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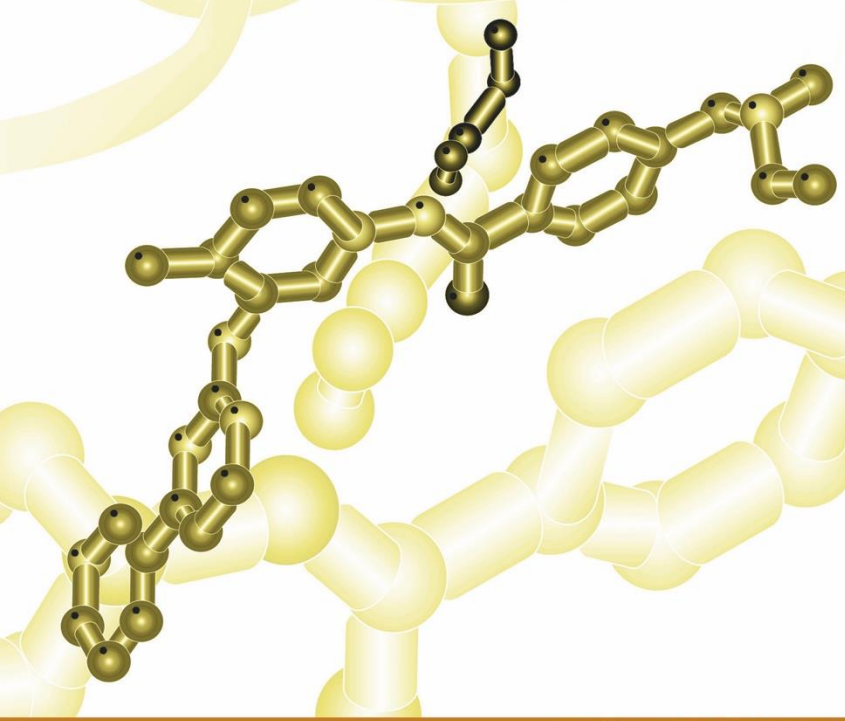


# New Drugs in Hematology

**President:** Pier Luigi Zinzani
**Co-President:** Michele Cavo

**Bologna,**
**Royal Hotel Carlton**
**January 15-17, 2024**

BOLOGNA BOLOGNA, ROYAL HOTEL CARLTON

# Mantle Cell Lymphoma

CAR-T, update clinical trials and RWE

**Javier Munoz**
Mayo Clinic
Arizona

# Disclosures

Consulting – Pharmacyclics/Abbvie, Bayer, Gilead/Kite, Beigene, Pfizer, Janssen, Celgene/BMS, Kyowa, Alexion, Fosunkite, Seattle Genetics, Karyopharm, Aurobindo, Verastem, Genmab, Genentech/Roche, ADC Therapeutics, Epizyme, Beigene, Novartis, Morphosys/Incyte, MEI, TG Therapeutics, AstraZeneca, Eli Lilly

Research funding – Bayer, Gilead/Kite, Celgene, Merck, Portola, Incyte, Genentech, Pharmacyclics, Seattle Genetics, Janssen, Millennium, Novartis, Beigene.

Honoraria - Targeted Oncology, OncView, Curio, Physicians' Education Resource.

# Agenda

| | |
|---|---|
| NEJM 2020 | Brexu-cel Initial approval |
| JCO 2022 | Brexu-cel 3-year follow-up |
| JCO 2023 | Brexu-cel RWE |
| ASH 2023 | Other targets: CD19/20, ROR1 |
| ASH 2023 | Liso-cel for MCL cohort |
| Unique Scenarios | CNS, TP53 |

# BACKGROUND

Brexucabtagene autoleucel (brexu-cel) is an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy approved in the United States for the treatment of adults with relapsed or refractory (R/R) mantle cell lymphoma (MCL) and in the European Union for adults with R/R MCL after ≥2 prior therapies, including a Bruton tyrosine kinase inhibitor (BTKi)


**FDA approves brexucabtagene autoleucel for relapsed or refractory mantle cell lymphoma**

July 2020


October 2020

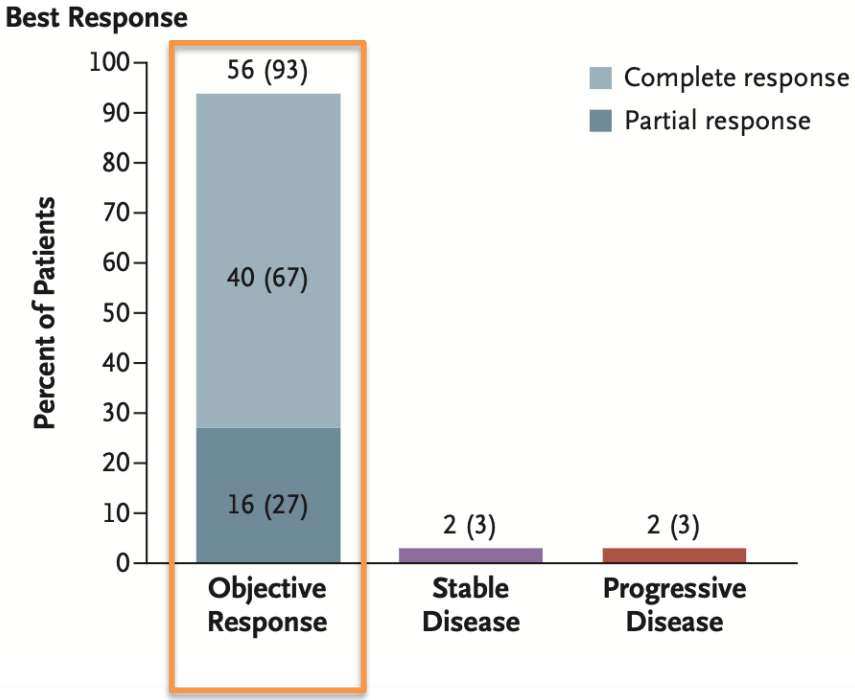
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

ABSTRACT




NEJM 2020

1ry Endpoint: ORR

# ZUMA-2 METHODS

**Phase 2**

| Leukapheresis | Optional Bridging | Lymphodepletion | CAR T-Cell | Follow-Up | |
|---|---|---|---|---|---|
| **R/R MCL** (1–5 prior lines of therapy) | 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 | $2\times10^6$ cells/kg brexu-cel single IV infusion on Day 0 | First tumor assessment on Day 28 | Long-term follow-up |

**Key ZUMA-2 Eligibility Criteria**

- Age ≥18 years with R/R MCL
- 1-5 prior regimens including anthracycline- or bendamustine-containing chemotherapy, anti-CD20 monoclonal antibody, and BTKi therapy

**Primary Endpoint**

- ORR (CR + PR; IRRC assessed per the Lugano classification)

**Key Secondary Endpoints**

- DOR, PFS, OS, AEs

Wang NEJM 2020

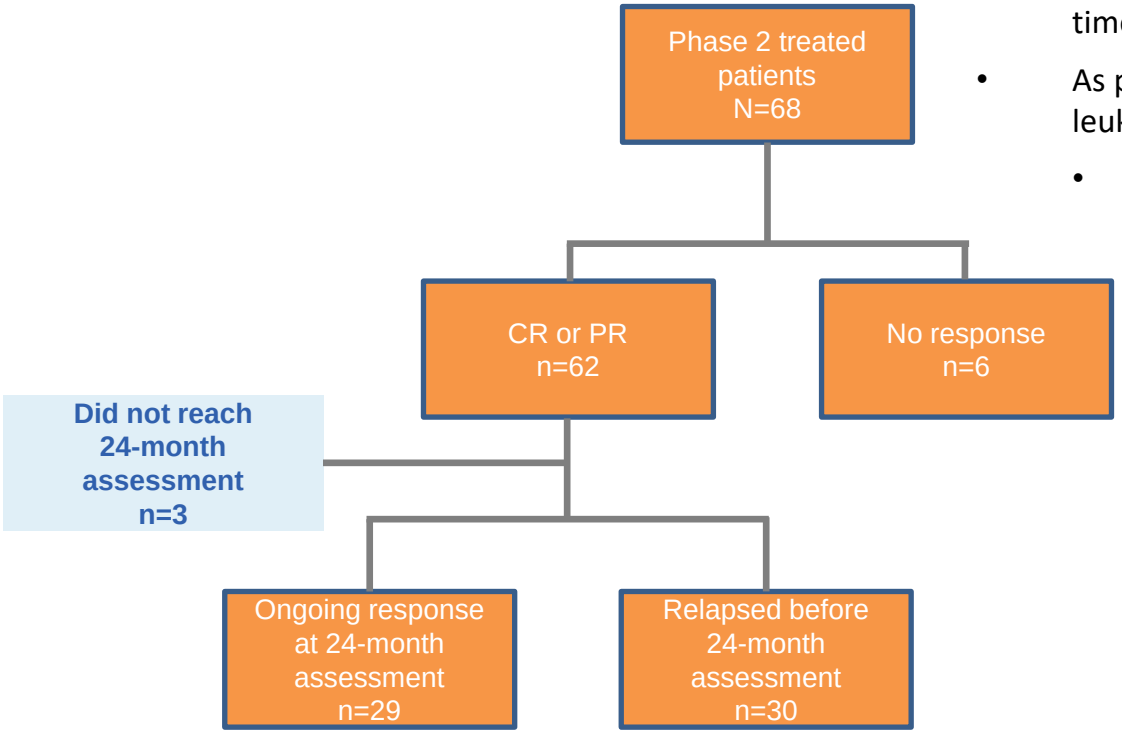
# Can we select patients in a better fashion? (2-year follow-up)

# Assessment of Durable Responses After Brexucabtagene Autoleucel (KTE-X19) in the ZUMA-2 Study in Relapsed/Refractory Mantle Cell Lymphoma

Javier Munoz, MD, MS, MBA[1]; Patrick M. Reagan, MD[2]; Andre Goy, MD, MS[3]; David B. Miklos, MD, PhD[4]; Dan Zheng, PhD[5]; Xiang Fang, PhD[5]; Rhine R. Shen, PhD[5]; Rubina Siddiqi, PhD[5]; Ioana Kloos, MD, FRCPC[5]; Marie José Kersten, MD, PhD[6]; and Michael Wang, MD[7]

- To **identify patient, product, and pharmacokinetic characteristics** associated with long-term response to brexu-cel, we assessed these characteristics by response status at **24 months** post–brexu-cel infusion in an exploratory analysis of ZUMA-2

# Patient Response Disposition at 24-Months




- At data cutoff (July 24, 2021), the median follow-up time was 35.6 months (range, 25.9-56.3)
- As previously reported, 74 patients were enrolled and leukapheresed, and 68 patients received brexu-cel[1]
  - 62 patients had achieved a CR or PR
    - **29 patients (47%) were in ongoing response at their 24-month assessment** (ongoing responders)
    - 30 patients (48%) had relapsed prior to their 24-month assessment (relapsed responders)
    - 3 patients with response did not reach their 24-month assessment at data cutoff and were excluded from this analysis
    - 6 patients did not respond (non-responders)

1. Wang M, et al. *J Clin Oncol*. 2023;41(3):555-567.
Brexu-cel, brexucabtagene autoleucel; CR, complete response; PR, partial response.

