# Three-Year Follow-up of Outcomes With KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma in ZUMA-2

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# BACKGROUND

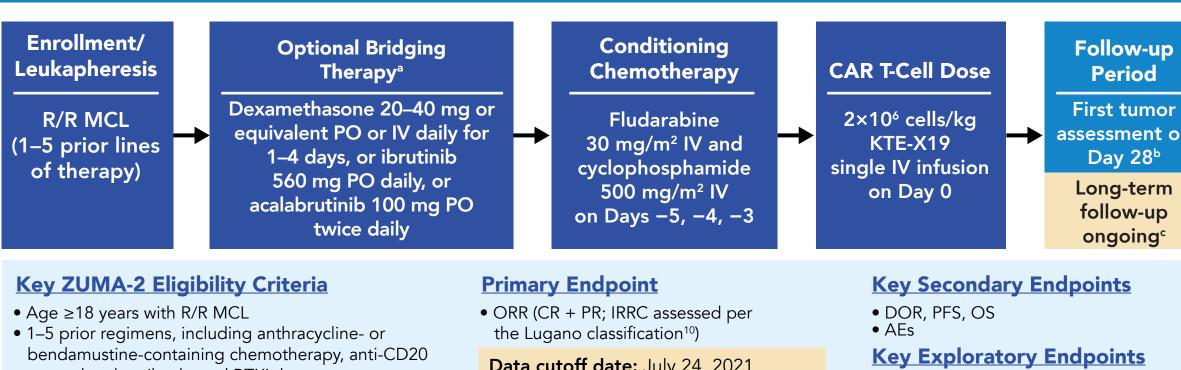
- Relapsed/refractory (R/R) mantle cell lymphoma (MCL) remains an area of high unmet need despite the availability of novel therapies, with low median overall survival (OS; 2.5–14.2 months) in patients who discontinue Bruton tyrosine kinase inhibitors (BTKis)<sup>1-5</sup>
- KTE-X19 (brexucabtagene autoleucel), an autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, is approved in the United States for the treatment of adults with R/R MCL and adults with R/R B-cell acute lymphoblastic leukemia and is approved in the European Union for the treatment of adults with R/R MCL after ≥2 prior treatments including a BTKi<sup>6,7</sup>
- ZUMA-2 (NCT02601313) is a pivotal, single-arm, multicenter, Phase 2 study of KTE-X19 in patients with heavily pretreated MCL who were R/R to a median of 3 prior therapies, including a BTKi<sup>8</sup>
- After a median follow-up of 17.5 months, overall response rate (ORR) in the first 60 efficacy-evaluable patients from ZUMA-2 was 92%, with a complete response (CR) rate of 67%<sup>9</sup>

# **OBJECTIVES**

- To present updated safety and efficacy outcomes in all-treated patients (N=68) after 2 years of additional follow-up since the primary analysis in the ZUMA-2 study of KTE-X19 in R/R MCL
- To present results from an exploratory post hoc assessment of patients previously treated with bendamustine • To present an exploratory analysis of minimal residual disease (MRD) status in relation to efficacy outcomes

# **METHODS**

#### Figure 1. ZUMA-2 Phase 2 Study Design<sup>8</sup>



bendamustine-containing chemotherapy, anti-CD2 Data cutoff date: July 24, 2021 monoclonal antibody, and BTKi therapy Median follow-up time: 35.6 months (range, 25.9–56.3)

<sup>a</sup> Administered after leukapheresis and completed ≥5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging. <sup>b</sup> Bone marrow biopsy was to be done at screening and, if positive, not done, or indeterminate, a biopsy was needed to confirm CR. c After 3 months, only targeted AEs (neurological, hematological, infections, GVHD, autoimmune disorders, and secondary d reported for 15 years after the initial anti-CD19 CAR T-cell infusion or until disease progression or initiation of subsequent anticancer therapy, whichever occurs first AE. adverse event: BTKi, Bruton tyrosine kinase inhibitor; CAR, chimeric antigen receptor; CR, complete response; DOR, duration of response; GVHD, graft-versus-host disease; IRRC, independent radiology review committee; IV, intravenous; KTE-X19, brexucabtagene autoleucel; MCL, mantle cell lymphoma; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PET-CT, positron emission tomography–computed tomography; PFS, progression-free survival; PO, orally; PR, partial response; R/R, relapsed/refractory.

