Tecartus® (brexucabtagene autoleucel)
Long-term Follow-up of the ZUMA-2 Study

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Summary

ZUMA-2 Study[1]

- ZUMA-2 was a Phase 2, single-arm, open-label, multicenter study assessing the safety and efficacy of Tecartus in adults with mantle cell lymphoma (MCL) who relapsed or were refractory to ≤5 prior therapies, including Bruton's tyrosine kinase inhibitor (BTKi) therapy (ibrutinib or acalabrutinib).
- The primary endpoint was the objective response rate (ORR) as assessed by an independent radiology review committee (IRRC). Duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, blood CAR T-cell levels, and serum cytokine levels were assessed as secondary endpoints.

Three-Year Follow-up Analysis[2]

- In the 3-year follow-up analysis in Cohort 1 (July 24, 2021 data cutoff date; median follow-up of 35.6 months), the IRRC-assessed ORR was 91%, with a 68% complete response (CR) rate.
- Subgroup analysis were performed for high-risk disease characteristics subgroups and found that ORRs were generally consistent.

Five-Year Follow-up Analysis[3]

- In the 5-year follow-up analysis in Cohort 2 (April 1, 2024 data cutoff date; median follow-up of 72.3 months), the IRRC-assessed ORR was 93%, with a 64% CR rate.
- No new safety signals were reported in either the 3-year and 5-year analysis. Grade ≥3 treatment-emergent adverse events (TEAEs) reported in >40% of patients in the 5-year analysis were neutrophil count decreased (53%), anemia (51%), and white blood cell (WBC) count decreased (41%) in Cohort 1 and hypotension (57%), white blood cell count decreased (50%), neutrophil count decreased (43%), and anemia (43%) in Cohort 2.
- There were no deaths due to cytokine release syndrome (CRS) or neurologic events, and no cases of secondary T-cell cancers.

Long-term Follow-up

Background

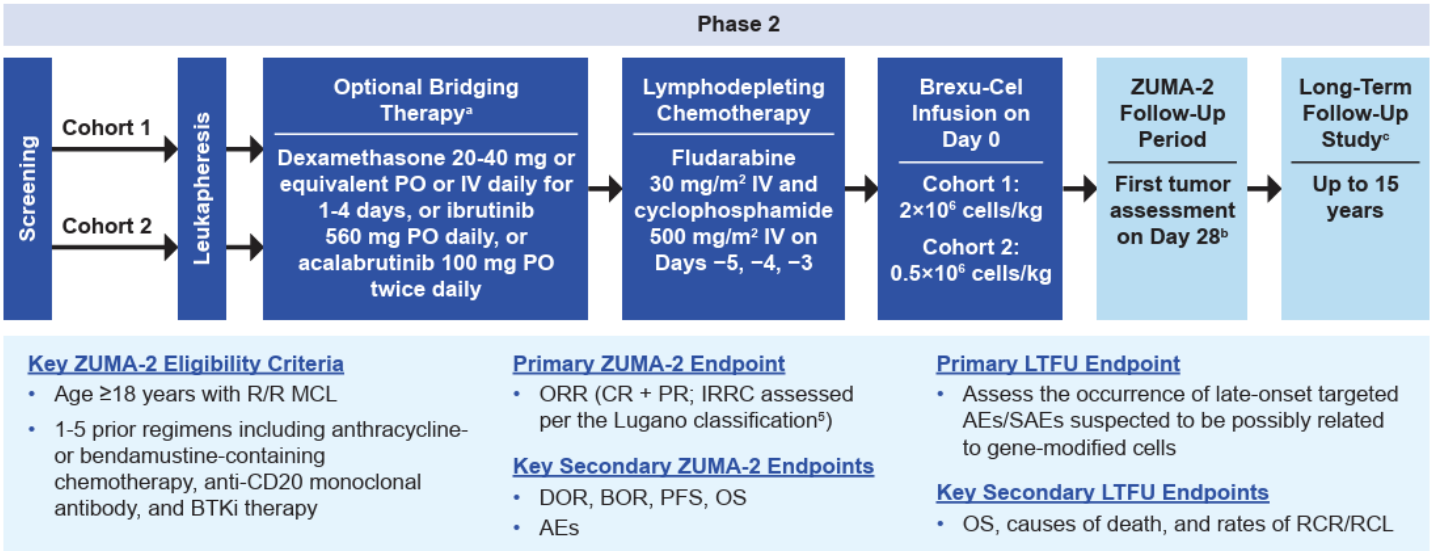
ZUMA-2 is a Phase 2, single-arm, open-label, registrational, multicenter, global study assessing the safety and efficacy of Tecartus, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in patients with MCL who relapsed or were refractory to ≤5 prior therapies, including BTKi therapy (ibrutinib or acalabrutinib).[1] Patients underwent leukapheresis and optional bridging therapy, followed by conditioning chemotherapy and a single infusion of Tecartus 2×10^6 CAR T-cells/kg in Cohort 1 (pivotal), or brexucabtagene autoleucel (brexu-cel) 0.5×10^6 CAR T-cells/kg in Cohort 2.[1,3] Per the US Prescribing Information, the approved dose of Tecartus is 2×10^6 CAR T-cells/kg body weight.[4]