# Baseline Patient Characteristics by Response Status at 24 Months

| Characteristic | Ongoing Responders (n=29) | Relapsed Responders (n=30) | Non-responders (n=6) |
|---|---|---|---|
| **Median age (range), years** | 65.0 (50-79) | 65.0 (38-75) | 66.5 (60-74) |
| **Male, n (%)** | 26 (90) | 24 (80) | 5 (83) |
| **ECOG PS of 0, n (%)** | 23 (**79**) | 17 (**57**) | 3 (50) |
| **Intermediate or high sMIPI, n (%)** | 19 (66) | 15 (50) | 4 (67) |
| **Received bridging therapy, n (%)** | 6 (**21**) | 16 (**53**) | 3 (50) |
| **Median no. of prior therapies, n (range)** | 3 (2-5) | 3 (2-5) | 3 (1-5) |
| **Prior platinum, n (%)** | 3 (**10**) | 12 (**40**) | 0 |
| **Prior anthracycline, n (%)** | 22 (76) | 22 (73) | 4 (67) |
| **Prior bendamustine, n (%)** | 13 (**45**) | 16 (**53**) | 6 (100) |
| **Prior lenalidomide, n (%)** | 7 (24) | 10 (33) | 2 (33) |
| **Prior proteasome inhibitor, n (%)** | 12 (41) | 11 (37) | 1 (17) |
| **Prior autologous SCT, n (%)** | 14 (48) | 11 (37) | 2 (33) |
| **Prior BTKi therapy, n (%)** | 29 (100) | 30 (100) | 6 (100) |
| Ibrutinib | 27 (93) | 24 (80) | 4 (67) |
| Acalabrutinib | 8 (28) | 6 (20) | 2 (33) |
| Both | 6 (21) | 0 | 0 |

- A **smaller proportion of ongoing responders received bridging therapy**, received **prior platinum**, and had **ECOG PS scores of 1** compared with relapsed responders
- The median number of prior therapies was 3 in all subgroups

Munoz JSMO 2023

# Baseline Patient Characteristics by Response Status at 24 Months

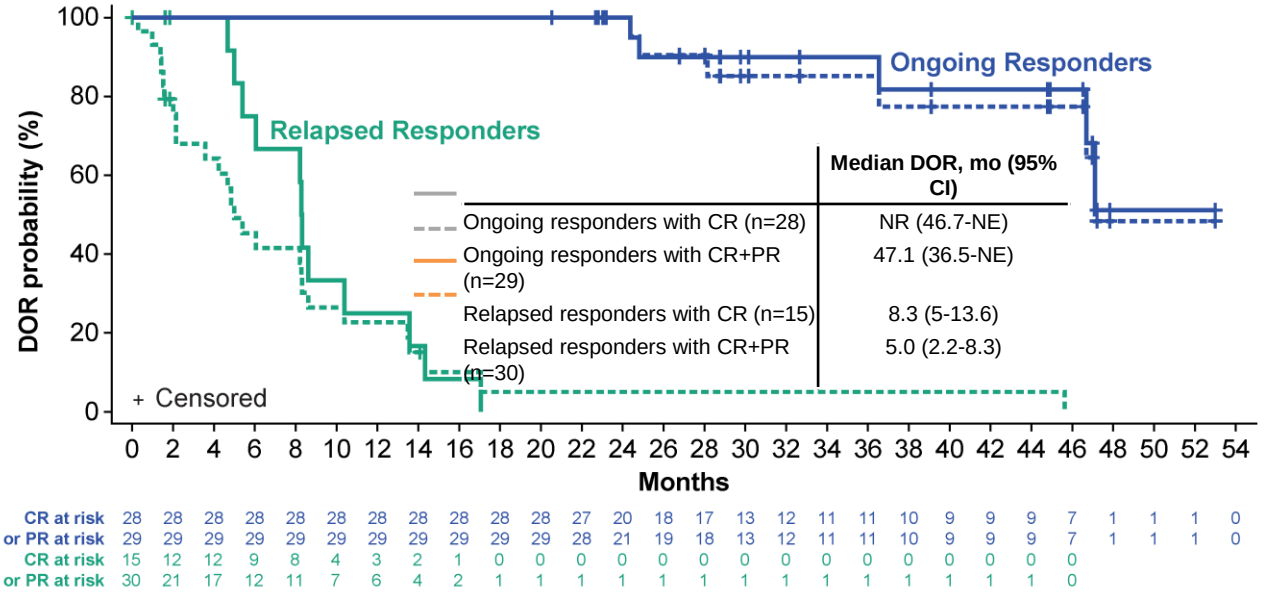
| Characteristic | Ongoing Responders (n=29) | Relapsed Responders (n=30) | Non-responders (n=6) |
|---|---|---|---|
| **Relapsed or refractory disease, n (%)** | | | |
| Relapse after autologous SCT | 14 (48) | 11 (37) | 2 (33) |
| Refractory to last MCL therapy | 10 (34) | 13 (43) | 3 (50) |
| Relapse after last MCL therapy | 5 (17) | 6 (20) | 1 (17) |
| **CD19-positive IHC by central lab, n (%)** | 22 (76) | 20 (67) | 3 (50) |
| **Tumor burden (SPD) by central read ($mm^2$)** | | | |
| n | 28 | 28 | 4 |
| Median (range) | **935.1** (260-6133) | **4233.6** (386-14,390) | **553.1** (293-16,878) |
| **Positive bone marrow assessment at baseline, n (%)** | 16 (55) | 16 (53) | 5 (83) |
| **Elevated LDH levels (ULN to ≥1.5 ULN), n (%)** | 13 (45) | 11 (37) | 2 (33) |
| **Ki-67 PI ≥30%, n (%)** | 19 (66) | 18 (60) | 4 (67) |

- The median tumor burden (SPD) at baseline was **~4 times** smaller in ongoing responders compared with relapsed responders

Munoz ASH 2022

Munoz JSMO 2023

# Duration of Response for Ongoing and Relapsed Responders in ZUMA-2

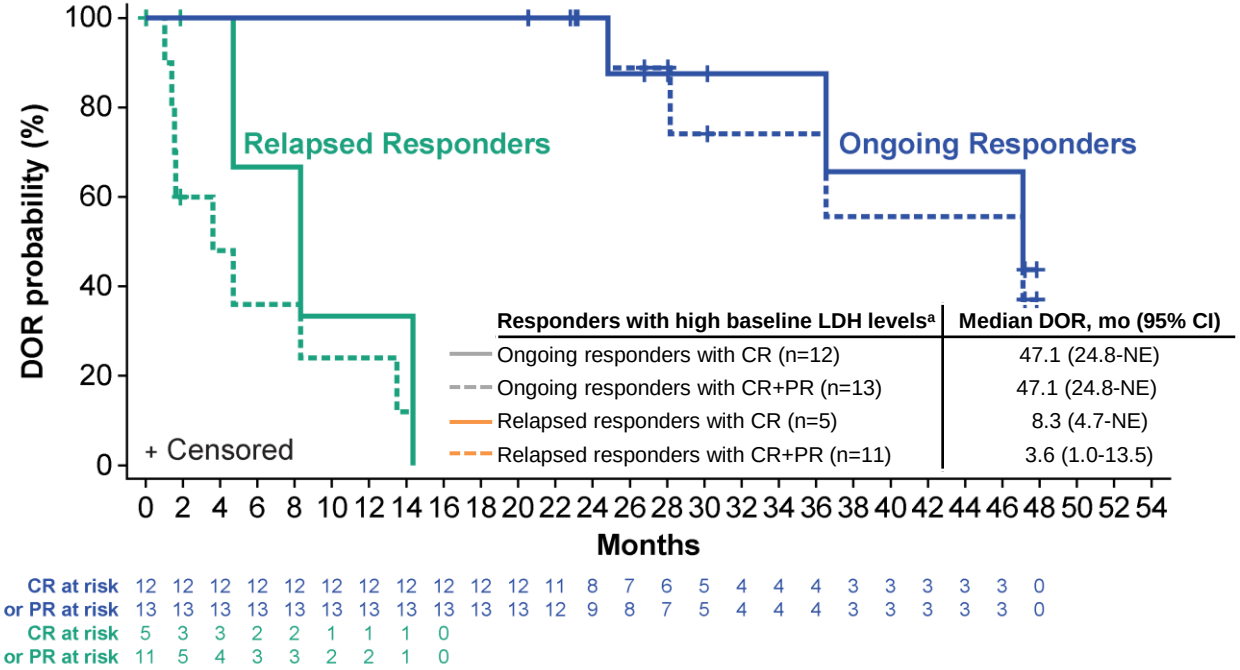



- Median DOR in ongoing responders with CR was **NR** and was **8.3 months** in relapsed responders with CR
- Median (range) time to initial response, time to CR, and time for conversion from SD or PR to CR for ongoing responders was 1 month (0.9-3.1; n=29), 3 months (0.9-35.1; n=28), and 2.3 months (1.8-34.1; n=16), respectively
- Median (range) time to initial response, time to CR, and time for conversion from SD or PR to CR for relapsed responders was 1 month (0.8-1.7; n=30), 3 months (0.8-9.0; n=15), and 2.4 months (2.0-8.1; n=8), respectively

CR, complete response; DOR, duration of response; mo, month; NE, not estimable; NR, not reached; PR, partial response; SD, stable disease.

Munoz JSMO 2023

# Duration of Response for Ongoing and Relapsed Responders With High Baseline LDH levels




| Responders with high baseline LDH levels[a] | Median DOR, mo (95% CI) |
|---|---|
| Ongoing responders with CR (n=12) | 47.1 (24.8-NE) |
| Ongoing responders with CR+PR (n=13) | 47.1 (24.8-NE) |
| Relapsed responders with CR (n=5) | 8.3 (4.7-NE) |
| Relapsed responders with CR+PR (n=11) | 3.6 (1.0-13.5) |

- The median (95% CI) DOR in ongoing responders with CR who had high LDH levels (n=12) was **47.1 months** (24.8-NE) and was **8.3 months** (4.7-NE) in relapsed responders with CR who had high baseline LDH levels (n=5)

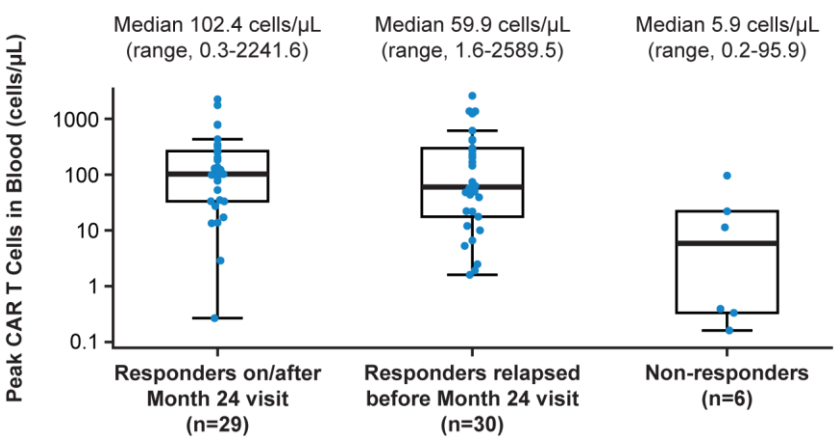
[a] Elevated LDH levels were defined as ULN to ≥1.5 ULN

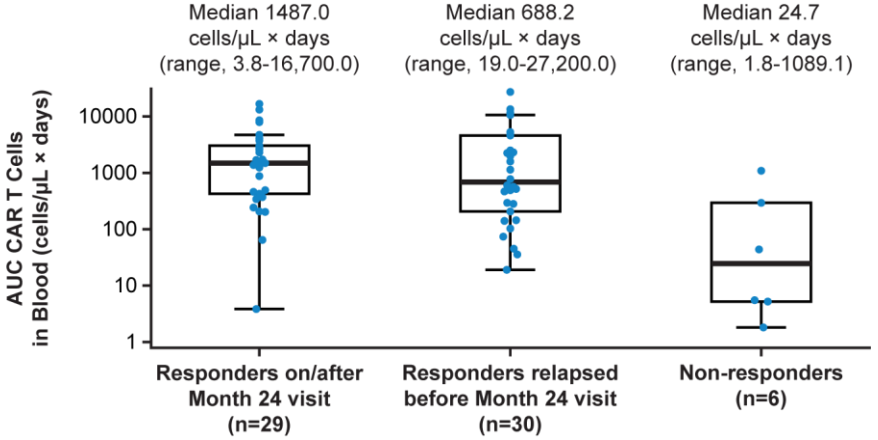
CR, complete response; DOR, duration of response; LDH, lactate dehydrogenase; mo, month; NE, not estimable; PR, partial response; ULN, upper limit of normal.