MRD

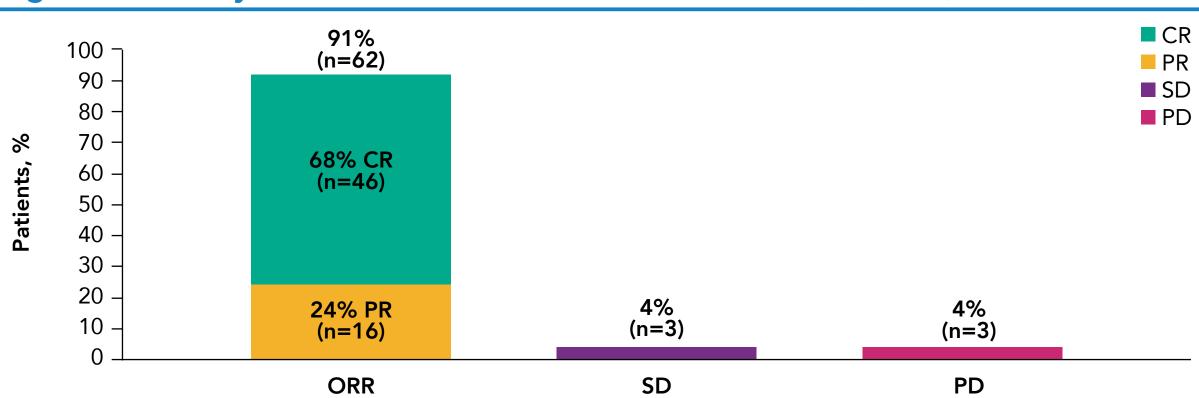
• Prior bendamustine

- Updated efficacy and safety outcomes are reported for all 68 patients treated with KTE-X19 (2×10<sup>6</sup> CAR T cells/kg)
- The intention-to-treat (ITT) population comprised all enrolled (leukapheresed) patients (N=74) • MRD was assessed as an exploratory endpoint in patients with available samples at Months 1, 3, and 6 using nextgeneration sequencing with a sensitivity of 1 in 100,000 cells<sup>8</sup>
- Based on observations that bendamustine-containing treatments may be associated with reduced T-cell number and function, potentially impacting cellular therapies,<sup>11</sup> an exploratory post hoc analysis, including propensity score matching, examined the impact of timing of prior bendamustine exposure

## RESULTS

- As of July 24, 2021 (data cutoff), the median follow-up time was 35.6 months (range, 25.9–56.3)
- As previously reported, 74 patients were enrolled and leukapheresed<sup>8</sup>
- KTE-X19 was successfully manufactured for 71 patients (96%) and administered to 68 (92%)<sup>8</sup>
- Baseline characteristics for the all-treated and ITT populations have been reported; high-risk features were common<sup>8</sup>





#### All-Treated Patients<sup>a</sup> (N=68)

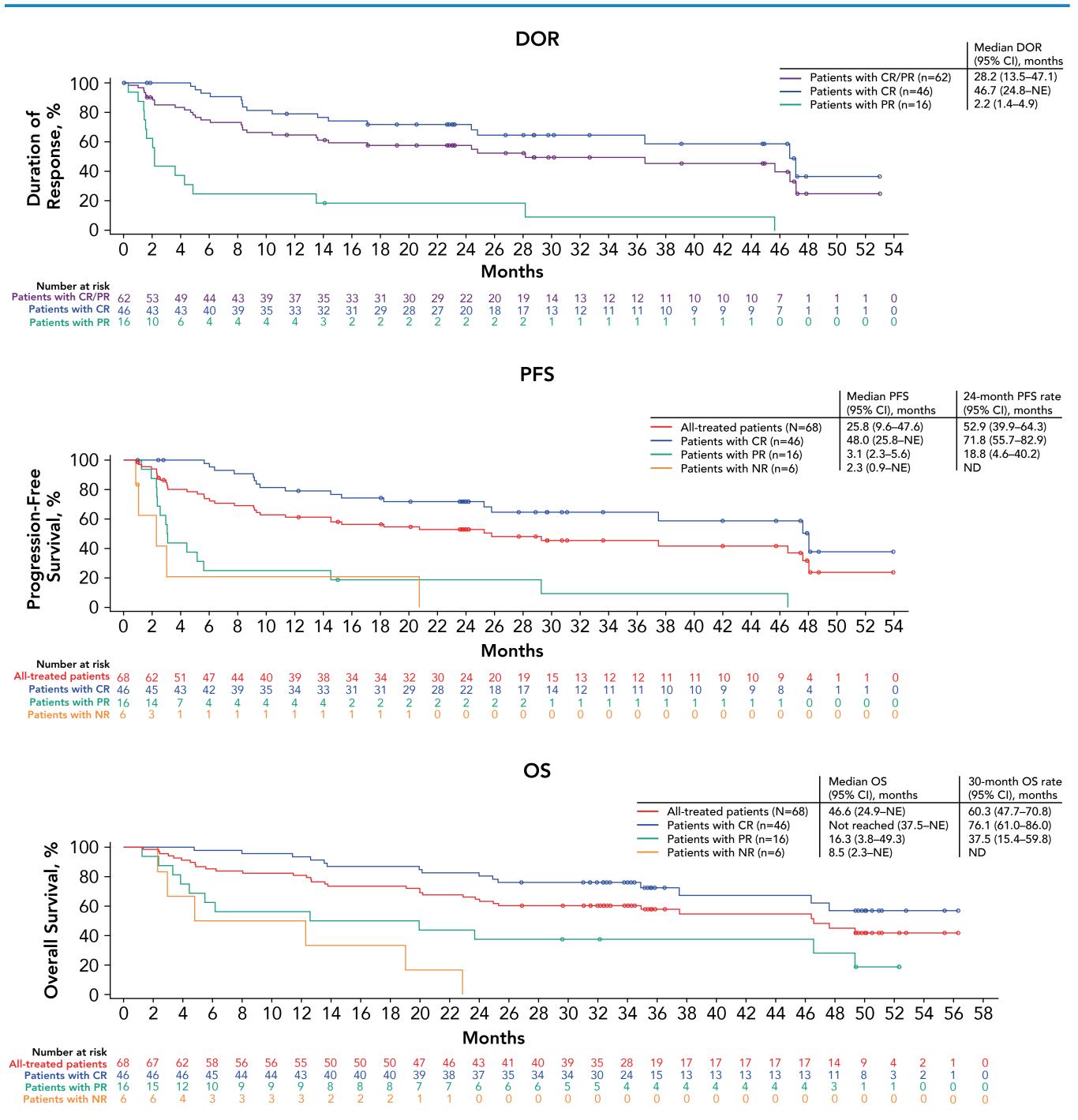
Assessed by an IRRC according to the Lugano Classification.<sup>10</sup> <sup>a</sup> Since the previous report,<sup>9</sup> IRRC review determined that 1 patient who was previously reported as best response of PR had no disease at baseline; this patient is reported as PD in the current report. CR, complete response; IRRC, independent radiology review committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