The dose administered to Cohort 1 was deemed optimal based on the ratio of risk to benefit before full enrollment in Cohort 2 was attained; therefore, efficacy analyses were performed with a modified intent-to-treat approach in Cohort 2.[3]

The primary endpoint was the ORR as assessed by IRRC per the Lugano classification. Secondary endpoints included DOR, PFS, OS, safety, blood CAR T-cell levels, and serum cytokine levels.[1]

A 5-year follow-up analysis assessed a primary endpoint of late-onset targeted adverse events (AEs) and serious AEs (SAEs) suspected of having a potential relationship to gene-modified cells, with secondary endpoints including OS, causes of any deaths, and rates of replication-competent lentivirus and replication-competent retrovirus.[3]

Figure 1. ZUMA-2 Long-Term Follow-Up Study Design[3]



[a] Administered after leukapheresis and completed ≥5 days before initiating conditioning chemotherapy; PET-CT was required post-bridging. [b] 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 study completion of ZUMA-2, patients were offered an opportunity to transition to a separate LTFU study, KT-US-982-5968, where they were and will continue to be monitored for occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to Tecartus for up to 15 years from the time of Tecartus infusion.
AE=adverse event; BOR=best objective response; BTKi=Bruton tyrosine kinase inhibitor; CR=complete response; DOR=duration of response; IRRC=independent radiology review committee; IV=intravenous; LTFU=long-term follow-up; MCL=mantle cell lymphoma; ORR=objective response rate; OS=overall survival; PET-CT=positron emission tomography–

computed tomography; PFS=progression-free survival; PO=orally; PR=partial response; RCL=replication-competent lentivirus; RCR=replication-competent retrovirus; R/R=relapsed/refractory; SAE=serious adverse event.

This response describes the results from the long-term follow-up analyses of the ZUMA-2 study.[2,3]

Efficacy

Of 74 patients enrolled in Cohort 1, Tecartus was successfully manufactured for 71 (96%) and administered to 68 (92%), and the median duration from leukapheresis to delivery of Tecartus to the trial site was 16 days.[1]

The median follow-up (as of the July 24, 2019 data cutoff date) was 12.3 months (range, 7.0–32.3) for the 60 efficacy evaluable patients treated with Tecartus in the primary analysis.[1]

For the 68 patients treated with Tecartus in Cohort 1, the median follow-up was 35.6 months (range, 25.9 – 56.3) in the 3-year follow-up analysis (July 24, 2021 data cutoff date) and 67.8 months (range, 58.2 – 88.6) in the 5-year follow-up analysis (April 1, 2024 data cutoff date).[2,3]

For the 14 patients treated with brexu-cel in Cohort 2, the median follow-up in the 5-year follow-up analysis was 72.3 months (range, 70.1–74.3).[3]

ORR

In the primary efficacy analysis in Cohort 1, the IRRC-assessed ORR was 93% (95% confidence interval [CI], 84–98), with a 67% (95% CI, 53–78) rate of CR.[1]

In the 3-year analysis of Cohort 1 all-treated population, the IRRC-assessed ORR was 91% (95% CI, 81.8–96.7), with a 68% complete response (CR) rate (95% CI, 55.2–78.5). Twenty-five patients who initially achieved a partial response (PR) or had stable disease converted to CR a median of 2.3 months after initial response.[2]

In the intent-to-treat (ITT) population (comprised all enrolled [leukapheresed] patients) in Cohort 1 (n=74) in the primary analysis, the ORR was 85%, with a 59% rate of CR.[1] At the 3-year analysis, the ORR was 84% (95% CI, 73.4–91.3) in the ITT population, including a CR rate of 62% (95% CI, 50.1–73.2) and a PR rate of 22% (95% CI, 12.9–32.7).[2]