Munoz JSMO 2023

# Summary of Product Characteristics and Pharmacokinetics Characteristics by Response Status at 24 Months

| Median (range) | Ongoing Responders (n=29) | Relapsed Responders (n=30) | Non-responders (n=6) |
|---|---|---|---|
| **CD4/CD8 ratio** | 0.86 (0.27-2.06) | 0.62 (0.04-3.73) | 0.40 (0.30-0.70) |
| **Total number of CCR7+ T cells infused ($10^6$)** | **119.8** (37.0-249.9) | **89.1** (6.1-353.4) | **88.2** (39.9-150.3) |




- Product characteristics were largely similar among ongoing and relapsed responders with a modest **increase** in the median total number of **infused CCR7+ T cells** observed in ongoing versus relapsed responders
- Median peak and **area under the curve** CAR T-cell levels were **~2× higher** in ongoing responders than in relapsed responders

AUC, area under the curve; CAR, chimeric antigen receptor; CCR7, chemokine receptor 7

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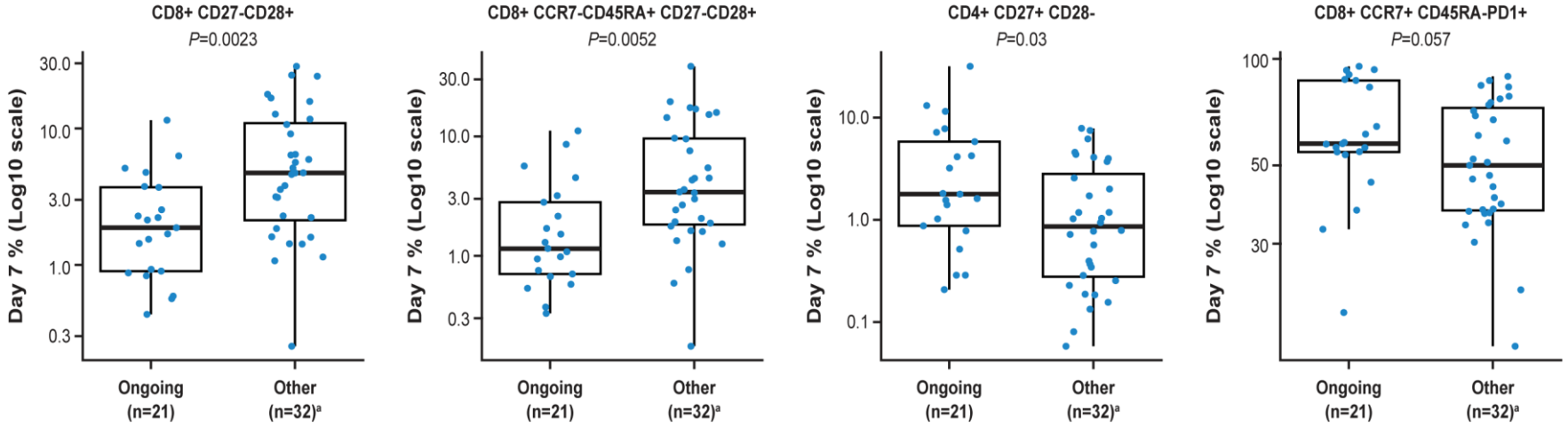
# Peripheral Blood T-Cell Phenotype at Day 7 by Response Status

Responders ↑CD8 **effector memory** T cells

Responders ↑CD4 **juvenile CD27** T cells




- Peripheral blood T cells of relapsed and non-responding patients exhibit a more prominent CD8+ **CD27-** CD28+ **effector memory phenotype** compared with patients with ongoing response
- Ongoing responders are enriched with peripheral CD4 T cells that maintain juvenile **CD27+** expression and activated CD8 effector memory T cells

[a] Other includes relapsed responders and non-responders.
CCR7, chemokine receptor 7.

Munoz JSMO 2023

# Z2 Highlights at 2-years

- In this exploratory analysis, after 35.6 months of median follow-up, brexu-cel continues to demonstrate durable responses with **47% of responders still in ongoing response at 24 months** post-infusion in ZUMA-2
- Ongoing responses were observed in patients with **high-risk disease characteristics**, suggesting that brexu-cel has the potential to produce durable responses in patients with R/R MCL who would typically have a poor prognosis
- Ibrutinib was more commonly the last prior therapy received by ongoing versus relapsed responders
- **Ongoing responders tended to have lower ECOG PS scores, lower tumor burden, and less frequent use of prior platinum therapy or bridging therapy compared** with relapsed responders, suggesting the potential for greater benefit with brexu-cel in earlier courses of disease
- **Median peak and AUC CAR T-cell levels were ~2× higher in ongoing responders** than in relapsed responders, suggesting that the degree of CAR T-cell expansion may predict durability of response
- A modest increase in the median total number of infused CCR7+ cells and maintenance of CD27+ peripheral T cells observed in ongoing versus relapsed responders may suggest a potential role of continuous memory T-cell differentiation in achieving durable responses

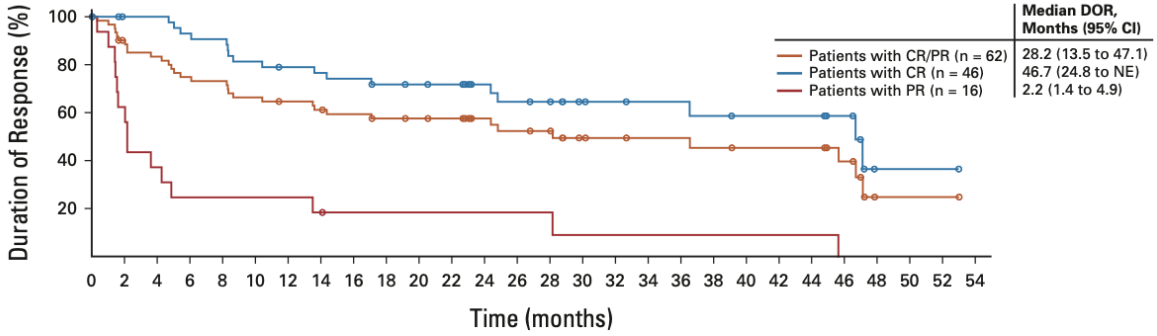
Munoz JSMO 2023

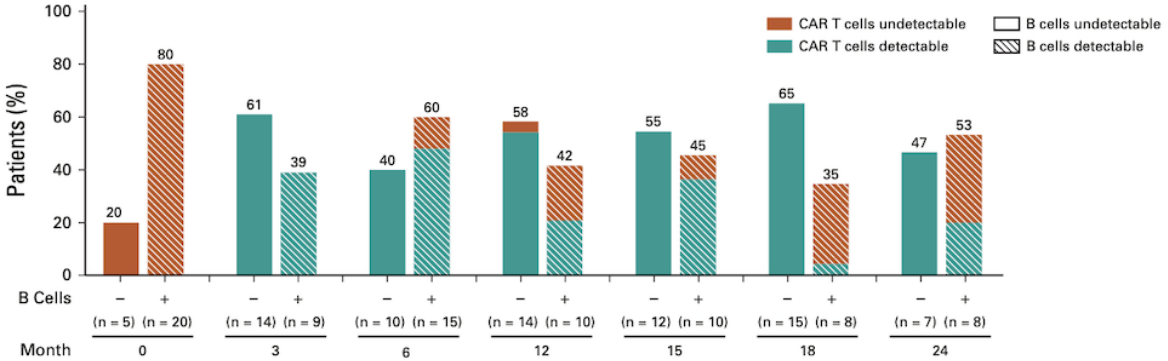
# What changed during the long-term update? (3-year follow-up)

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

# Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study

Michael Wang, MD[1]; Javier Munoz, MD, MS, MBA[2]; Andre Goy, MD, MS[3]; Frederick L. Locke, MD[4]; Caron A. Jacobson, MD, MMSc[5]; Brian T. Hill, MD, PhD[6]; John M. Timmerman, MD[7]; Houston Holmes, MD, MBA[8]; Samantha Jaglowski, MD[9]; Ian W. Flinn, MD, PhD[10]; Peter A. McSweeney, MB, ChB[11]; David B. Miklos, MD, PhD[12]; John M. Pagel, MD, PhD, DSc[13]; Marie José Kersten, MD, PhD[14]; Krimo Bouabdallah, MD[15]; Rashmi Khanal, MD[16]; Max S. Topp, MD[17]; Roch Houot, MD, PhD[18]; Amer Beitinjaneh, MD[19]; Weimin Peng, PhD[20]; Xiang Fang, PhD[20]; Rhine R. Shen, PhD[20]; Rubina Siddiqi, PhD[20]; Ioana Kloos, MD[20]; and Patrick M. Reagan, MD[21]

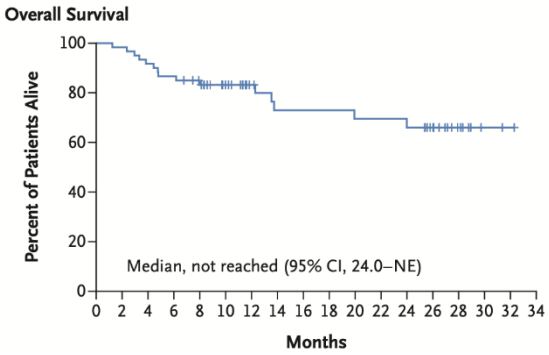


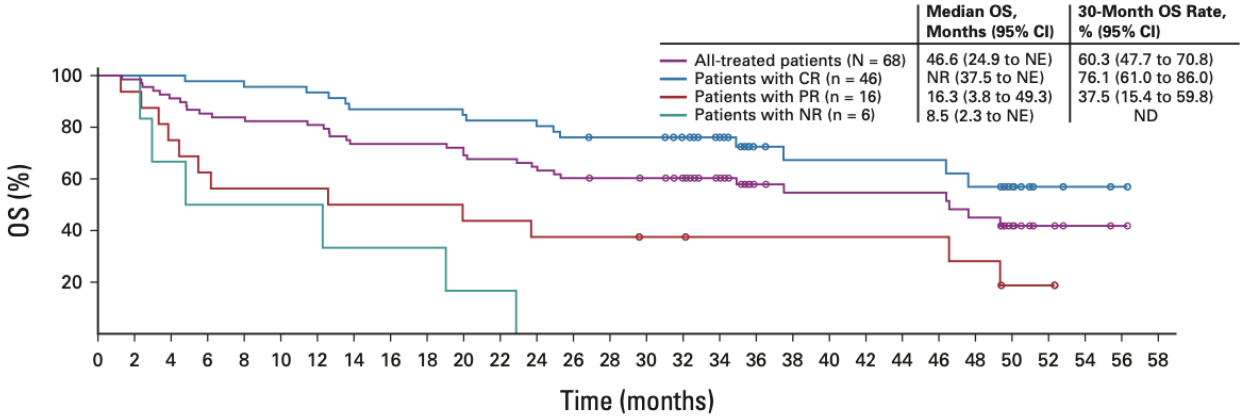

JCO 2022

CAR T detection, B-cell recovery, DOR

# Z2 OVERALL SURVIVAL




NEJM 2020




JCO 2022

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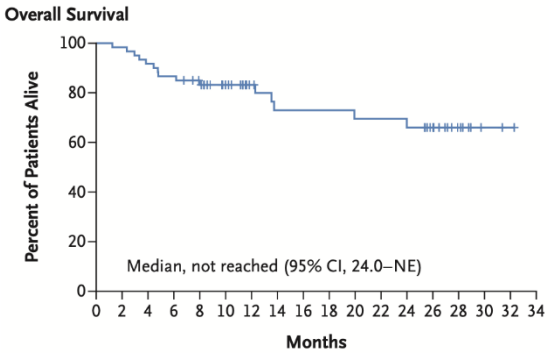
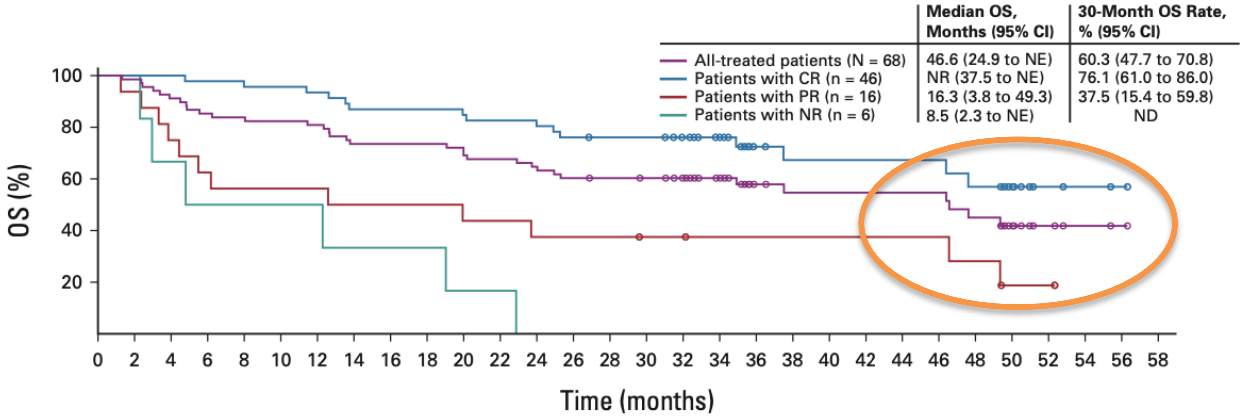
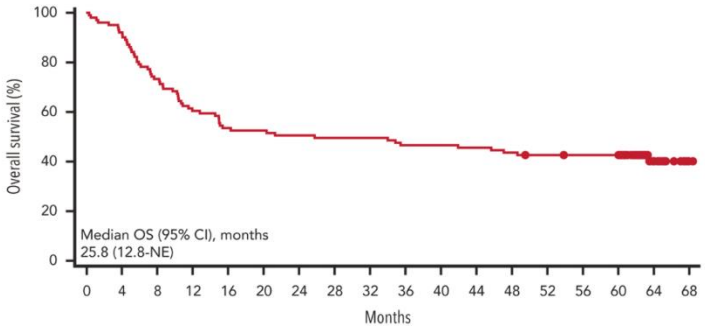