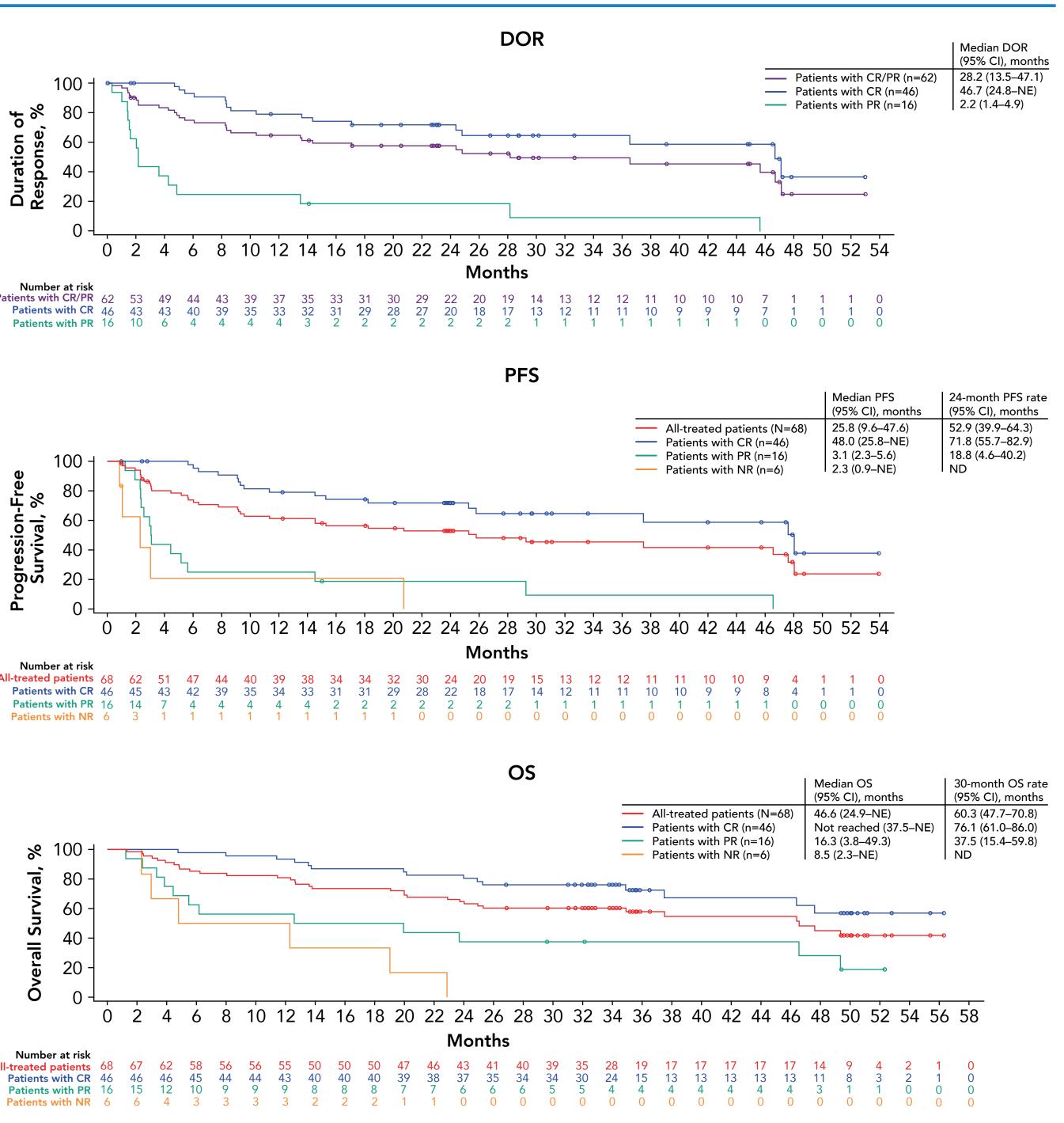
• After 35.6 months median follow-up (range, 25.9–56.3), the ORR (CR + partial response [PR]) was 91% (95% CI,

