9th POSTGRADUATE
Lymphoma
Conference

CAR-T Cells in Mantle Cell Lymphoma

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Florence,
March 20-21, 2025

Hotel Brunelleschi

President:
P.L. Zinzani

Disclosures

Consultancy: AstraZeneca, Bristol Myers Squibb, Boxer Capital, Galapagos NV, Genmab, InnoCare, Janssen, Kite Pharma, Lilly, Merck, PER, Pepromene Bio, Pfizer, Oncternal

Research: Abbvie, AstraZeneca, Bantam Pharma, BeiGene, Genmab, Genentech, Innocare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Nurix Therapeutics, Oncternal, Pharmacyclics

Honoraria: AstraZeneca, BeiGene, Binaytara Foundation, Bristol Myers Squibb, CAHON, Editorial Medica AWWE SA, East Virginia Medical School, Instituto Scientifico Romagnolo, Janssen, Kite Pharma, Mayo Clinic, MJH Life Sciences, Merck, MSC National Research Institute of Oncolgy, Pfizer, Physicians Education Resources (PER), Plexus Communications, PromCon S.R.E., Research to Practice, Studio ER Congressi, Medscape/WebMD, VJHemonc

Five-Year Outcomes of Patients With Relapsed or Refractory Mantle Cell Lymphoma Treated With Brexucabtagene Autoleucel in ZUMA-2 Cohorts 1 and 2

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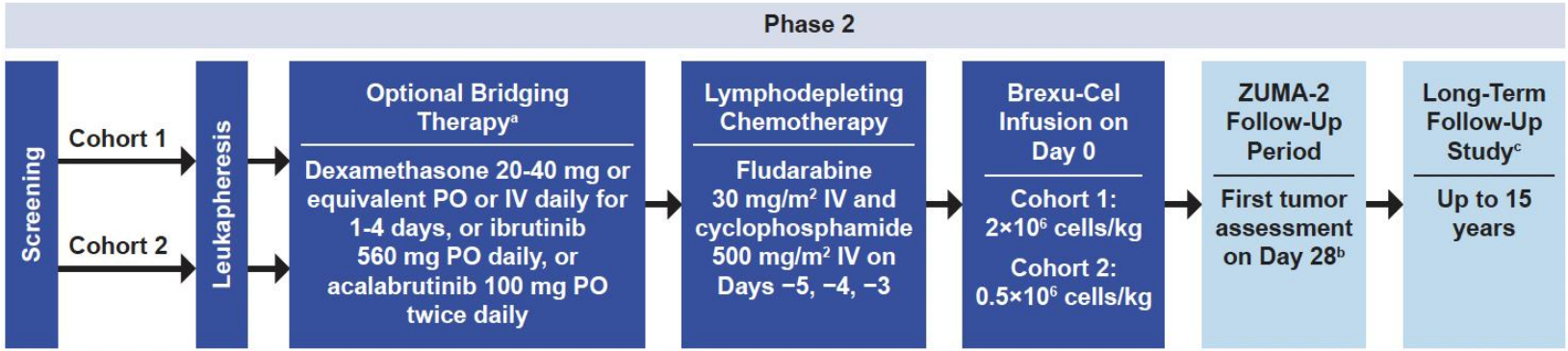
ZUMA-2 and LTFU Study Design



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 ZUMA-2 Endpoint

- ORR (CR + PR; IRRC assessed per the Lugano classification[1])

Key Secondary ZUMA-2 Endpoints

- DOR, BOR, PFS, OS
- AEs

Primary LTFU Endpoint

- Assess the occurrence of late-onset targeted AEs/SAEs suspected to be possibly related to gene-modified cells