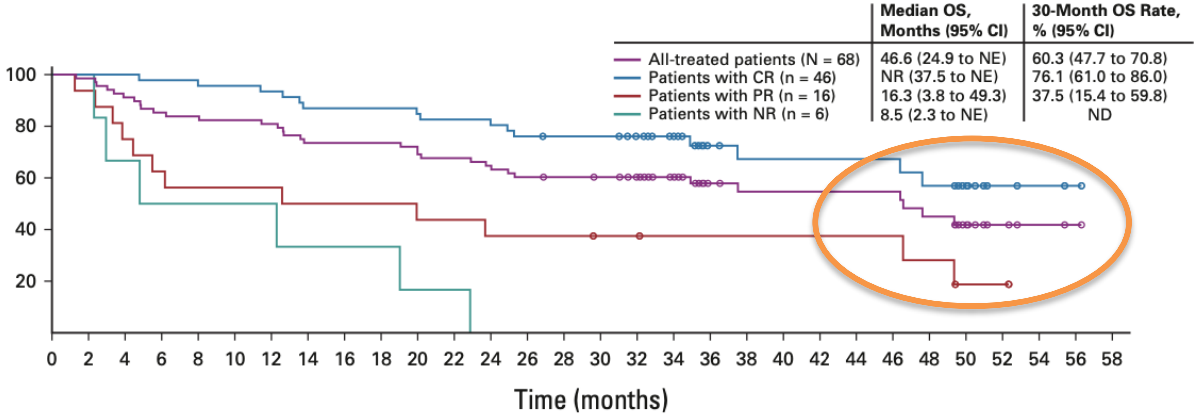

NEJM 2020




JCO 2022

# OVERALL SURVIVAL



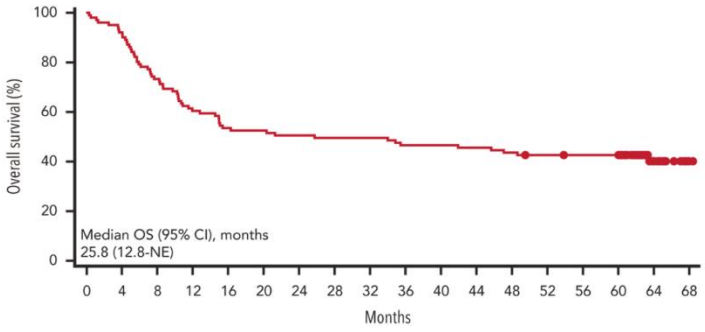

ZUMA-1
DLBCL

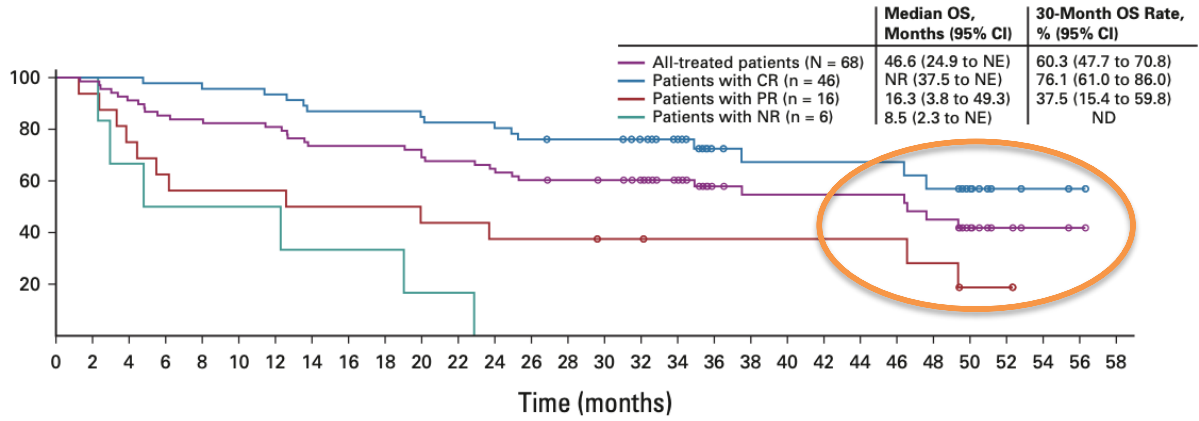
ZUMA-2
MCL

# OVERALL SURVIVAL

CLINICAL TRIALS AND OBSERVATIONS | MAY 11, 2023

**Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma**




ZUMA-1
DLBCL
5-years

ZUMA-2
MCL
3-years

# The Bendamustine Dilemma

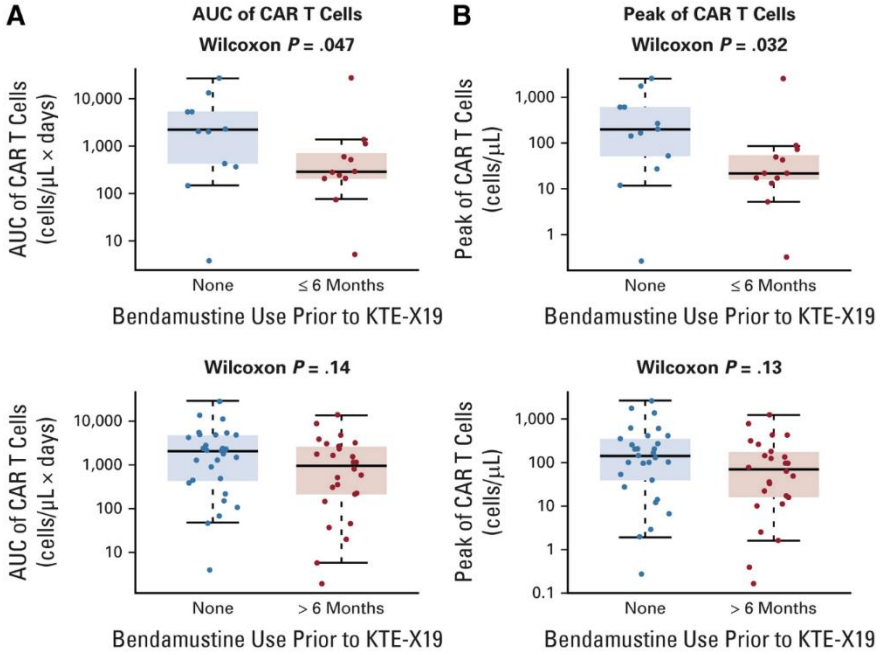
**TABLE 2.** Comparison of Efficacy and Safety Outcomes, Pharmacokinetics, Pharmacodynamics, and Product Attributes After 1:1 Propensity Score Matching of Patients With Prior Bendamustine Use Within 6 Months or > 6 Months Versus No Use

| | Benda Use ≤ 6 Months *v* No Benda Use[a] | | Benda Use > 6 Months *v* No Benda Use[b] | |
|---|---|---|---|---|
| **Outcome or Measure** | **Benda Use ≤ 6 Months (n = 11)** | **No Benda Use (n = 11)** | **Benda Use > 6 Months (n = 25)** | **No Benda Use (n = 25)** |
| Efficacy, No. (%) | | | | |
| ORR | 9 (81.8) | 11 (100) | 21 (84.0) | 25 (100.0) |
| CR rate | 6 (54.5) | 9 (81.8) | 15 (60.0) | 20 (80.0) |
| Ongoing response at 18 months | 2 (18.2) | 4 (36.4) | 8 (32.0) | 13 (52.0) |
| Safety, No. (%)[c] | | | | |
| Grade ≥ 3 neurologic events | 1 (9.1) | 7 (63.6) | 5 (20.0) | 11 (44.0) |
| Grade ≥ 3 CRS | 0 (0) | 3 (27.3) | 3 (12.0) | 5 (20.0) |
| Pharmacokinetics, median (Q1, Q3) | | | | |
| Peak CAR T-cell levels, cells/μL | 22.14 (15.53, 61.86) | 167.23 (40.15, 440.65) | 62.66 (15.60, 182.41) | 129.29 (27.30, 267.10) |
| AUC, cells/μL × day | 293.86 (224.40, 868.60) | 2,090.42 (398.80, 3,803.58) | 775.83 (202.76, 2,569.28) | 1,725.29 (371.04, 4,087.57) |
| Doubling time, days | 1.51 (1.34, 2.08) | 1.28 (1.19, 1.33) | 1.46 (1.28, 1.58) | 1.31 (1.25, 1.50) |

In those with and without prior bendamustine, the **ORR** was **84%** (CR 58%) and **100%** (CR 77%), respectively. At data cutoff, **29%** and **48%** of patients, respectively, remained in **ongoing response**. In patients with and without prior bendamustine, the **median DOR was 28.2 months and 46.7 months**, respectively, but the two DOR curves were not statistically significantly different

Wang JCO 2022

# Bendamustine: Post hoc evaluation Z2




Patients with prior bendamustine within 6 months of apheresis had **lower peak CAR T-cell levels postinfusion, lower numbers of CD4+ T cells in product, levels of peak effector serum biomarkers, and doubling time**. These trends were not pronounced for patients with prior bendamustine within 12 months

Wang JCO 2022

# CAR Real world evidence

Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

## Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma in Standard-of-Care Practice: Results From the US Lymphoma CAR T Consortium

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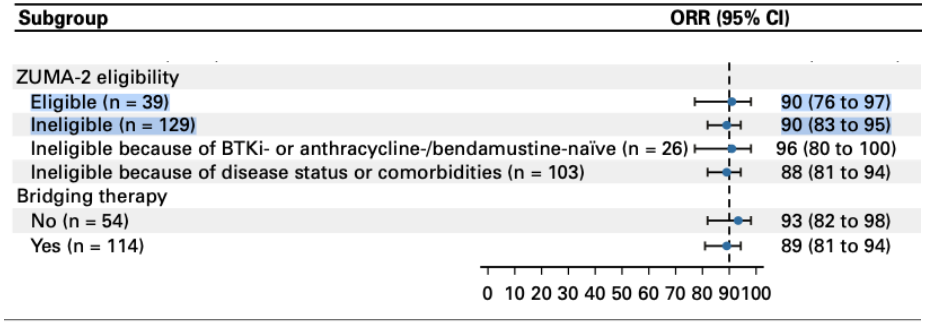
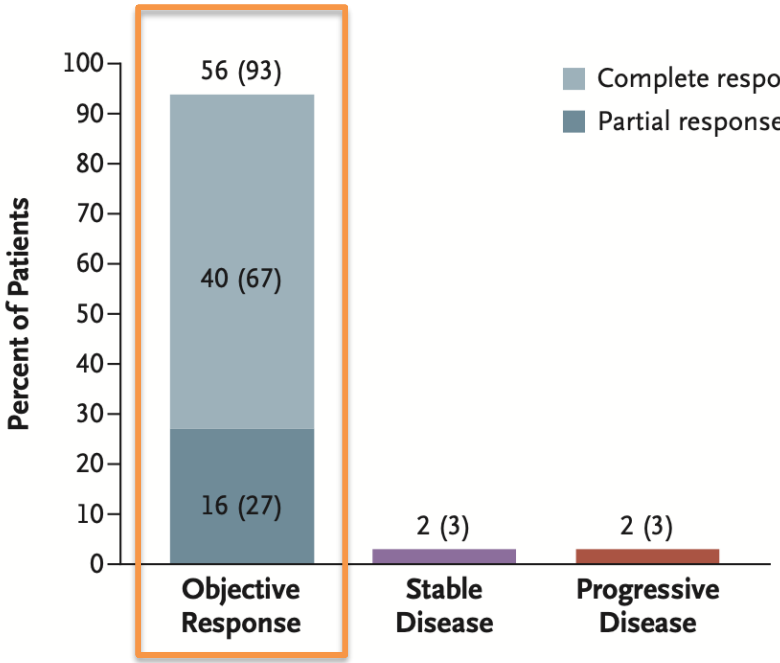