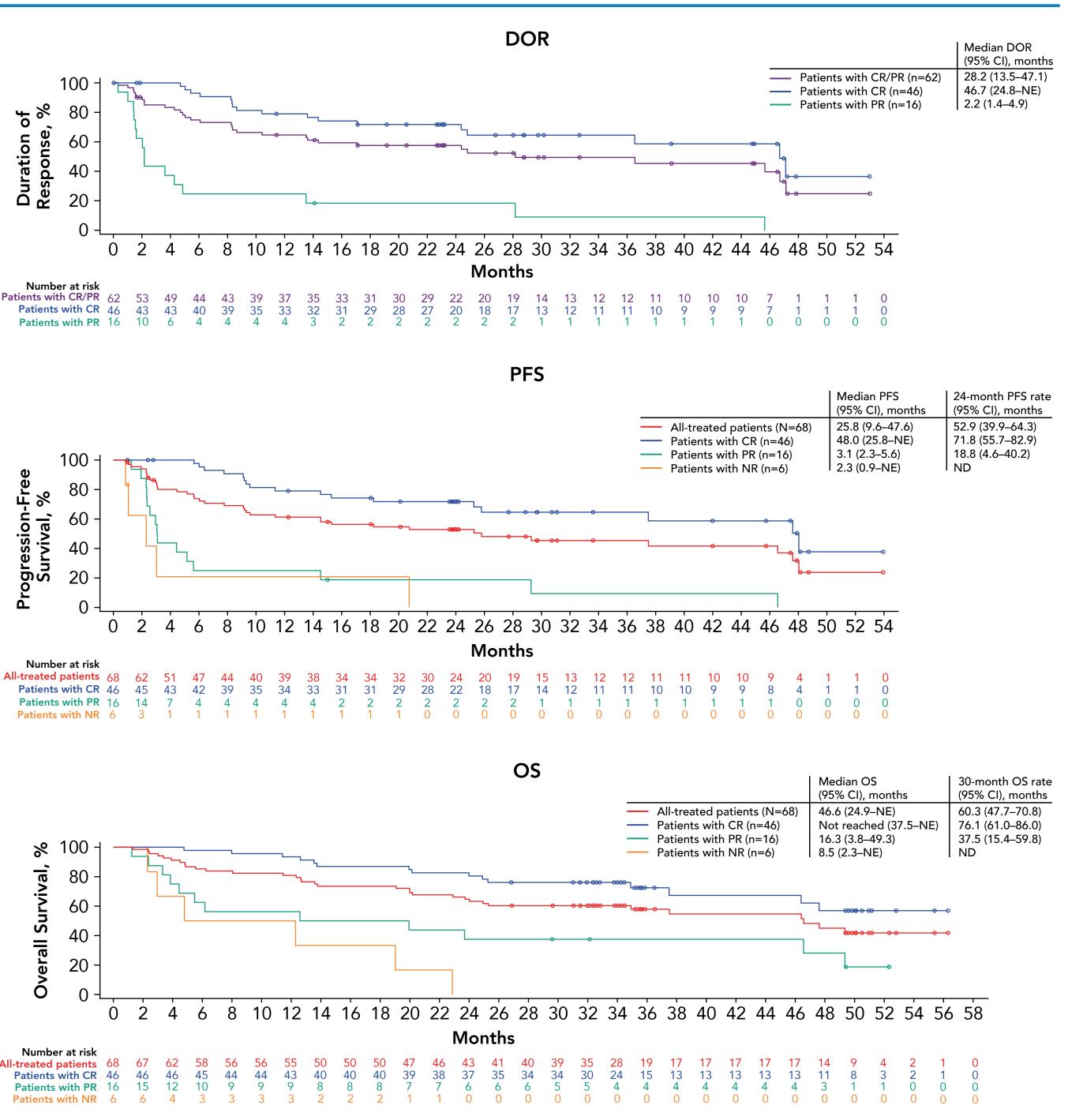
- 81.8–96.7), with a 68% CR rate (95% CI, 55.2–78.5) in all-treated patients (**Figure 2**)
- In the ITT population, ORR was 84% (95% CI, 73.4–91.3), with a 62% CR rate (95% CI, 50.1–73.2)