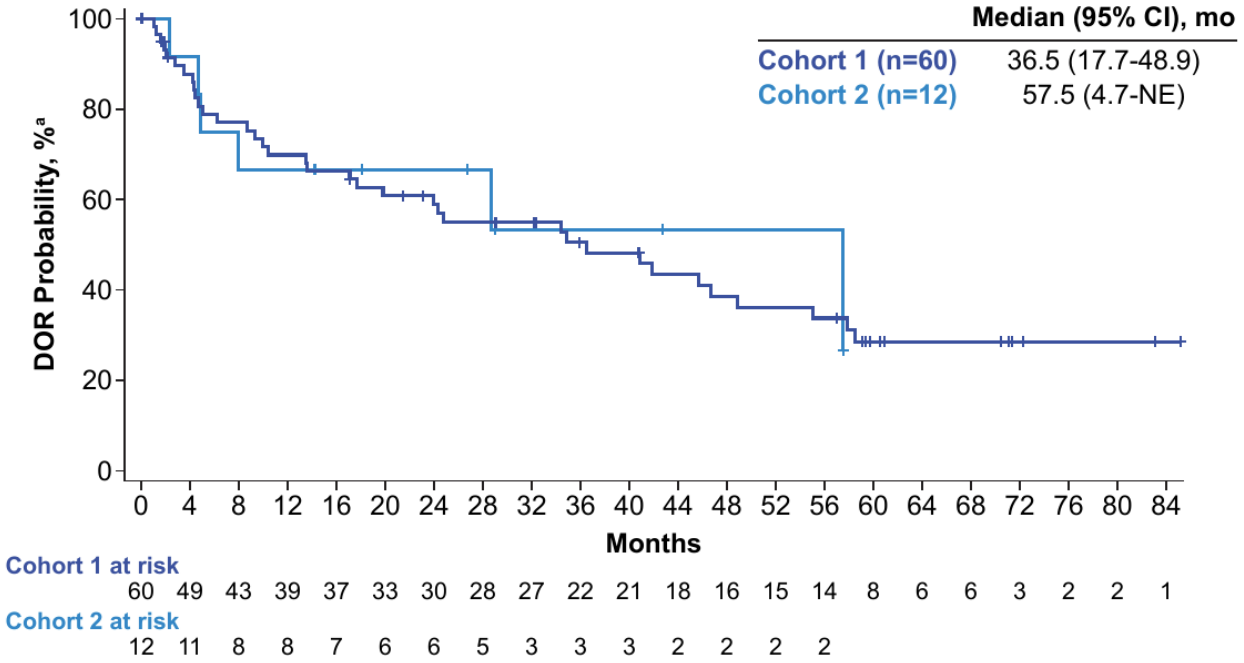
In Cohort 2, the 5-year analysis was the primary analysis (n=13); the IRRC-assessed ORR was 93% (95% CI, 66.1–99.8), with a 64% CR rate, and no stable or progressive disease.[3]

DOR, PFS, and OS

The median DOR, median PFS, and median OS were not reached in the primary analysis of ZUMA-2 Cohort 1. Fifty-seven percent of patients remained in remission at data cutoff, and the estimated 12-month PFS and OS rates were 61% and 83%, respectively.[1]

As of the 5-year follow-up analysis, DOR was 36.5 months (95% CI, 17.7–48.9) among 60 responders in Cohort 1 and 57.5 months (95% CI, 4.7–NE) among 12 responders in Cohort 2.[3] At data cutoff, 17 patients in Cohort 1 and 3 patients in Cohort 2 remained in response (all CR). Figure 2 presents the Kaplan-Meier estimates of DOR.

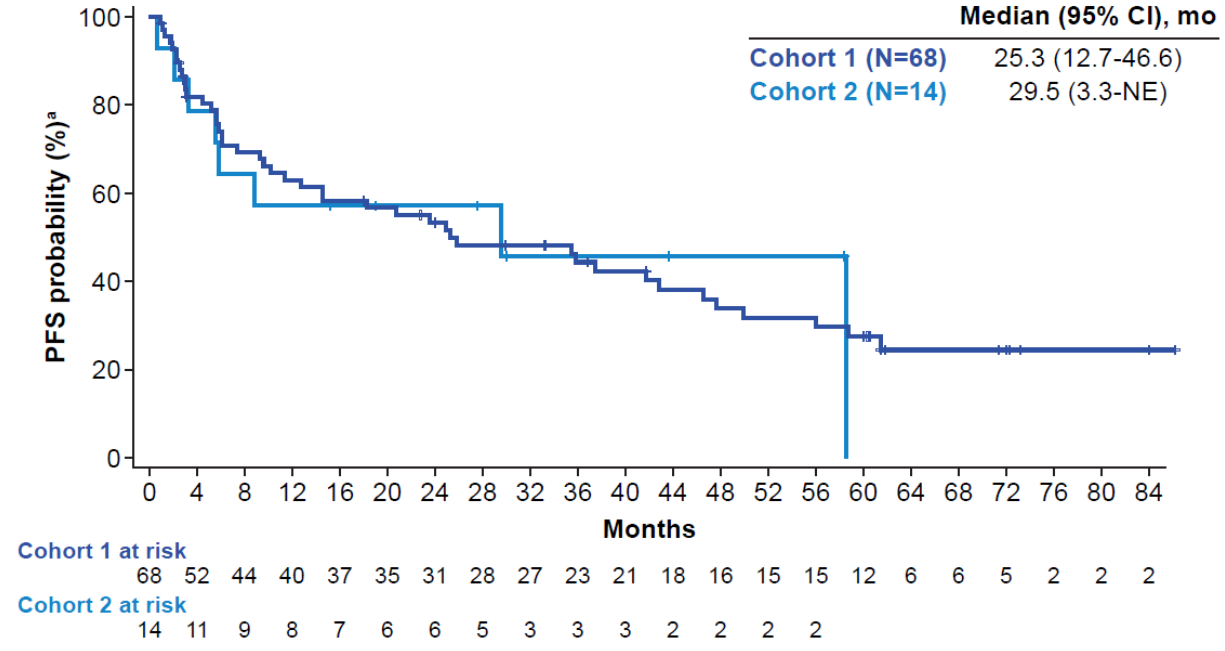
Figure 2. DOR in ZUMA-2 5-Year Follow Up Analysis[3]