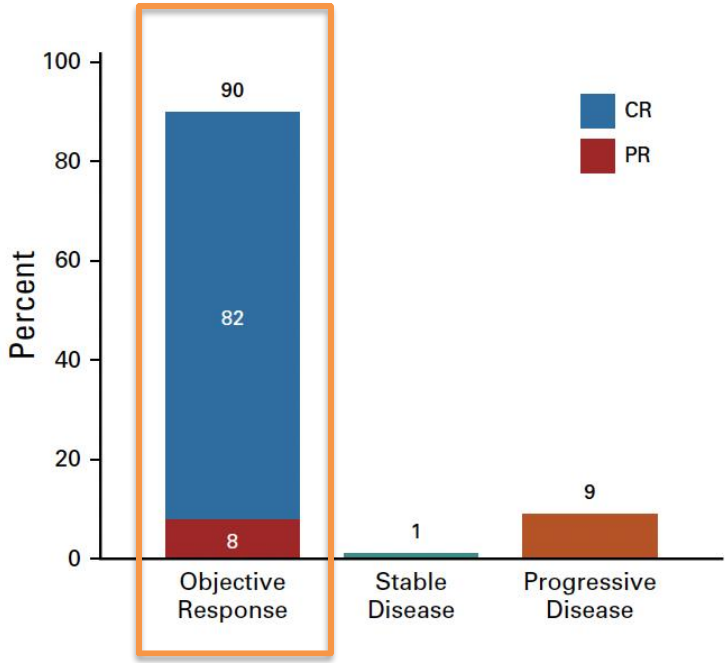

JCO 2023

Of apheresed patients, 79% would <u>not</u> have met ZUMA-2 eligibility

# CAR Real world evidence

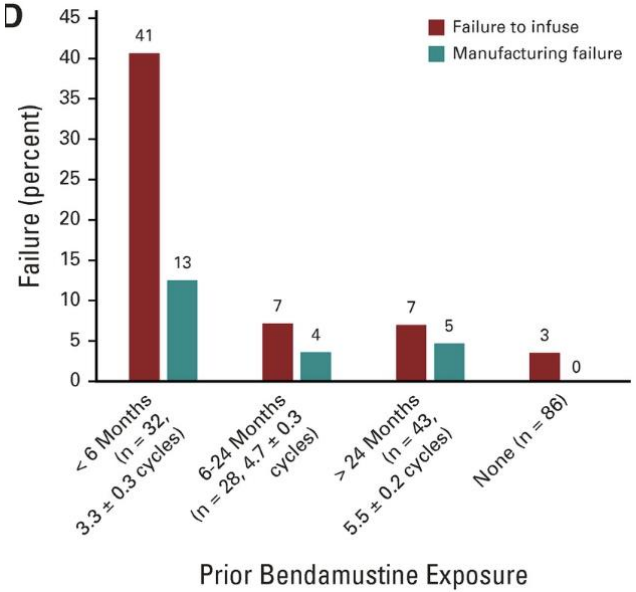


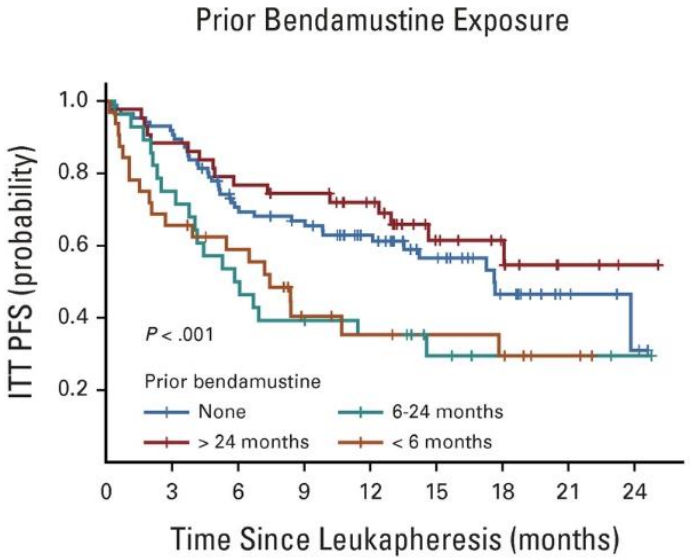

NEJM 2020
ZUMA-2




JCO 2023
US Lymphoma Consortium

# Bendamustine: US Lymphoma Consortium




A higher proportion of patients who had **bendamustine exposure within 6 months** before leukapheresis did not receive brexu-cel infusion (41% v 3%-7%, P < .001) because of **manufacturing failure** (13% v 0%-5%). These patients also had **lower ORR** (53% v 71%-91%, P < .001) and **CR rate** (47% v 64%-84%, P < .001). In ITT analysis, patients who had bendamustine exposure within 6 months or 6-24 months before leukapheresis had inferior PFS (P < .001) and OS (P = .009). However, after adjusting for sMIPI and Ki-67, the association with PFS and OS was no longer statistically significant.

Wang JCO 2023

# Not the same as Bendamustine for lymphodepletion

FREE ACCESS | Hematologic Malignancies—Lymphoma and Chronic Lymphocytic Leukemia | May 31, 2023

## Outcomes with bendamustine lymphodepletion prior to brexucabtagene autoleucel for mantle cell lymphoma.

**Authors**: Elise A. Chong, James N. Gerson, Sunita Dwivedy Nasta, Daniel J Landsburg, Stefan K. Barta, Jakub Svoboda, Elizabeth Weber, Emeline R. Chong, and Stephen J. Schuster | AUTHORS INFO & AFFILIATIONS

**Publication**: Journal of Clinical Oncology • Volume 41, Number 16_suppl

| | Zuma-2 FC LD | US Consortium FC LD | Benda LD |
|---|---|---|---|
| CR | 67% | 82% | 69% |
| ORR | 93% | 90% | 81% |
| 12-month PFS | 61% | 59% | 63% |

Conclusions: Bendamustine LD prior to brexu-cel for MCL is **feasible**, and, although these numbers are small (**16 patients**), appears to have comparable outcomes

# ASH Updates 2023

| | |
|---|---|
| 4394 | Brexu-cel RWE Europe |
| 107 | Brexu-cel RWE CIBMTR |
| 2120 | Brexu-cel Early intervention |
| 3505 | Liso-cel for MCL cohort |
| 1024 | CD19/20 |
| 4857 | ROR1 |

# CAR Real world evidence

**4394 Real World Results of Brexucabtagene Autoleucel for Patients with Relapsed/Refractory Mantle Cell Lymphoma - First German/Swiss Analysis**

**107 Real-World Outcomes of Brexucabtagene Autoleucel (Brexu-cel) for Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL): A CIBMTR Subgroup Analysis of High-Risk Characteristics**

| | Zuma-2 | US Consortium | German/Swiss | CIBMTR |
|---|---|---|---|---|
| Patients | 60 | 189 | 111 | 446 |
| Z2 ineligible | NA | 79% | NR | 67% |
| ORR | 93% | 90% | 86% | 91% |
| >G3 CRS | 15% | 8% | 18% | 11% |
| >G3 ICANS | 31% | 32% | 25% | 28% |

Hess ASH 2023

Kambhampati ASH 2023

# Can we manage toxicity better?

# It is Toxic…

| | Brexucabtagene autoleucel | Axicabtagene ciloleucel | Lisocabtagene maraleucel | Idecabtagene vicleucel |
|---|---|---|---|---|
| Disease | MCL | DLBCL | DLBCL | MM |
| >G3 CRS | 15% | 13% | 2% | 5% |
| >G3 ICANS | **31%** | 28% | 10% | 3% |

Marjoncu JHOP 2021

# Assessment of Early Intervention Strategies for Management of Cytokine Release Syndrome and Neurologic Events After Brexucabtagene Autoleucel Treatment in Patients With Relapsed or Refractory Mantle Cell Lymphoma in ZUMA-2

Olalekan O. Oluwole, MD, MBBS, MPH[1]; Patrick M. Reagan, MD[2]; David B. Miklos, MD, PhD[3]; Frederick L. Locke, MD[4]; Andre Goy, MD[5]; Caron A. Jacobson, MD, MMSc[6]; Javier Munoz, MD, MS, MBA, FACP[7]; Edouard Forcade, MD, PhD[8]; Max S. Topp, MD[9]; Dan Zheng, PhD[10]; Ana Nunes, PharmD[10]; Wangshu Zhang, PhD[10]; Rhine R. Shen, PhD[10]; Ioana Kloos, MD[10]; Marie José Kersten, MD, PhD[11]; and Michael L. Wang, MD[12]

In August 2018, the safety management strategies for CRS and NEs for patients in ZUMA-2 were updated to initiate treatment for these adverse events (AEs) earlier, at the onset of Grade 1 events to improve safety outcomes

# METHODS

## Tocilizumab and Corticosteroid Medication Strategies for CRS and NEs by Management Group

### CRS Management

| | CRS Grade | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| LIG | Tocilizumab | No | Yes[a] | Yes | Yes |
| LIG | Steroids | No | Yes[a] | Yes | Yes, high dose |
| EIG | Tocilizumab | Yes[b] | Yes | Yes | Yes |
| EIG | Steroids | No | Yes[c] | Yes | Yes, high dose |

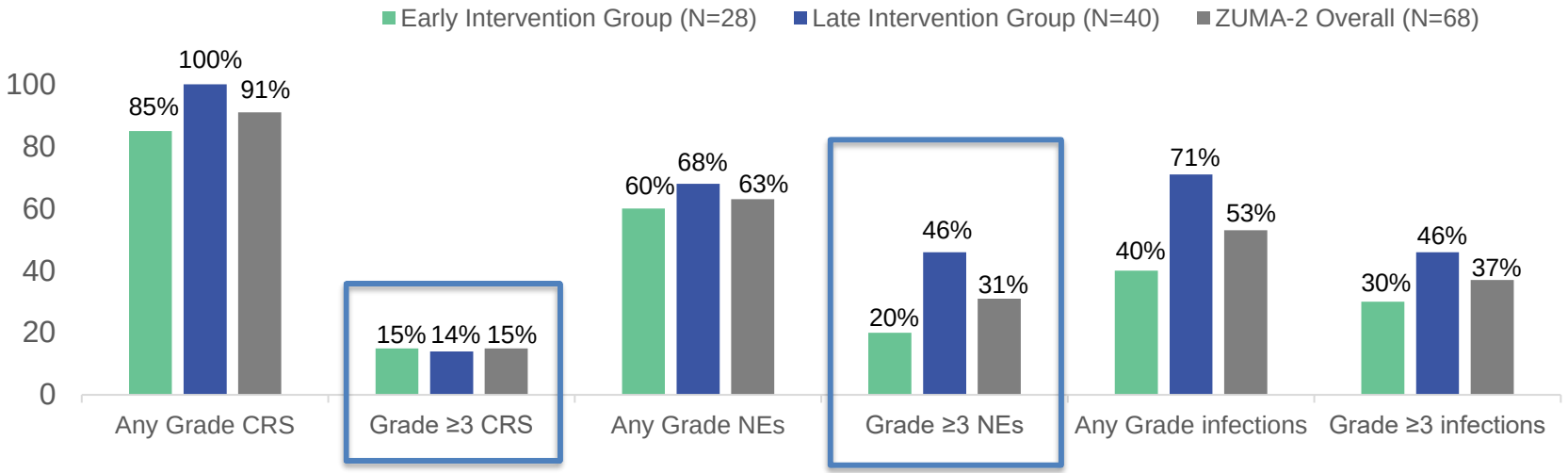
### NE Management

| | NE Grade | 1 | 2 | 3 | 4 |
|---|---|---|---|---|---|
| LIG | Tocilizumab | No | Yes[a] | Yes | Yes |
| LIG | Steroids | No | No | Yes | Yes, high dose |
| EIG | Tocilizumab | No | Yes[d] | Yes | Yes |
| EIG | Steroids | No | Yes | Yes | Yes, high dose |

[a] Only in case of comorbidities or older age. [b] If no improvement after 24 hours. [c] If no improvement after 24 hours of tocilizumab administration. [d] With concurrent CRS.
CRS, cytokine release syndrome; EIG, Early Intervention Group; LIG, Late Intervention Group; NE, neurologic event.