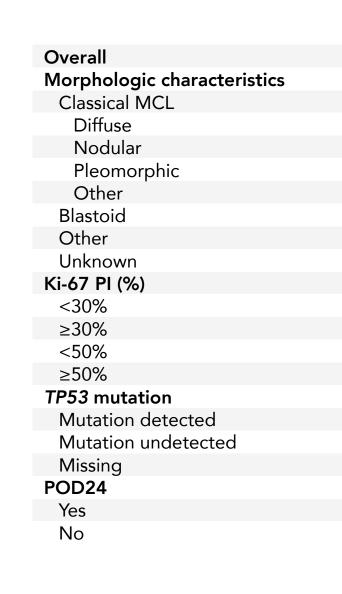
# **RESULTS** (Continued)

Patients (N=68)









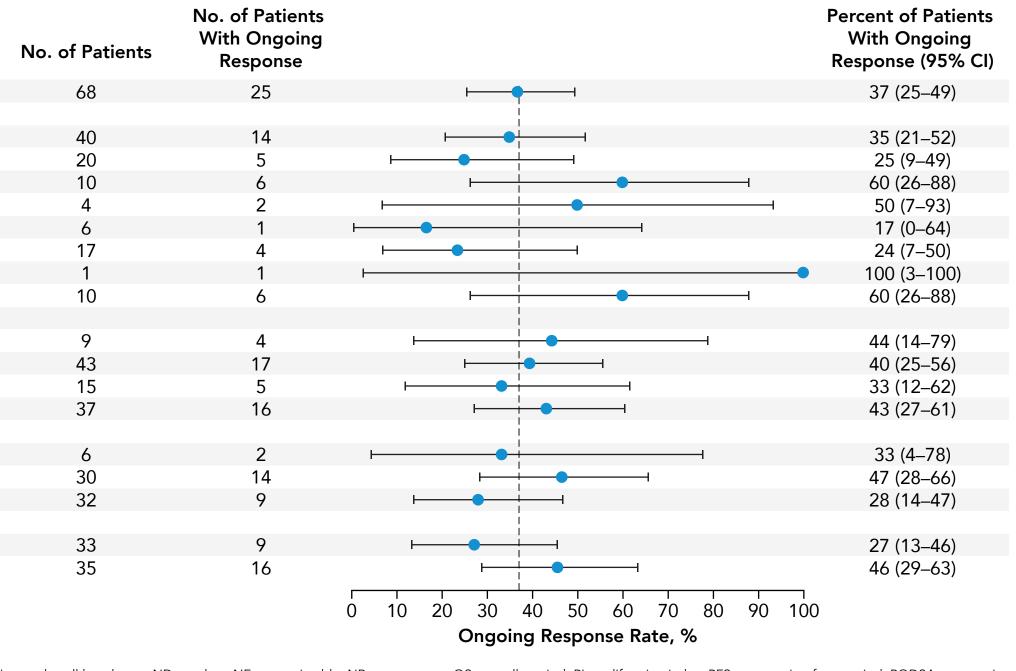
CR, complete response; DOR, duration of response; MCL, mantle cell lymphoma; ND, no data; NE, not estimable; NR, no response; OS, overall survival; PI, proliferation index; PFS, progression-free survival; POD24, progression of disease within 2 years; PR, partial response

- 60.3%; **Figure 3**)

- rate, 49%; 30-month OS rate, 56%)

#### Figure 3. DOR, PFS, OS, and Subgroup Analysis of Ongoing Response in All-Treated





• Median OS among treated patients was 46.6 months and was not reached among those who achieved CR (30-month OS rate was

• At data cutoff, 25 of 68 treated patients (37%) were still in ongoing response (all CR)

- Ongoing responses were consistent among prespecified subgroups by high-risk disease characteristics (**Figure 3**)

• Late relapse >24 months post-infusion was infrequent (n=3 patients)

• In the ITT population, median progression-free survival (PFS) was 24.0 months and median OS was 47.4 months (24-month PFS)