Key Secondary LTFU Endpoints

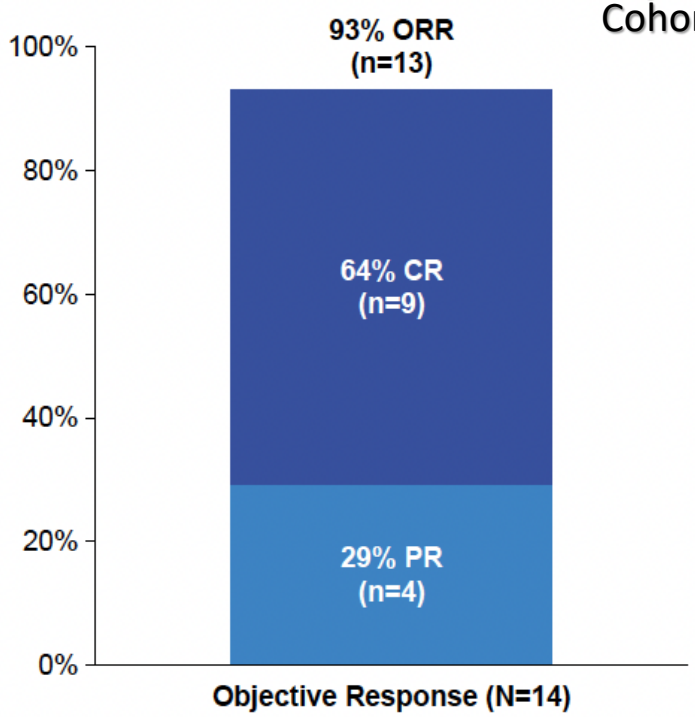
- OS, causes of death, and rates of RCR/RCL

[a] Administered after leukapheresis and completed ≥5 days before initiating conditioning chemotherapy; PET-CT was required postbridging. [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 brexu-cel for up to 15 years from the time of brexu-cel infusion.

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

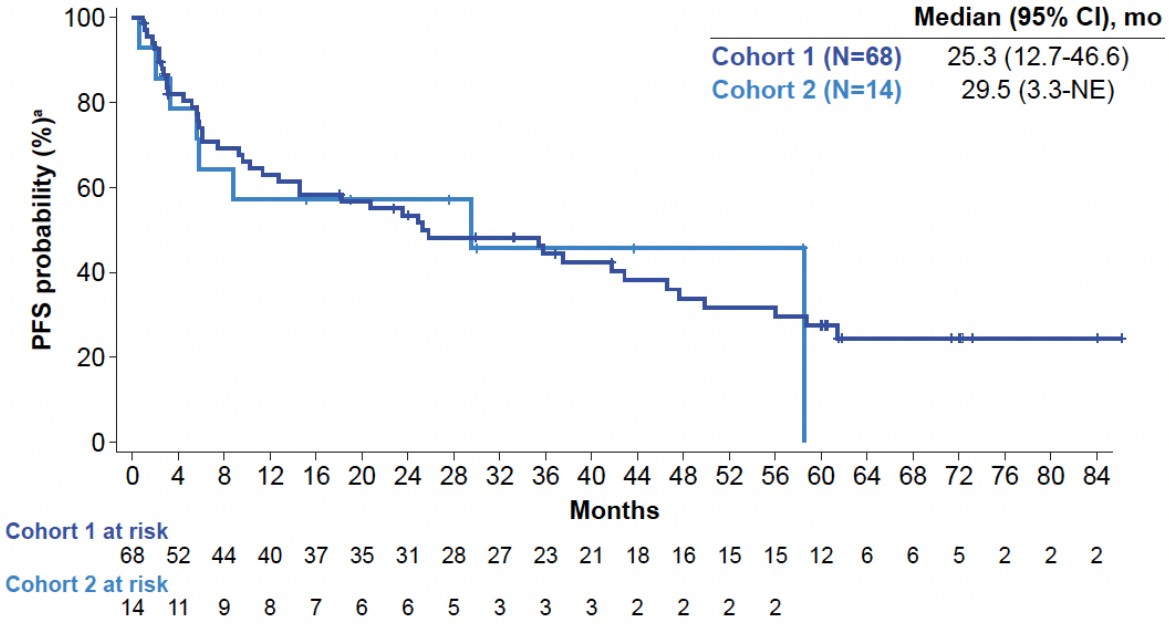
AE, adverse event; BOR, best objective response; brexu-cel, brexucabtagene autoleucel; BTKi, Bruton tyrosine kinase inhibitor; CR, complete response; DOR, duration of response; IRRC, independent radiology review committee; IV, intravenous; LTFU, long-term follow-up; MCL, mantle cell lymphoma; ORR, objective 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 or refractory; SAE, serious adverse event.