# RESULTS

## Incidence and Resolution of CRS, NEs and Infections

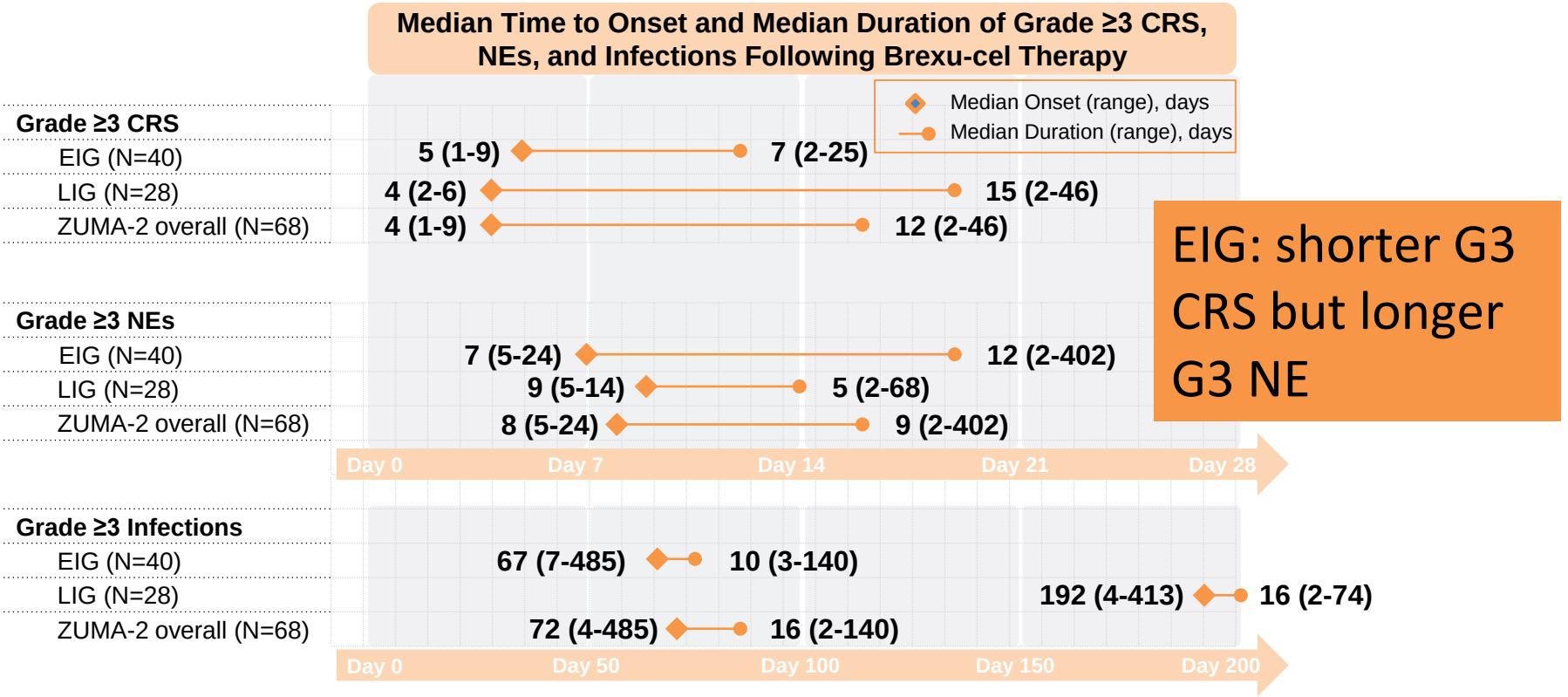



CRS, cytokine release syndrome; NE, neurologic event

- **Grade ≥3 NEs and Grade ≥3 infections were experienced less often in the EIG** versus the LIG. Grade ≥3 CRS events occurred at similar rates in both groups
  - CRS and NEs were resolved at similar rates in the EIG (100% and 92%, respectively) and LIG (100% and 95%, respectively), but a smaller proportion of patients in the EIG had resolved infections versus the LIG (75% vs 95%; data not shown)

# RESULTS

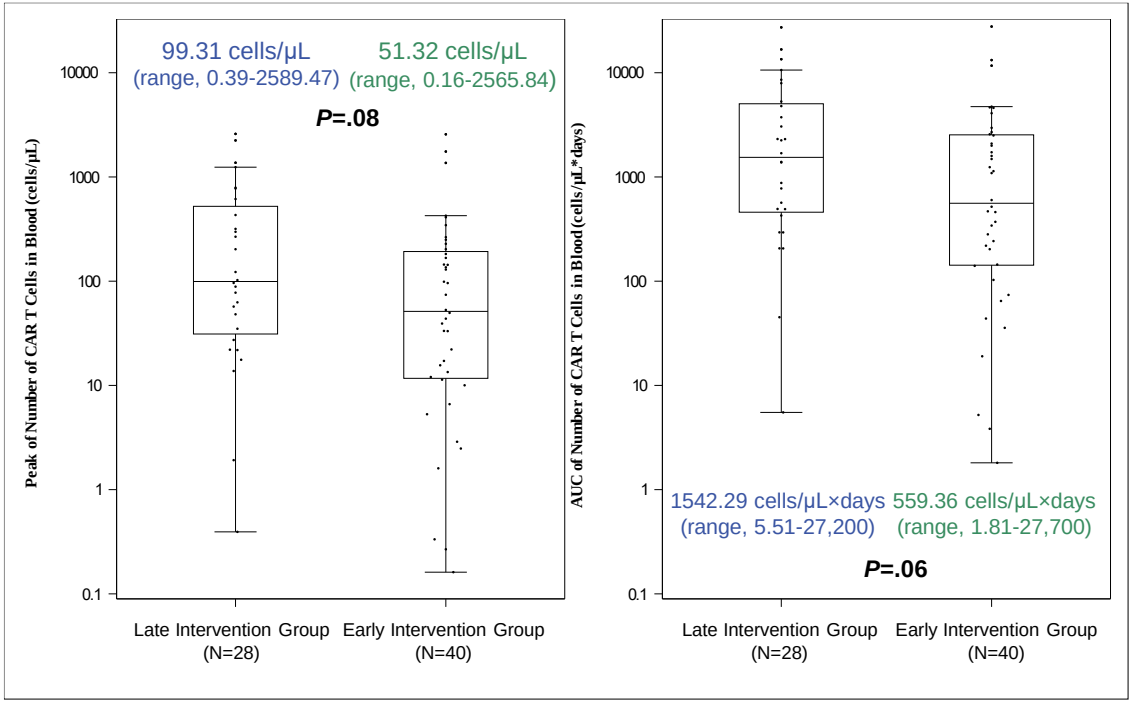
## Median Time to Onset and Median Duration of Grade ≥3 CRS, NEs, and Infections




CRS, cytokine release syndrome; EIG, Early Intervention Group; LIG, Late Intervention Group; NE, neurologic event

# RESULTS

## CAR T-cell Expansion by Safety Management Group

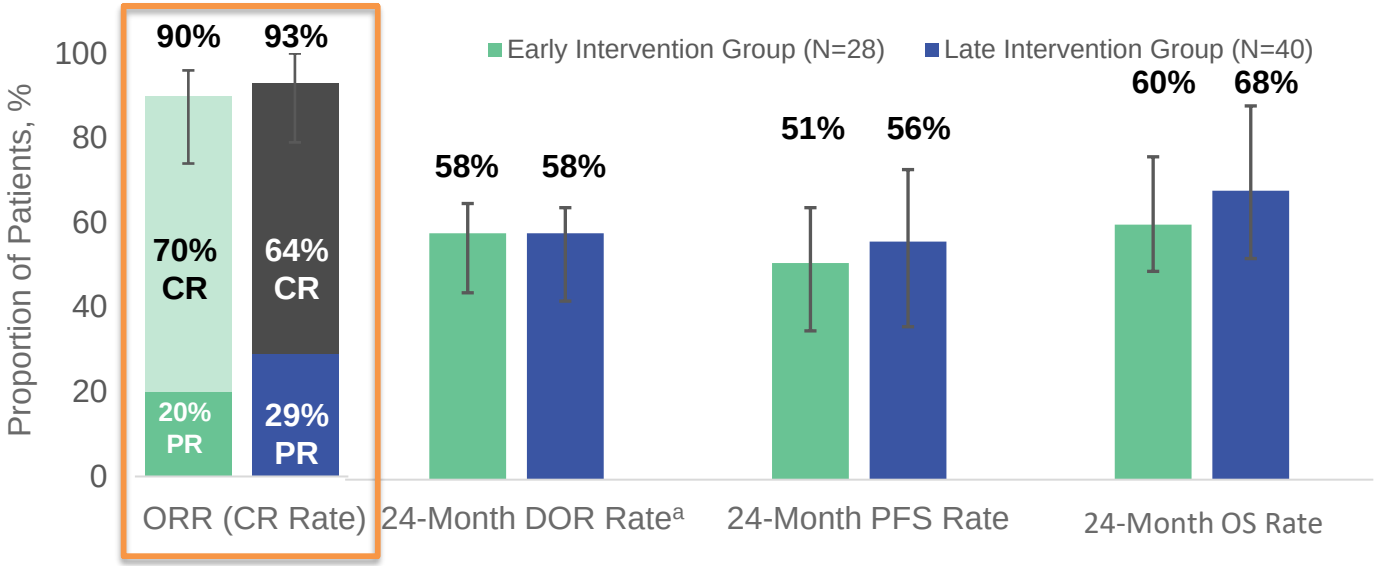



- Peak and AUC CAR T-cell levels were not significantly different between the EIG and the LIG (*P*=.08 and *P*=.06, respectively)
- Time to peak CAR T-cell levels was comparable for both the EIG and the LIG (median 15 [range, 8-464] versus 15 [range, 8-17] days, respectively)

AUC, area under the curve; CAR, chimeric antigen receptor.

# RESULTS

## Efficacy Outcomes by Safety Management Group




[a] Among responders only.
CR, complete response; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

ORR and 24-month DOR, OS, and PFS rates were similar across EIG and LIG subgroups

**Efficacy was not compromised**

Oluwole ASH 2023

# HIGHLIGHTS EIG

- In this post-hoc exploratory subgroup analysis, patients who received earlier intervention for CRS and NEs experienced improved safety outcomes compared with patients who received late intervention
  - Notably, patients in the EIG experienced lower rates of Grade ≥3 NEs (20% vs 46%) and infections (30% vs 46%) than patients in the LIG
  - Additionally, a lower percentage of EIG patients required steroid, vasopressor, and/or immunoglobulin use than the LIG
- The EIG demonstrated numerically lower peak and AUC CAR T-cell expansion levels compared with the LIG, but efficacy results appear to be similar between subgroups
- Although limited by small patient numbers, these findings suggest that the current clinical guidance for safety management (based on earlier intervention for CRS and NE) may be associated with a better safety profile than the one reported for the overall population in the ZUMA-2 study (N=68)

# New CAR Targets

| |
|---|
| ROR1 |
| CD20/19 |

704.CELLULAR IMMUNOTHERAPIES: EARLY PHASE AND INVESTIGATIONAL THERAPIES | NOVEMBER 28, 2023

# Trial-in-Progress: A Phase 1/2 Multi-Center Study of Onct-808, a ROR1-Specific CAR T, in Adult Patients with Relapsed/Refractory Aggressive B Cell Lymphoma

Michael L. Wang, Matthew J. Frigault, Salim Yazji, Yisrael Katz, James Robinson, James B. Breitmeyer, Matthew G. Mei, Caron A Jacobson

Check for updates

*Blood* (2023) 142 (Supplement 1): 4857.

**After birth ROR1 is predominantly expressed on malignant cells**; therefore, this selective expression pattern may reduce the risk of toxicities, including off-tumor target elimination and non-specific activation of immune cells. The ROR1 binding moiety for ONCT-808 is derived from zilovertamab.

# 1024 Adaptive Manufacturing of LV20.19 CAR T-Cells for Relapsed, Refractory Mantle Cell Lymphoma

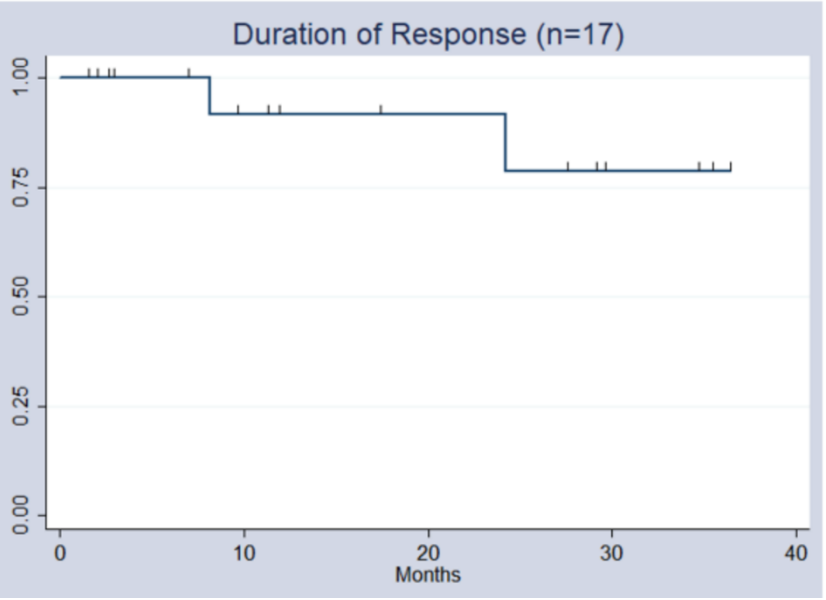



**Table 1: Clinical characteristics of MCL patients receiving LV20.19 CAR T-cells**

| | MCL patients (n=17) |
|---|---|
| Median Age, years | 63 (50-74) |
| Male % (n) | 88% (15) |
| Prior auto-HCT % (n) | 41% (7) |
| Prior allo-HCT % (n) | 12% (2) |
| BTKi exposed % (n) | 94% (16) |
| BTKi progressed % (n) | 76% (13) |
| Non-covalent BTKi progressed % (n) | 35% (6) |
| Median Prior Lines (including transplant) | 4 (3-8) |
| Complex Cytogenetics | 3 patients |
| p53 aberrations (not uniformly assessed) | 3 patients with p53 deletion<br>4 patients with p53 somatic mutation |

Dual targeted lentiviral **anti-CD20/anti-CD19** (LV20.19) CAR T-cells. **17 pts**. 28-Day **ORR: 100%. CR: 76%.**