[a] Per investigator assessment. DOR=duration of response; mo=months; NE=not estimable.

At the 5-year follow-up, median PFS was 25.3 months (95% CI, 12.7–46.6) in all treated patients in Cohort 1 (n=68) and 29.5 (95% CI, 3.3–NE) in all treated patients in Cohort 2 (n=14).[3] Figure 3 shows the Kaplan-Meier estimates of PFS.

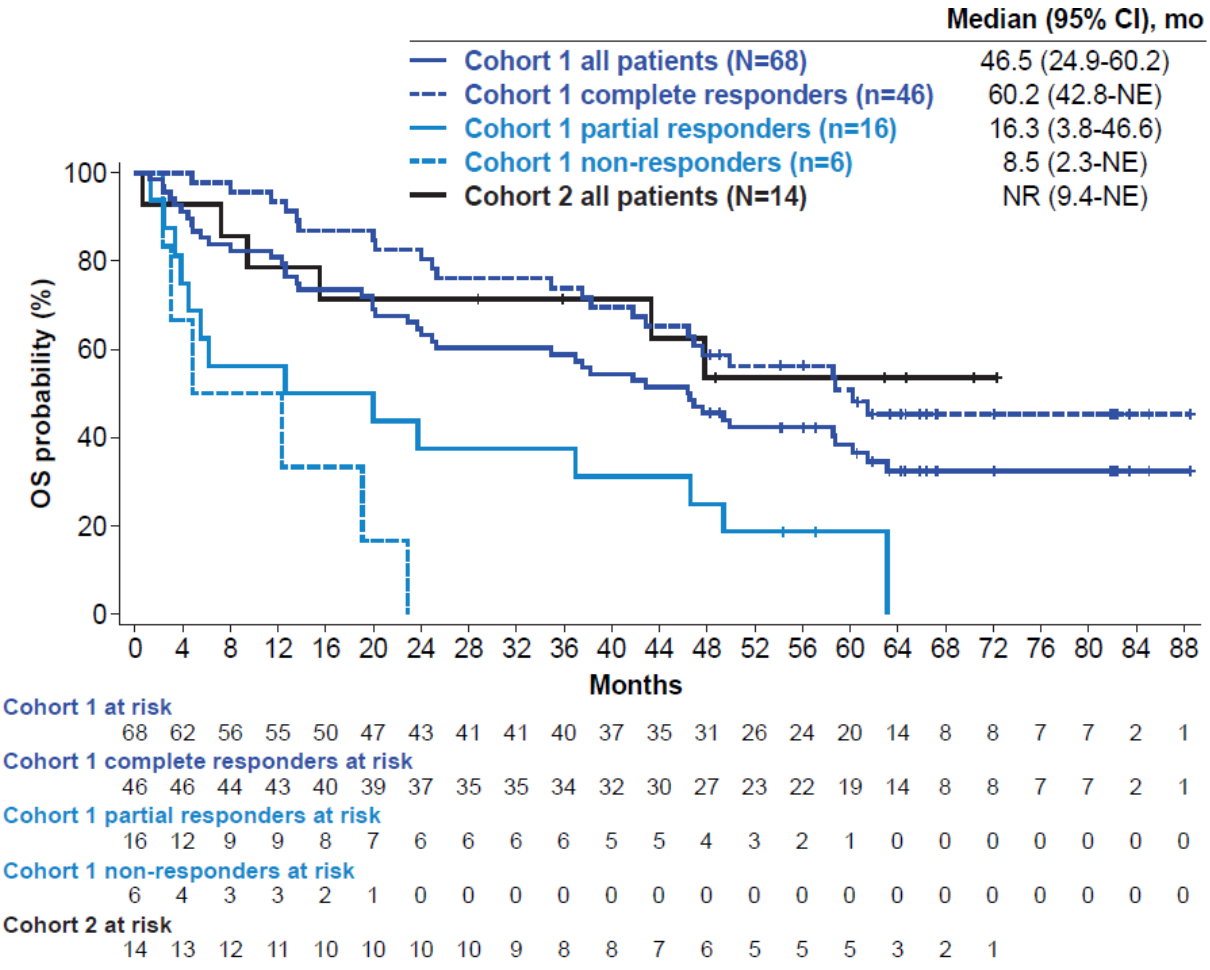
Figure 3. PFS in ZUMA-2 5-Year Follow Up Analysis[3]



[a] Per assessment. mo=months; NE=not estimable; PFS=progression-free survival.