Best Objective Response by IRRC for Cohort 2 Primary Analysis



- In Cohort 2 primary analysis, ORR was 93% (95% CI, 66.1-99.8); 64% of patients had a CR and 29% had a PR
  - No patients had stable disease or progressive disease
  - One patient was not assessed at the time of analysis

Progression-Free Survival in ZUMA-2 5-Year Outcomes



- Median investigator-assessed PFS was 25.3 months (95% CI, 12.7-46.6; N=68) and 54-month PFS rate was 32% (95% CI, 20.0-44.2) in Cohort 1
- In Cohort 2, median PFS was 29.5 months (95% CI, 3.3-NE) and 54-month PFS rate was 46% (17.3-70.5; N=14)

[a] Per investigator assessment. NE, not estimable; PFS, progression-free survival.

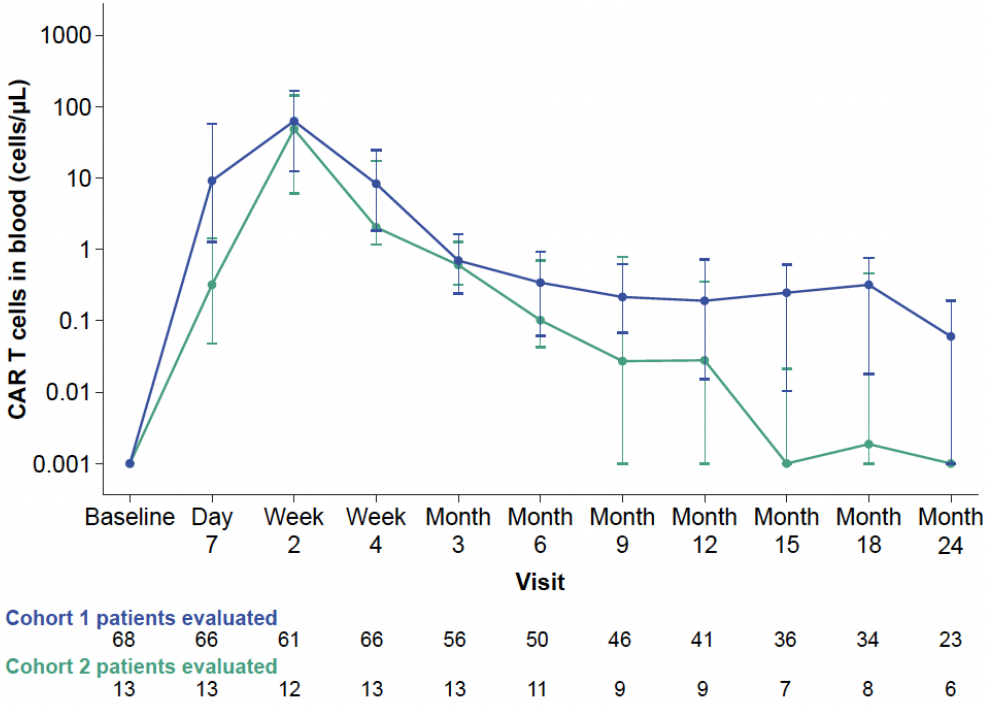
Adverse Events of Special Interest in ZUMA-2