### Table 1. Overall AEs and AEs Occurring Since the Primary Analysis Report<sup>8</sup>

	All-Treated Patients (N=68)								
		AEs Occurring Since the Primary Analysis Report							
	Overall Any Grade AEs Occurring Since Infusion	Any Grade	Grade 3	Grade 4	Grade 5				
AEs, n (%) Any Any KTE-X19 related	68 (100) 66 (97)	18 (26) 9 (13)	4 (6) 2 (3)	7 (10) 6 (9)	3 (4) 0				
Serious AEs, n (%) Any Serious KTE-X19 related	48 (71) 37 (54)	8 (12) 2 (3)	4 (6) 2 (3)	0 0	3 (4) 0				
CRS or neurologic events, n (%) CRSª Neurologic events Serious neurologic event	63 (93) 62 (91) 43 (63) 22 (32)	2 (3) 0 2 (3) 1 (1)	1 (1) O 1 (1) <sup>b</sup> 1 (1) <sup>b</sup>	0 0 0 0	0 0 0 0				
Cytopenias, n (%) Thrombocytopenia Neutropenia Anemia	50 (74) 59 (87) 47 (69)	2 (3) 8 (12) 3 (4)	0 1 (1) 2 (3)	2 (3) 7 (10) 0	0 0 0				
Infection, n (%) Any Serious COVID-19–associated viral Non–COVID-19 associated viral	36 (53) 21 (31) 0 11 (16)	7 (10) 4 (6) 0 3 (4)	3 (4) 3 (4) 0 1 (1)	0 0 0 0	1 (1) 1 (1) 0 0				
Hypogammaglobulinemia, n (%)	14 (21)	1 (1)	0	0	0				
Tumor lysis syndrome, n (%)	1 (1)	0	0	0	0				

Data cutoff for the primary analysis was July 19, 2019 (median follow-up was 12.3 months)<sup>8</sup>; data cutoff for the present analysis was July 24, 2021. Numbers (percentage) of patients with worst grade of AE are shown; AEs occurring after retreatment are not included. <sup>a</sup> CRS events were graded per revised Lee et al. 2014 grading system<sup>12</sup>; all other AEs were graded per Common Terminology Criteria for Adverse Events version 4.03. <sup>b</sup> This serious neurologic event of encephalopathy began on day 397; the event resolved on day 408 and was considered unrelated to KTE-X19. AE, adverse event; CRS, cytokine release syndrome; KTE-X19, brexucabtagene autoleucel.

• No new safety signals were observed with longer follow-up

- Since the time of the primary analysis report<sup>8</sup>
- Only 3% of all adverse events (AEs) of interest on study occurred since the primary analysis - Grade  $\geq$ 3 serious AEs occurred in 7 patients (10%; **Table 1**)

- respectively)

#### Table 2. Efficacy and Durability Outcomes in Patients by MRD Status

	N	ORR, n (%)	CR, n (%)	PR, n (%)	SD, n (%)	PD, n (%)	mDOR, mo (95% Cl) [n]	mPFS, mo (95% Cl) [n]	mOS, mo (95% Cl) [n]
MRD status at Month 6									
Positive	4	3 (75)	2 (50)	1 (25)	0 (0)	1 (25)	6.1 (5.4–NE) [3]	7.1 (0.9–NE) [4]	27.0 (13.5–NE) [4]
Negative	15	15 (100)	14 (93)	1 (7)	0	0	NR (10.4–NE) [15]	NR (11.3–NE) [15]	NR (46.4–NE) [15]

IRRC review determined that one patient who was previously reported as best response of PR had no disease at baseline; this patient is reported as PD in the current report. CR, complete response; IRRC, independent radiology review committee; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; mo, month; MRD, minimal residual disease; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

- At Month 6, there were 19 MRD-assessable patients (**Table 2**) - Of the 15 MRD-negative patients (79%), the ORR was 100%
- medians not yet reached

• One patient had serious Grade 3 encephalopathy (13.0 months post-infusion) that was considered unrelated to KTE-X19 • Two patients had KTE-X19-related serious AEs: 1 patient with Grade 3 pneumonia and Grade 3 upper respiratory tract infection, and 1 with Grade 3 influenza, indicating that infectious disease may have been observed with longer follow-up There were 3 new Grade 5 AEs (none considered related to KTE-X19): salmonella bacteremia (24.9 months post-infusion) and 2 secondary malignancies (myelodysplastic syndrome and acute myeloid leukemia; 25.2 and 37.5 months post-infusion,

• There were no secondary malignancies or replication-competent retrovirus cases related to KTE-X19 at any time on study

• At data cutoff, 60% of MRD-negative patients remained in ongoing response, with duration of response (DOR), PFS, and OS