At the 5-year follow-up, median OS was 46.5 months (95% CI, 24.9–60.2) in Cohort 1 and was not reached in Cohort 2 (95% CI, 9.4–NE).[3] The 60-month OS rates were 39% (95% CI, 26.7–50.1) and 54% (95% CI, 23.8–76.2), respectively. Figure 4 shows the Kaplan-Meier estimates of OS.

Figure 4. OS in ZUMA-2 5-Year Follow Up Analysis[3]



mo=months; NE=not estimable; NR=not reached; OS=overall survival.

Response According to MRD Status[2]

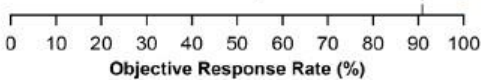
Minimal residual disease (MRD) was evaluated as an exploratory end point using next-generation sequencing assay. Of 19 patients with available MRD data at month 6, 15 (79%) remained MRD-negative, with an ORR of 100% among the negative patients.

Subgroup Analysis of Response[5]

Results of post hoc subgroup analyses of response in Cohort 1 at the 3-year analysis, including patients with high-risk characteristics, are presented in Figure 5.

Figure 5. Subgroup Analysis of ORR at the 3-Year Follow-Up Analysis[5]

	No. of Patients	No. of Patients With Objective Response	Percent of Patients With Objective Response (95% CI)
Overall	68	62	91 (82–97)
Morphologic characteristics			
Classical MCL	40	37	93 (80–98)
Diffuse	20	17	85 (62–97)
Nodular	10	10	100 (69–100)
Pleomorphic	4	4	100 (40–100)
Other	6	6	100 (54–100)
Blastoid	17	14	82 (57–96)
Other	1	1	100 (3–100)
Unknown	10	10	100 (69–100)
Ki-67 PI (%)			
<30%	9	9	100 (66–100)
≥30%	43	39	91 (78–97)
<50%	15	15	100 (78–100)
≥50%	37	33	89 (75–97)
Prior ibrutinib			
Yes	58	54	93 (83–98)
No	10	8	80 (44–97)
Prior acalabrutinib			
Yes	16	14	88 (62–98)
No	52	48	92 (81–98)
***TP53* mutation**			
Mutation detected	6	6	100 (54–100)
Mutation undetected	30	30	100 (88–100)
Missing	32	26	81 (64–93)
MRD at month 6 (10^{-5} sensitivity)			
Positive	4	3	75 (19–99)
Negative	15	15	100 (78–100)
Indeterminate	0	0	NA (NA–NA)
Missing	49	44	90 (78–97)
POD24			
Yes	33	31	94 (80–99)
No	35	31	89 (73–97)
BTKi subgroup			
Ibrutinib only	52	48	92 (81–98)
Acalabrutinib only	10	8	80 (44–97)
Both	6	6	100 (54–100)



BTKi=Bruton tyrosine kinase inhibitor; CI=confidence interval; MCL=mantle cell lymphoma; MRD=minimal residual disease; NA=not available; PI=proliferation index; POD24=progression of disease <24 months after initial diagnosis; TP53=tumor protein p53 gene.

Safety

No new safety signals were observed in the 5- year follow-up analysis.[3]

Rates of AEs, including TEAEs, TEAEs related to Tecartus or brexu-cel treatment, TEAEs reported in ≥40% of patients in either cohort, and AEs of special interest reported in either cohort, are presented in Table 1 and Table 2.

Table 1. Treatment-Emergent Adverse Events ≥40% in Cohort 1 or Cohort 2[3]