AEs of Interest, n (%)	Cohort 1 (N=68)	Cohort 2 (N=14)
Any CRS[a]	62 (91)	13 (93)
Grade ≥3	10 (15)	2 (14)
Any neurologic event[b]	43 (63)	13 (93)
Grade ≥3	21 (31)	6 (43)
Any thrombocytopenia	50 (74)	7 (50)
Grade ≥3	36 (53)	6 (43)
Any neutropenia	59 (87)	11 (79)
Grade ≥3	58 (85)	11 (79)
Any anemia	47 (69)	7 (50)
Grade ≥3	36 (53)	6 (43)
Any infection	37 (54)	7 (50)
Grade ≥3	26 (38)	3 (21)
Any hypogammaglobulinemia	14 (21)	0
Grade ≥3	1 (1)	0

- Rates of Grade ≥3 CRS and neurological events were 15% and 31% in Cohort 1, and 14% and 43% in Cohort 2, respectively; no cases of Grade 5 CRS or neurological events occurred
  - CRS and neurological events resolved within a median of 10 days and 15 days in Cohort 1, and 10 days and 17 days in Cohort 2, respectively

[a] CRS events were graded per the revised grading system of Lee et al. 2014.[1] [b] Neurologic events were identified based on Topp et al. 2015.[2] All other events were graded per CTCAE v.4.03.
[1] Lee DW, et al. *Blood* 2014. [2] Topp MS, et al. *Lancet Oncol*. 2015;16(1):57-66.
AE, adverse event; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events.

CAR T-Cell Expansion (IQR) Over Time[1,2]



- As previously reported, in Cohort 1, median time to peak CAR T-cell levels was 15 days (IQR, 8-15) with a median peak and AUC_{0-28} CAR T-cell levels of 83.12 cells/µL (IQR, 17.40-265.71) and 1112.86 cells/µL × 3day (230.75-3005.32)[1,2]
- In Cohort 2, median time to peak CAR T-cell levels was 15 days (IQR, 15-29) with a median peak and AUC_{0-28} CAR T-cell levels of 56.07 cells/µL (IQR, 26.34-139.16) and 688.40 cells/µL × 3day (IQR, 286.72-1477.66), respectively

1. Wang M, et al. *N Engl J Med*. 2020; 382:1331-1342. 2. Wang M, et al. *J Clin Oncol*. 2023;41(3):555-567.
AUC, area under the curve; CAR, chimeric antigen receptor; IQR, interquartile range.

Primary Analysis of ZUMA-2 Cohort 3: Brexucabtagene Autoleucel in Patients With Relapsed/Refractory Mantle Cell Lymphoma Who Are Naive to Bruton Tyrosine Kinase Inhibitors

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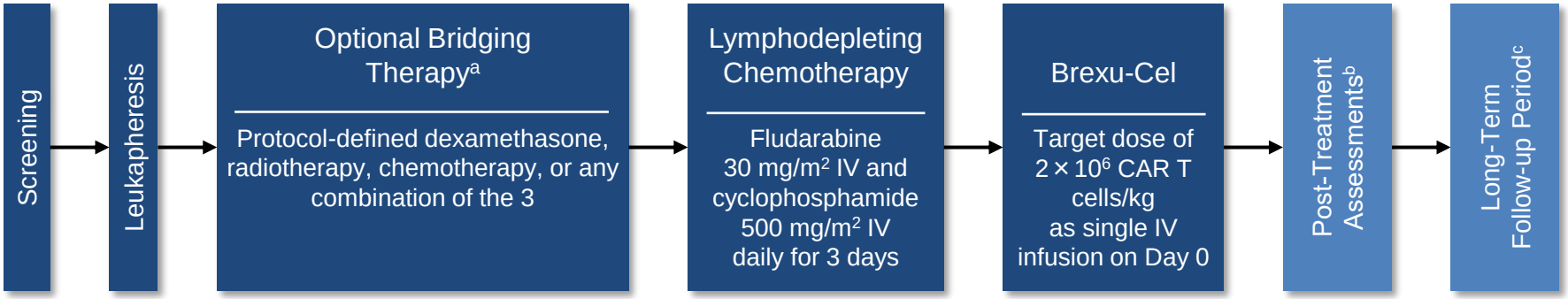
ZUMA-2 Cohort 3 Study Methodology