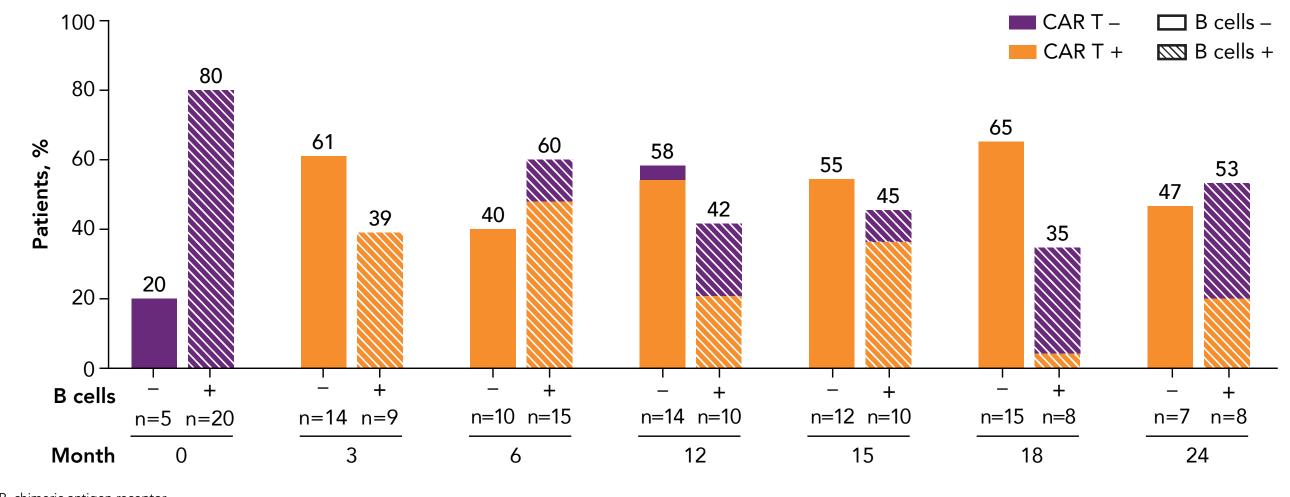
### Figure 4. MRD Detection at 3 and 6 Months Predicts Relapse CAR T+ Month 1 Month 3 Month Month 1 Month 3 Month 6 (n=22) (n=14) (n=13)n=60 (n=49) **ROC Curve for Model (Monta** ROC Curve for Model (Month ( AUC=0.6667 0.50 -0.50-0.50 0.00 0.25 0.50 0.75 1 0.00 0.25 0.50 0.75 1.00 Specificit Specificity

• MRD-negative status at Months 1, 3, and 6 was associated with durable response, with 55%, 71%, and 69% of MRD-negative patients at those timepoints remaining in ongoing CR at data cutoff (median follow-up, 35.6 months; **Figure 4**)

AUC, area under the curve; CAR, chimeric antigen receptor; MRD, minimal residual disease; ROC, receiver operating characteristics.

• Receiver operating characteristic curves of true-positive (sensitivity) versus false-positive (specificity) rates were analyzed for MRD predictability of relapse and nonresponse (**Figure 4**) - Analysis of MRD at Months 3 and 6 was found to be predictive of relapse potential (AUC 0.80 and 0.75, respectively)

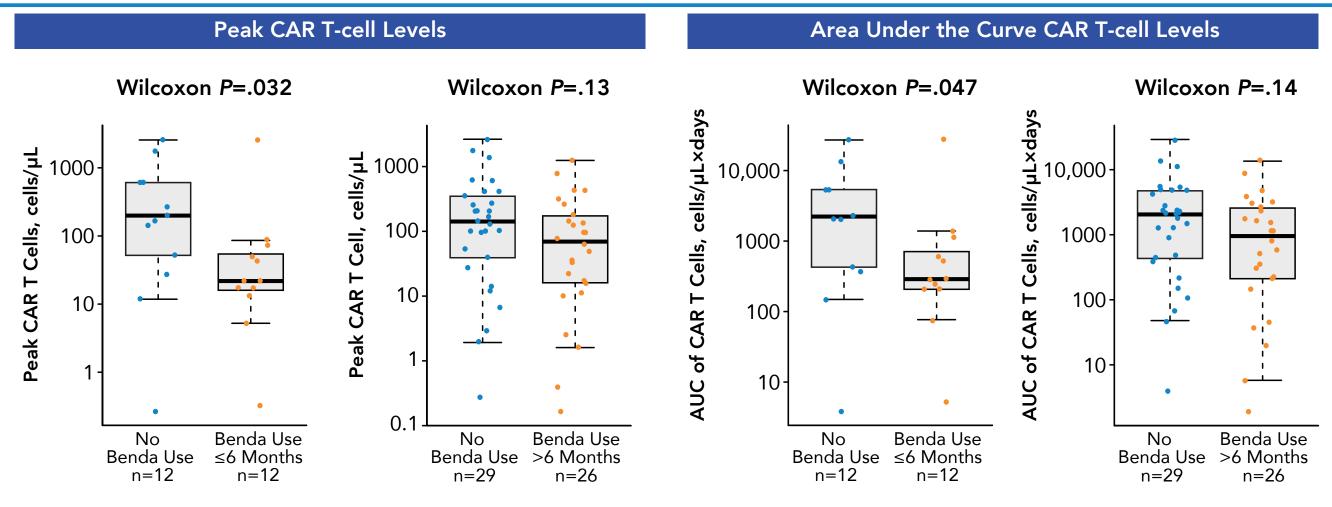




CAR, chimeric antigen receptor.