TEAEs,[a] n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
Any TEAE	68 (100)	14 (100)
Grade ≥3	67 (99)	13 (93)
Treatment-related TEAE[a]	66 (97)	14 (100)
Grade ≥3	54 (79)	10 (71)
TEAEs reported in ≥40% of patients in either cohort		
Pyrexia	64 (94)	13 (93)
Grade ≥3	9 (13)	3 (21)
Anemia	46 (68)	7 (50)
Grade ≥3	35 (51)	6 (43)
Neutrophil count decreased	37 (54)	6 (43)
Grade ≥3	36 (53)	6 (43)
Hypotension	36 (53)	11 (79)
Grade ≥3	15 (22)	8 (57)
Platelet count decreased	35 (51)	5 (36)
Grade ≥3	26 (38)	5 (36)
Chills	28 (41)	6 (43)
Grade ≥3	0	0
WBC count decreased	28 (41)	7 (50)
Grade ≥3	28 (41)	7 (50)
Fatigue	26 (38)	7 (50)
Grade ≥3	1 (1)	0
Hypoxia	26 (38)	7 (50)
Grade ≥3	14 (21)	2 (14)
Tremor	24 (35)	7 (50)
Grade ≥3	0	2 (14)
Nausea	22 (32)	7 (50)
Grade ≥3	1 (1)	0
Decrease in appetite	15 (22)	7 (50)
Grade ≥3	0	0
Confusional state	14 (21)	6 (43)
Grade ≥3	8 (12)	1 (7)
Dyspnea	14 (21)	6 (43)
Grade ≥3	2 (3)	3 (21)

[a] TEAEs are defined as any AE with onset on or after initiation of Tecartus or brexu-cel infusion. AEs that occurred on/after retreatment are not included. AEs are coded using MedDRA version 26.0 and graded per CTCAE version 4.03. Multiple incidences of the same AE in 1 patient are counted once at the highest grade for that patient.
AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event; WBC=white blood cell count.

Table 2. Adverse Events of Special Interest in ZUMA-2[3]

AEs of Interest, n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
CRS[a]	62 (91)	13 (93)
Grade ≥3	10 (15)	2 (14)
Neurologic events[b]	43 (63)	13 (93)
Grade ≥3	21 (31)	6 (43)
Thrombocytopenia	50 (74)	7 (50)
Grade ≥3	36 (53)	6 (43)
Neutropenia	59 (87)	11 (79)
Grade ≥3	58 (85)	11 (79)
Anemia	47 (69)	7 (50)
Grade ≥3	36 (53)	6 (43)
Infection	37 (54)	7 (50)
Grade ≥3	26 (38)	3 (21)
Hypogammaglobulinemia	14 (21)	0
Grade ≥3	1 (1)	0

[a] CRS events were graded per the revised grading system of Lee et al. 2014.[6] [b] Neurologic events were identified based on Topp et al. 2015.[7] All other events were graded per CTCAE v.4.03.
AE=adverse event; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events.

Between the Cohort 1 primary analysis and the 3-year analysis data cutoff, 3 additional Grade 5 AEs had occurred (salmonella bacteremia, myelodysplastic syndrome, and acute myeloid leukemia), none of which were considered related to Tecartus.[2] Any-grade AEs occurred in 18 patients (26%) and Grade ≥3 AEs in 14 patients (21%) in that time period.[2]

No cases of replication-competent retroviruses were reported at the time of the 3-year analysis, and their presence or absence was not noted at the time of the 5-year analysis.[2,3] No cases of secondary T-cell cancers in ZUMA-2 had been reported as of the 5-year analysis.[3]

Intravenous immunoglobulin therapy was administered to 26 patients (38%) in Cohort 1 as of the 3-year analysis data cutoff.[2]

As of the 5-year follow-up, there was a 40% (24/60) rate of death related to progressive disease (PD) and 22% (13/60) rate of death not related to PD, among Cohort 1 responders.[3]

CRS and Neurologic Events[3]

Rates of CRS and neurologic events through the 5-year analysis are presented in Table 2. There were no deaths due to CRS or neurologic events; no cases of Grade 5 CRS or neurological events occurred.[3]

In Cohort 1, the median time to resolution was 10 days for CRS events and 15 days for neurologic events.[3] In Cohort 2, the median times to resolution were 10 days and 17 days, respectively.