Nirav Shah ASH 2023

# Unique Scenarios

| |
|---|
| CNS involvement |
| TP53 |

blood How I Treat

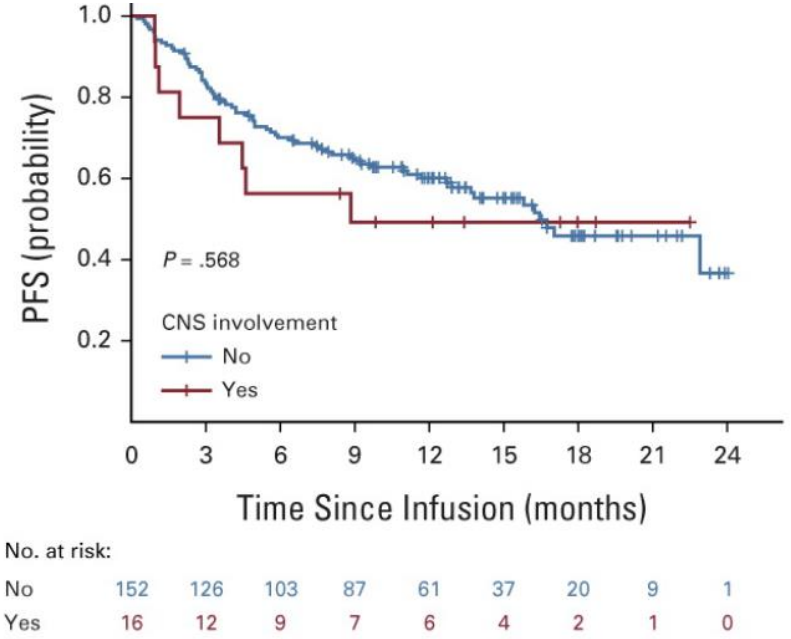
# How I treat secondary CNS involvement by aggressive lymphomas

Juan Pablo Alderuccio,[1,*] Lakshmi Nayak,[2,*] and Kate Cwynarski[3,*]

## Clinical case 5: MCL with isolated CNS relapse

lymphomas.[130,131] Clinical trials testing selective BTK degraders in CNS lymphomas are ongoing, and these compounds may represent an option for patients progressing with ibrutinib in the future. In MCL, similar to DLBCL, the ZUMA-2 trial led to the approval of brexucabtagene autoleucel, but patients with SCNSL were excluded.[132] The role of CAR T-cell therapy in this setting remains unclear; however, a postapproval study demonstrated a CR rate of 75% without shorter PFS or higher grade ≥3 neurotoxicity in 16 patients with SCNSL.[133]

**Clinical decision-making** For patients with SCNSL by MCL, we favor the use of ibrutinib over immunochemotherapy regimens. For those progressing with ibrutinib, enrollment to BTK degraders or CAR T-cell clinical trials emerge as an attractive option.




**Out of 168 Pts that received CAR, 16 had CNS involvement (10%).** Patients with CNS involvement **did not have higher** incidence of grade ≥ 3 **ICANS** and had a **CR of 75%** and a 12-month **PFS** rate of **60%**

Alderuccio Blood 2023

Wang JCO 2023

# 3505 Lisocabtagene Maraleucel (liso-cel) in Patients (Pts) with R/R MCL: Subgroup Analyses in Pts with High-Risk Disease Features from the MCL Cohort of the TRANSCEND NHL 001 Study

**7 (8%) pts had SCNSL**, of which 5 had refractory disease, 5 had Ki-67 ≥ 30%, and 1 each had TP53 mutation and blastoid morphology. Among the 7 pts with SCNSL, response rates were high (**ORR, 86%** [n = 6]; **CR, 71%** [n = 5]), and **3 of 5 pts who achieved CR were in an ongoing response** at data cutoff.

| | Overall (n = 83) | Ki-67 proliferation index | | *TP53* mutation | | Blastoid morphology | |
|---|---|---|---|---|---|---|---|
| | | ≥ 30% (n = 62) | < 30% (n = 14) | Yes (n = 19) | No (n = 32) | Yes (n = 27) | No (n = 45) |
| ORR, % (95% CI)[a] | 83 (73.3–90.5) | 85 (74.2–93.1) | 71 (41.9–91.6) | 89 (66.9–98.7) | 87.5 (71.0–96.5) | 70 (49.8–86.2) | 91 (78.8–97.5) |
| n | 69 | 53 | 10 | 17 | 28 | 19 | 41 |
| CR rate, % (95% CI)[a] | 72 (61.4–81.6) | 76 (63.3–85.8) | 57 (28.9–82.3) | 58 (33.5–79.7) | 84 (67.2–94.7) | 63 (42.4–80.6) | 82 (67.9–92.0) |
| n | 60 | 47 | 8 | 11 | 27 | 17 | 37 |
| DOR, mo | | | | | | | |
| Median (95% CI)[b] | 15.7 (6.2–24.0) | 15.7 (6.7–24.0) | NR (1.5–NR) | 6.2 (2.3–NR) | 9.7 (3.3–NR) | 11.3 (2.3–NR) | 15.8 (5.6–NR) |
| Median FU (95% CI)[c] | 22.8 (16.7–23.0) | 22.8 (16.6–23.0) | 22.6 (0.0–23.0) | 16.9 (10.9–22.9) | 22.6 (11.7–22.8) | 23.0 (16.2–23.3) | 17.1 (11.9–22.8) |
| PFS, mo | | | | | | | |
| Median (95% CI)[b] | 15.3 (6.6–24.9) | 15.3 (6.6–24.9) | 24.0 (2.4–NR)[d] | 7.4 (3.3–NR) | 16.6 (4.0–24.0) | 7.8 (3.1–NR) | 16.6 (6.5–NR) |
| Median FU (95% CI)[c] | 23.5 (17.7–23.8) | 18.2 (17.6–24.0) | 23.6 (2.6–24.0) | 18.0 (5.7–23.8) | 23.5 (12.4–24.0) | 23.5 (18.2–24.0) | 18.0 (12.4–24.0) |
| OS, mo | | | | | | | |
| Median (95% CI)[b] | 18.2 (12.9–36.3) | 18.2 (10.7–NR) | 13.5 (2.4–NR)[d] | 17.1 (6.6–NR) | 15.7 (8.3–36.3) | 12.9 (5.6–NR) | 20.7 (13.5–36.3) |
| Median FU (95% CI)[c] | 24.0 (23.7–24.2) | 23.8 (23.6–24.2) | 24.2 (8.4–35.8) | 23.7 (11.8–60.5) | 23.8 (23.6–24.2) | 24.2 (23.7–26.8) | 23.8 (18.1–24.0) |

**20 (23%) had a TP53 mutation present** and 34 (39%) did not (TP53 mutation was indeterminate in 4 [5%] pts and not reported in 30 [34%] pts). Pts with TP53 mutation had a **numerically lower median DOR, likely due to** a higher proportion of **responders achieving a PR** than CR; **however**, pts with TP53 who achieved CR had durable responses with **6 of 11 pts in an ongoing response** at data cutoff.

Palumbo ASH 2023

# TP53: AN EXCEPTION FOR 1L MCL (FIT)

blood

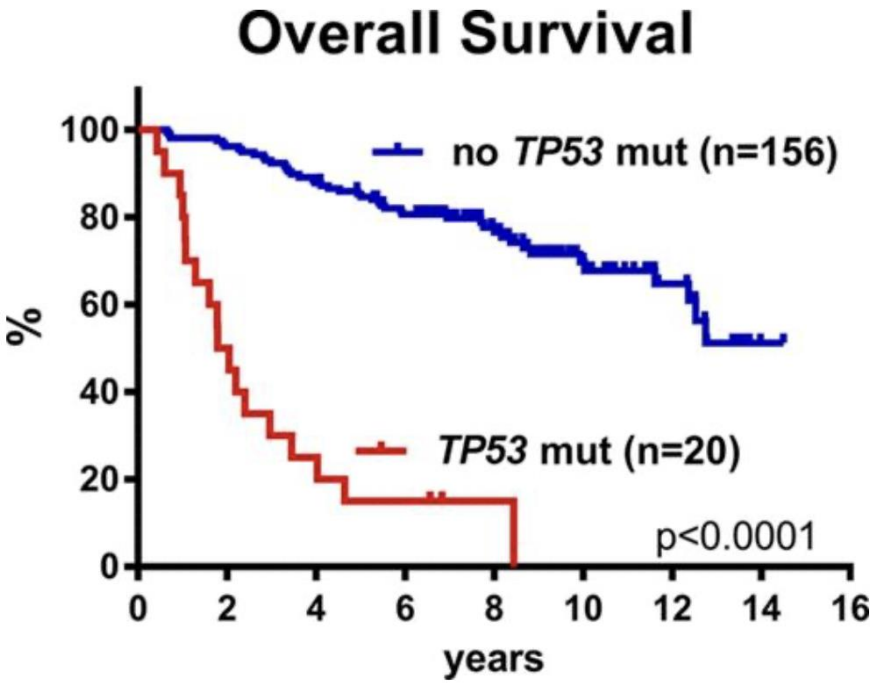
***TP53* mutations identify younger mantle cell lymphoma patients who do not benefit from intensive chemoimmunotherapy**

Christian W. Eskelund, Christina Dahl, Jakob W. Hansen, Maj Westman, Arne Kolstad,

- The intensified standard-of-care regimens for younger patients with MCL do not overcome the deleterious effects of *TP53* mutations.
- MCLs with *TP53* mutations should be considered for alternative frontline treatment.

OS 12.7 y vs 1.8 y (Consider trials!)

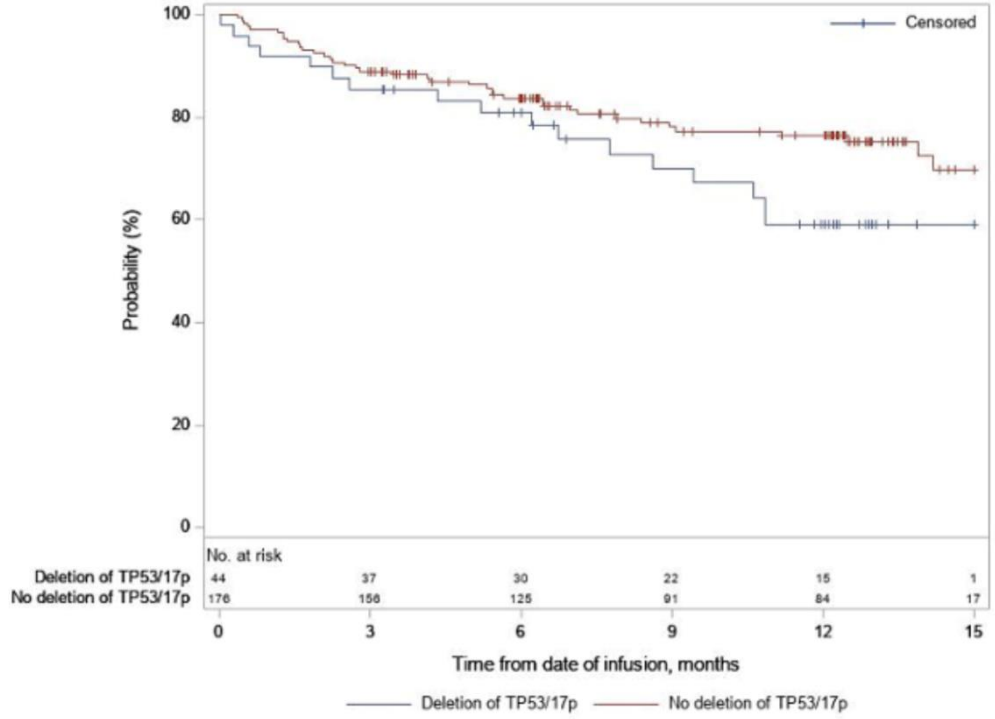
TP53 → NO SCT




Blood 2017

# 107 Real-World Outcomes of Brexucabtagene Autoleucel (Brexu-cel) for Relapsed or Refractory (R/R) Mantle Cell Lymphoma (MCL): A CIBMTR Subgroup Analysis of High-Risk Characteristics

Figure 1. Adjusted OS for patients receiving brexu-cel for R/R MCL by deletion of TP53/17p at diagnosis




Of the **446** pts, **20%** (44/220) had deletion of TP53/17p at diagnosis. **After multivariable adjustment**, all effectiveness and most safety **outcomes were consistent regardless** of deletion of TP53/17p. Deletion of TP53/17p **approached an association with decreased OS** (HR 1.79).