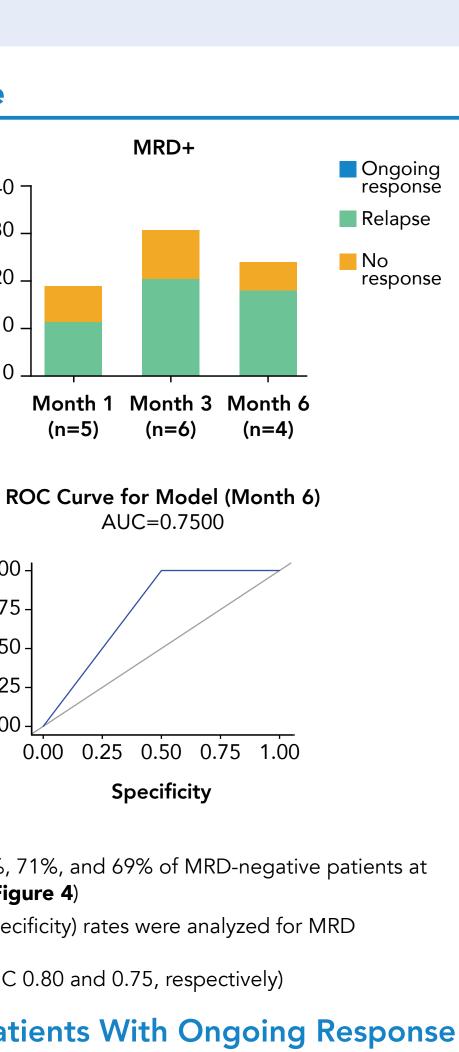
• Among evaluable patients in ongoing response at Months 18 and 24, B cells were detectable in 35% and 53%, and gene-marked CAR T cells were detectable in 70% and 67%, respectively (**Figure 5**)

#### Figure 6. Comparison of Pharmacokinetics of Patients With and Without Prior Bendamustine Exposure



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

- Over half of treated patients in ZUMA-2 (n=37 [54%]) received prior bendamustine<sup>9</sup> and strong outcomes continue to be observed in the ZUMA-2 patient population - Median time from last bendamustine exposure to KTE-X19 infusion was 20.9 months (range, 1.0–70.3)
- An exploratory analysis in all evaluable patients estimated the impact of timing of bendamustine (≤6 months and >6 months before CAR T-cell infusion) on outcomes and product attributes (**Figure 6**)
- Peak and AUC CAR T-cell levels were significantly lower in patients with prior bendamustine use within 6 months of CAR T-cell infusion, compared with levels in patients with no prior bendamustine use. Results were consistent when analyzed using propensity score matching
- The observations from this small exploratory post hoc analysis may indicate that patients being treated with KTE-X19 could benefit from longer time spans between prior bendamustine and cell therapy, though further analyses are warranted



# CONCLUSIONS

- These 3-year ZUMA-2 follow-up data demonstrate that a single infusion of KTE-X19 resulted in high rates of durable responses in R/R MCL
- Median DOR was 28.2 months; median OS was 46.6 months and was not reached among those who achieved CR
- Long-term safety was manageable, with only 3% of AEs of interest occurring during this longer follow-up, few late-onset events, and no new CRS
- DOR, PFS, and OS were not reached in patients with MRD-negativity at 6 months, suggesting MRD-negativity may predict for a longer response duration, although sample size of this exploratory analysis was limited and further investigation is warranted
- Results of an exploratory post hoc analysis suggest that bendamustine use shortly before leukapheresis requires careful consideration due to its potential effects on patient T-cell fitness and CAR T-cell expansion
- Although a majority of patients (54%) in the overall ZUMA-2 population had prior bendamustine, it may be advantageous to consider administering the potentially curative therapy KTE-X19 after an extended period following bendamustine exposure, in order to obtain a quality immune response and maximize the benefit of KTE-X19
- Collectively, these findings confirm the durable benefits of KTE-X19 and support future investigations of CD19-directed CAR T-cell therapy in patients with high-risk MCL in earlier treatment lines
- Additional studies aimed at understanding mechanisms of relapse are ongoing

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### DISCLOSURES

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