CAR T-Cell Persistence and Expansion

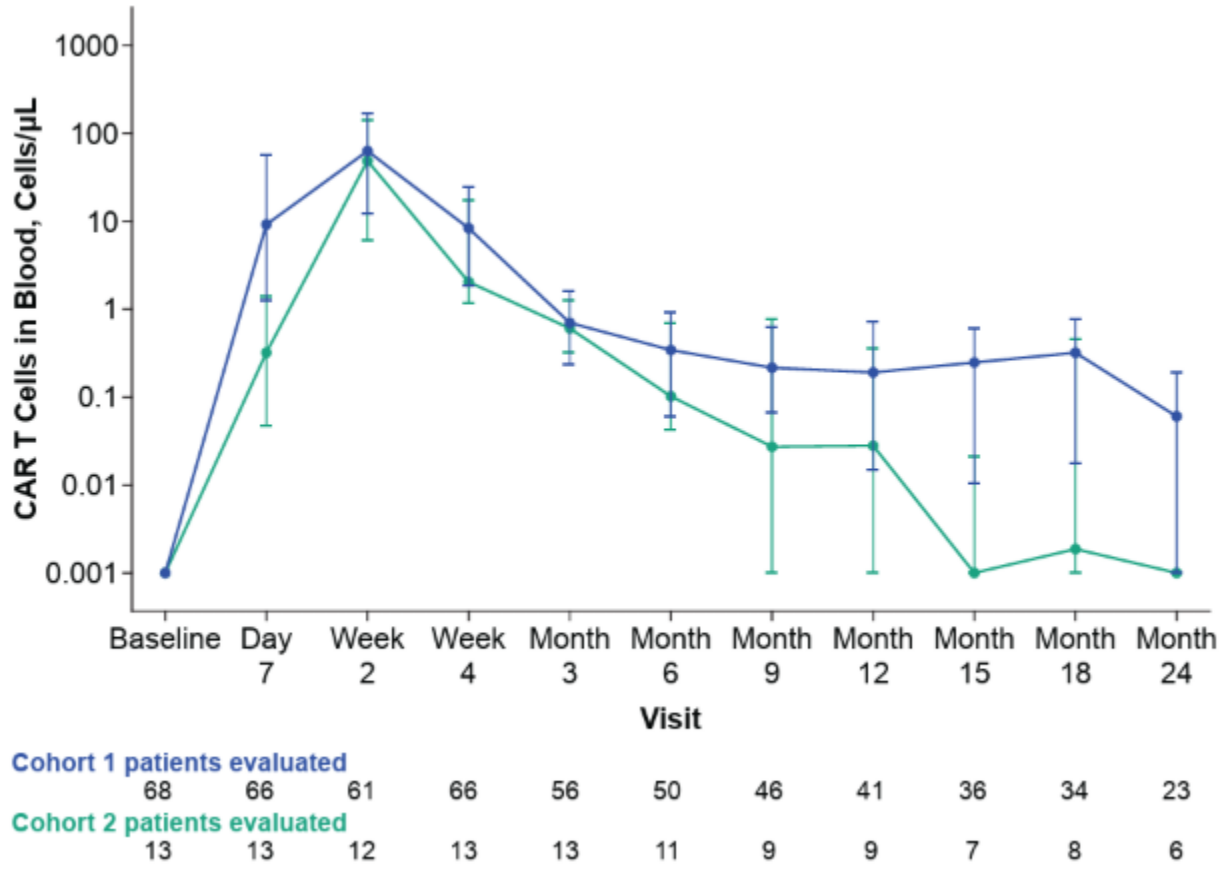
Of the patients in Cohort 1 with ongoing response at Months 18 and 24, B-cells were detectable in 35% and 53% of patients, respectively, and gene-marked CAR T-cells were detectable in 70% and 67% of patients, respectively.[2]

The follow-up analyses noted that CAR T-cell levels in both cohorts reached their peak (83.12 cells/µL in Cohort 1 and 56.07 cells/µL in Cohort 2) at a median of 15 days post-infusion.[2,3]

In Cohort 1, median CAR T-cell levels plateaued at 0.19–0.34 cells/µL from months 6 to 18.[2] Peak CAR T-cell expansion was highest in patients with ongoing responses compared with those who relapsed at 24 months or were nonresponders.[2]

The area under the curve from Day 0 to Day 28 (AUC_{0-28}) of CAR T-cell levels was 1112.86 cells/µL×days (IQR, 230.75–3005.32) in Cohort 1 and 688.40 cells/µL×day (IQR, 286.72–1477.66) in Cohort 2.[2,3]

Figure 6. CAR T-Cell Expansion Over Time[3]



