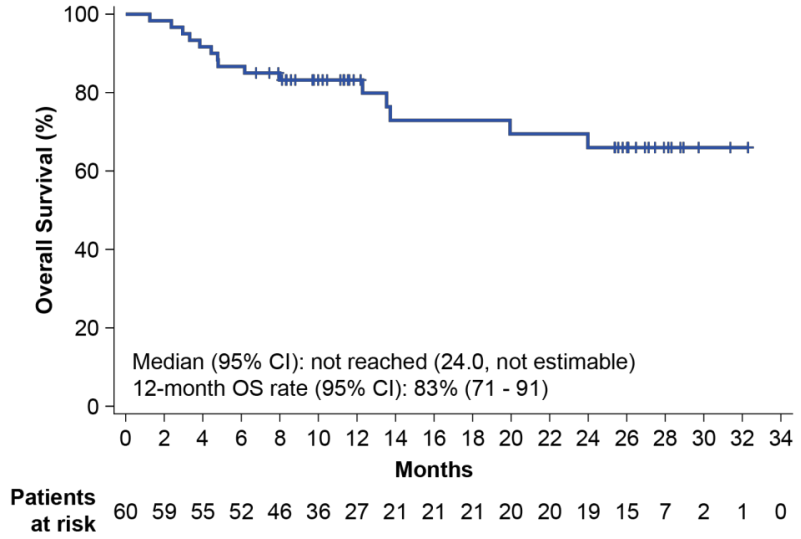
Progression-Free Survival and Overall Survival

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





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

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Conclusions

- KTE-X19, in a single infusion, demonstrates high rates of durable responses in R/R MCL
  - The 93% ORR, which includes a 67% CR rate, is the highest reported rate of disease response in patients with prior BTKi failure
  - Of the initial 28 patients treated, 43% are in remission after ≥ 2 years of follow-up
- The safety profile is consistent with that reported in prior studies of anti-CD19 CAR T cell therapies in aggressive NHL
  - No deaths due to CRS or neurologic events; most symptoms occurred early and were generally reversible
- The efficacy, reliable and rapid manufacturing, and manageable toxicities identify an important and promising role for KTE-X19 in treating patients with R/R MCL who have an urgent unmet medical need

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