Phase 2, Open-Label Study



Key Cohort 3 Eligibility Criteria

- Age ≥18 years with R/R MCL
- 1-5 prior regimens including anthracycline-, bendamustine-, or high-dose cytarabine-containing chemotherapy and anti-CD20 monoclonal antibody therapy
- No prior BTKi

Primary Endpoint

- ORR (CR + PR; by IRRC assessed per the Lugano classification[1])

Key Secondary Endpoints

- DOR, BOR, PFS, OS, and safety

Statistical Considerations

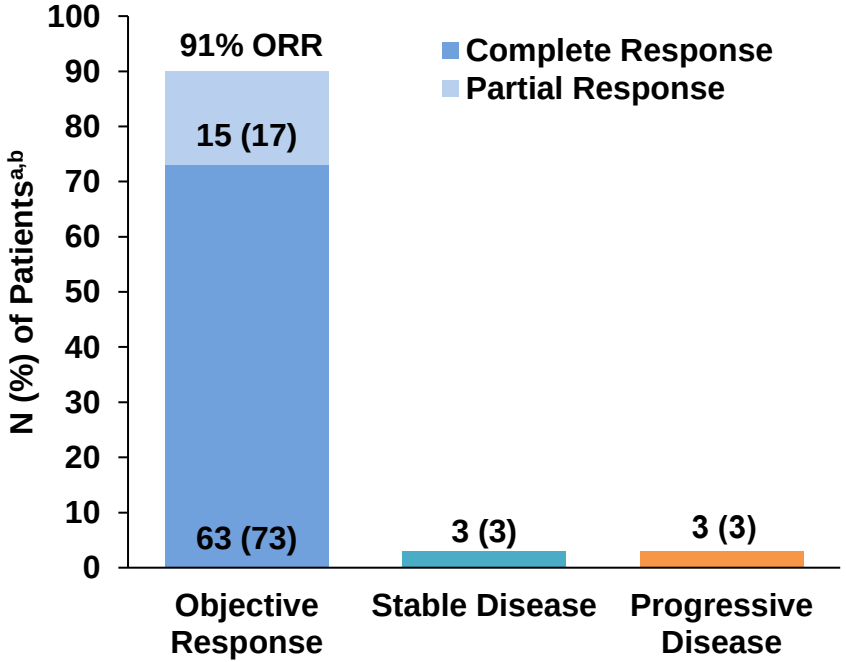
- Primary efficacy analysis was conducted after 86 patients were enrolled, treated, and assessed for 6 months after the first objective response and was powered at ≥90% to distinguish between a 75% response rate and a response rate of ≤57%
- Time-to-event endpoints were analyzed using the Kaplan–Meier method
- All treated patients were included in both efficacy and safety analyses

[a] Administered after leukapheresis and completed at least 7 days or 5 half-lives, whichever is shorter, prior to initiating conditioning chemotherapy. [b] Bone marrow biopsy was to be done at screening and, if positive, not done or indeterminate, a biopsy was needed to confirm CR. First post–brexu-cel disease assessment was 4 weeks after infusion. [c] After 3 months, only targeted AEs (neurological, hematological, infections, GVHD, autoimmune disorders, and secondary malignancies) were monitored and 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.

1. Cheson BD, et al. J Clin Oncol. 2014;32:3059-3068. [a] At the discretion of the investigator, bridging therapy was recommended for all patients, particularly those with rapidly progressing disease, clinical deterioration, or high disease burden at screening.

Brexu-cel, brexucabtagene autoleucel; CAR, chimeric antigen receptor; CR, complete response; BOR, best objective response; DOR, duration of response; IRRC, independent radiology review committee; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R/R, relapsed/refractory mantle cell lymphoma.