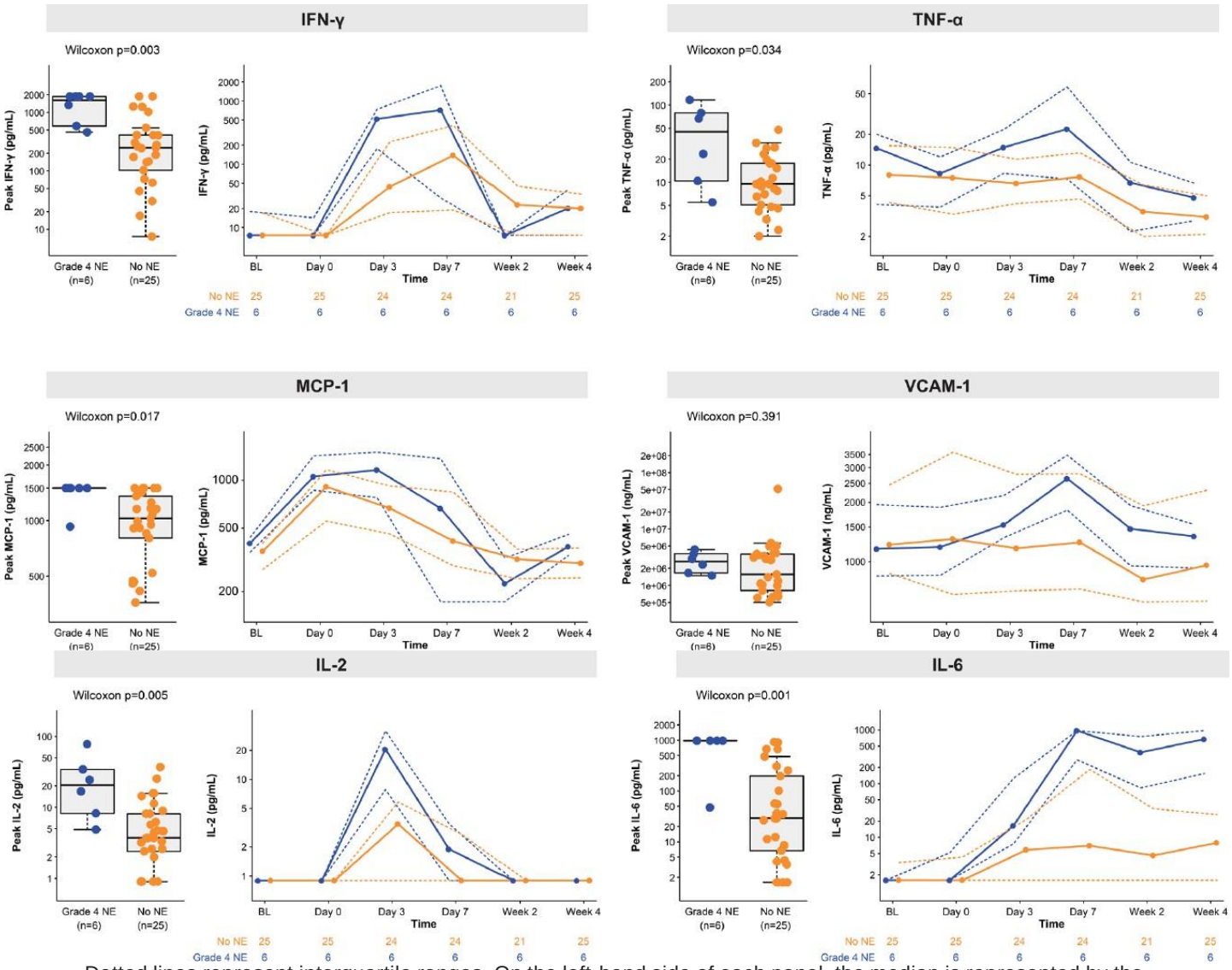
CAR=chimeric antigen receptor; IQR=interquartile range.

Pharmacodynamics

Serum Analyte[5]

Serum levels of selected cytokines among patients with and without Grade 4 neurologic events are shown in Figure 7.

Figure 7. Serum Levels of Selected Cytokines Among Patients with and without Grade 4 Neurologic Events[5]



Dotted lines represent interquartile ranges. On the left-hand side of each panel, the median is represented by the horizontal line within each box, and the 25th and the 75th percentiles are represented by the lower and upper borders of each box.

BL=baseline; IFN-γ=interferon gamma; IL=interleukin; MCP-1=monocyte chemoattractant protein 1; NE=neurologic event; TNF-α=tumor necrosis factor alpha; VCAM-1=vascular adhesion molecule.

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Abbreviations

AE=adverse event
AUC_{0-28}=area under the curve from Day 0-28
BL=baseline
BOR=best objective response
BTKi=Bruton's tyrosine kinase inhibitor
CAR=chimeric antigen receptor
CI=confidence interval
CR=complete response
CRS=cytokine release syndrome
CTCAE= Common Terminology Criteria for Adverse Events
DOR=duration of response
IFN-γ=interferon gamma
IL=interleukin
IQR=interquartile range
IRRC=Independent Radiologic Review Committee
ITT=intent-to-treat
IV=intravenous
LTFU=long-term follow-up
MCL=mantle cell lymphoma
MCP-1=monocyte chemoattractant protein-1
mo=months
MedDRA=Medical Dictionary for Regulatory Activities
MRD=minimal residual disease
N/A=not available
NE=not evaluable
NR=not reached
ORR=objective response rate
OS=overall survival
PD=progressive disease
PET-CT=positron emission tomography–computed tomography
PFS=progression-free survival
PI=proliferation index
PO=orally
POD24= progression of disease <24 months after initial diagnosis
PR=partial response
RCL=replication-competent lentivirus
RCR=replication-competent retrovirus
R/R=relapsed/refractory
SAE=serious adverse event
TEAE=treatment-emergent adverse event
TNF-α=tumor necrosis factor-alpha
TP53=tumor protein p53 gene
VCAM= vascular adhesion molecule
WBC=white blood cell count

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Follow Up

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