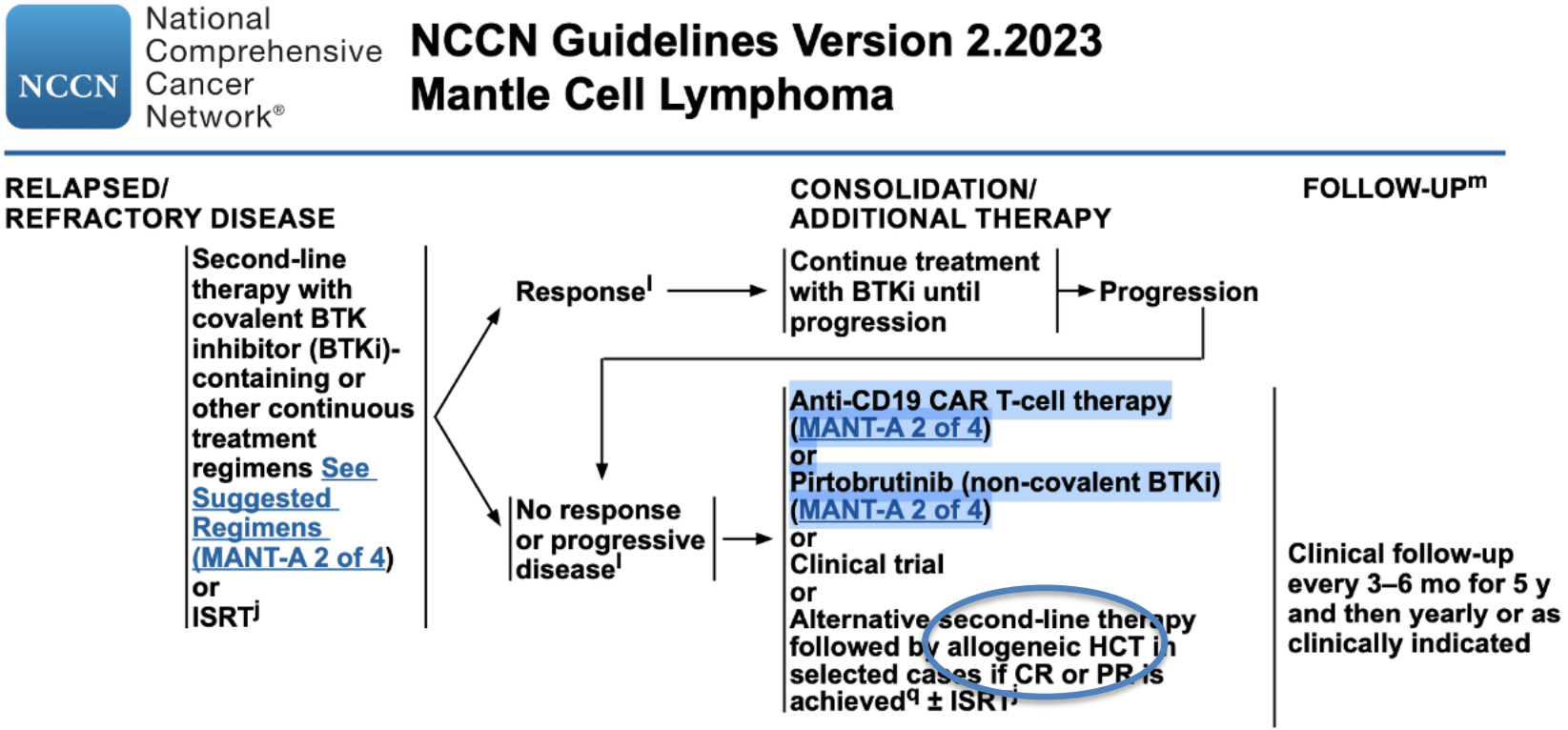
Conclusions: Although pts without deletion TP53/17p appeared to have longer OS, **the data further support brexu-cel as the standard of care across pts with R/R MCL, including those with high-risk features.**

Kambhampati ASH 2023

# Comparisons

| | |
|---|---|
| 5136 | CAR vs Pirtobrutinib |
| 3494 | CAR vs allo-SCT |

# CAR vs Pirto vs Allo-SCT

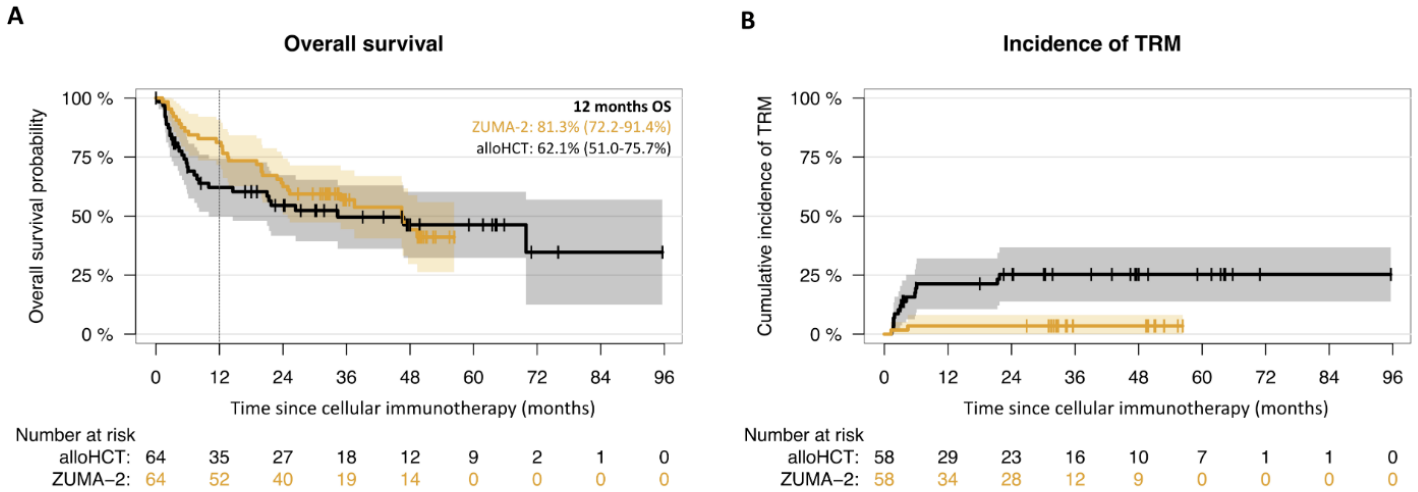


# 3494 A Propensity Score-Matched Analysis on the Outcomes of Brexucabtagene Autoleucel from Zuma-2 Study and Allogeneic Stem Cell Transplantation from the EBMT Database in Relapsed and Refractory Post-Btki Mantle Cell Lymphoma

## Conclusion

Brexu-cel is an effective treatment in pts with r/r MCL post-BTKi with a superior safety profile compared with alloSCT, as indicated by lower 12-month mortality, lower TRM, and absence of chronic GVHD-related morbidity. Despite efforts to match pts between the cohorts, the inherent limitations of this study, such as incongruent data sources and case selection bias, have to be considered. Additional analyses will be presented.

**Figure 1: (A) Overall survival and (B) cumulative incidence of treatment related mortality (TRM)**



# 5136 Matching-Adjusted Indirect Comparison (MAIC) of Brexucabtagene Autoleucel (Brexu-cel) and Pirtobrutinib in Patients with Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) Previously Treated with a Covalent Bruton Tyrosine Kinase Inhibitor (cBTKi)

**Table 2: Comparison of OS, PFS, and DOR between brexu-cel (ZUMA-2) and pirtobrutinib (BRUIN)**

| Outcome | Brexu-cel | | Pirtobrutinib | | Brexu-cel vs pirtobrutinib | |
|---|---|---|---|---|---|---|
| | N or ESS | Median (months) | N | Median (months) | Hazard ratio (95% CI) | *P* value |
| **Unadjusted (naïve) comparison** | | | | | | |
| OS | 68 | 46.4 | 90 | 23.5 | 0.68 (0.41-1.12) | 0.13 |
| PFS | 68 | 25.8 | 90 | 6.9 | **0.48 (0.31-0.75)** | <0.01 |
| DOR | 62 | 28.2 | 51 | 17.6 | 0.67 (0.38-1.17) | 0.16 |
| **MAIC: Base case model with 5 variables** | | | | | | |
| OS | 41.7 | 46.6 | 90 | 23.5 | 0.65 (0.37-1.14) | 0.13 |
| PFS | 41.7 | 29.3 | 90 | 6.9 | **0.45 (0.27-0.77)** | <0.01 |
| DOR | 37.7 | 36.5 | 51 | 17.6 | 0.62 (0.33-1.19) | 0.15 |
| **MAIC: Sensitivity analysis model with 7 variables** | | | | | | |
| OS | 17.0 | 58.5 | 90 | 23.5 | 0.54 (0.25-1.18) | 0.12 |
| PFS | 17.0 | 29.3 | 90 | 6.9 | **0.43 (0.21-0.87)** | 0.02 |
| DOR | 15.8 | 28.2 | 51 | 17.6 | 0.62 (0.27-1.43) | 0.26 |

***Notes:*** *All bolded hazard ratio values are statistically meaningful at the 0.05 significance level.* ***Abbreviations:*** *CI, confidence interval; DOR, duration of response; ESS, effective sample size; MAIC, matching-adjusted indirect comparison; N, sample size; OS, overall survival; PFS, progression-free survival.*

**Conclusions:** While acknowledging the inherent limitations of an unanchored indirect comparison, our findings suggest that brexu-cel offers clinically and statistically significant efficacy benefits in terms of ORR, CR, and PFS compared to pirtobrutinib in patients with R/R MCL after prior cBTKi therapy. Both treatments were not statistically different in terms of OS and DOR although the estimated hazard ratios indicated a favorable trend for brexu-cel; however, given the relatively shorter follow-up and the high degree of censoring in BRUIN, an updated analysis incorporating longer follow-up data with more events from BRUIN

Chen ASH 2023

# Which choices set you up for CAR success?

| 1L |
| --- |
| Bridging |
| Lymphodepletion |
| Consolidation |

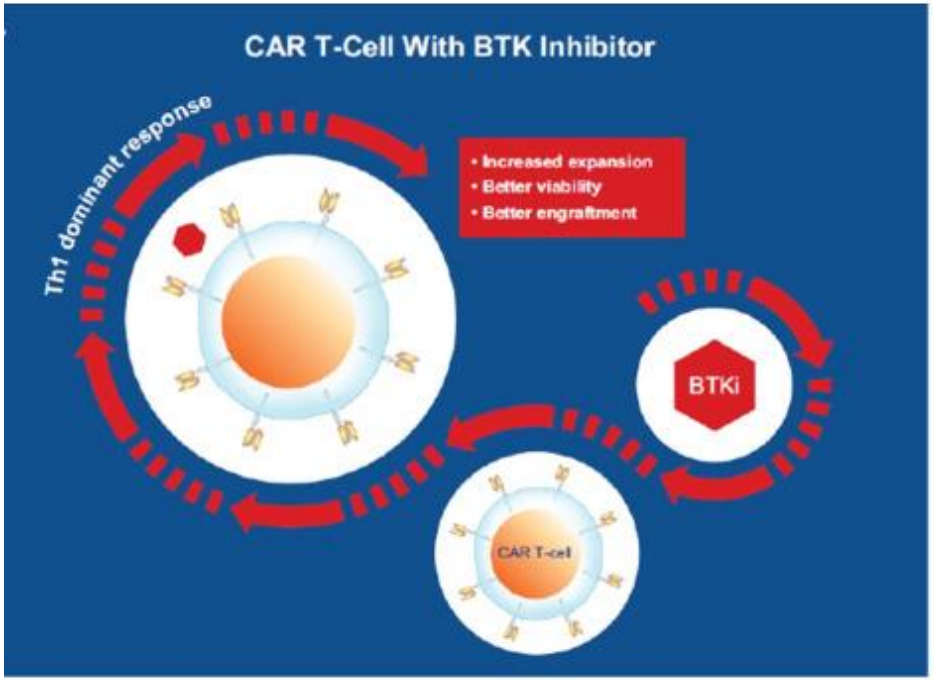
Improve **depth** of response

Improve DOR, PFS and **OS**

Improve **tolerability** of treatments

# BTKi and CAR T-Cell — Finding a Dancing Partner

A. Potential benefit of BTK inhibitors on CAR T-cell efficacy




Munoz, Wang, Jain, Wang. Curr Oncol Rep. 2022; 24(10): 1299–1311.

# In Summary

| | |
|---|---|
| NEJM 2020 | Brexu-cel Initial approval |
| JCO 2022 | Brexu-cel 3-year follow-up |
| JCO 2023 | Brexu-cel RWE |
| ASH 2023 | Liso-cel for MCL cohort |
| ASH 2023 | Other targets: CD19/20, ROR1 |

It is an exciting time for patients with MCL!

# QUESTIONS & DISCUSSION

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**Thank you!**

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