Best Objective Response

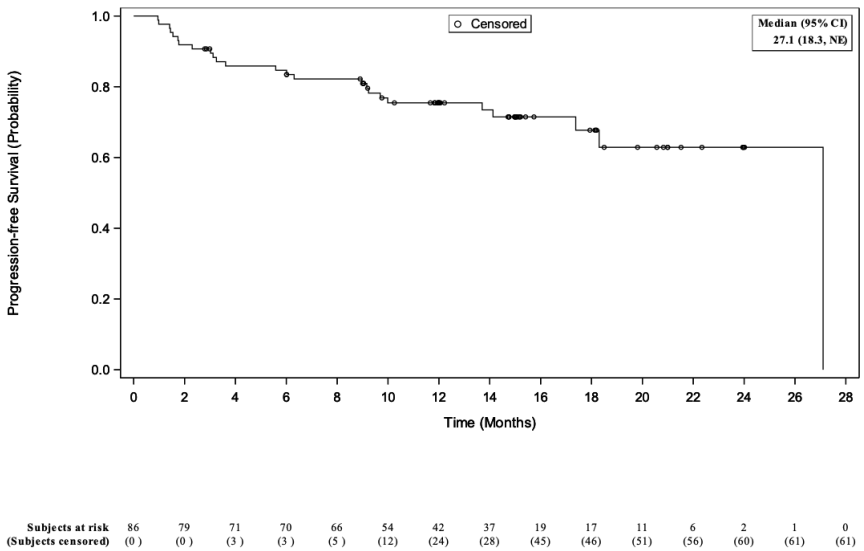


- The primary endpoint was met with an ORR of 91%, including a 73% CR rate

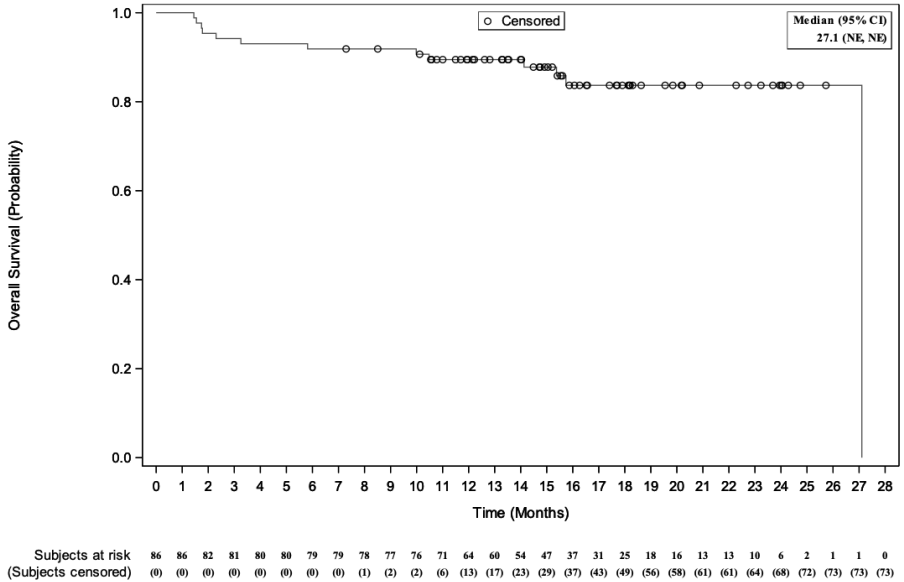
[a] Per IRRC assessment. [b] Two patients were not assessable.
IRRC, independent radiology review committee; NE, not estimable; ORR, objective response rate.

Progression-Free Survival and Overall Survival

Progression-Free Survival[a,b]



Overall Survival[b]



- The median PFS was 27.1 months, and the 12-month PFS rate was 75%
- The median OS was 27.1 months, and the 12-month OS rate was 90%, with 85% of patients (73/86) still alive at data cutoff

[a] Per IRRC assessment. [b] KM median estimates for PFS and OS were unstable due to heavy censorship.
IRRC, independent radiology review committee; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Adverse Events of Special Interest

AEs of Special Interest	Cohort 3 (N=86)	
	Any Grade	Grade ≥3
CRS,[a] n (%)	82 (95)	5 (6)
Neurological events,[b] n (%)	67 (78)	23 (27)
ICANS,[c] n (%)	57 (66)	18 (21)
Thrombocytopenia,[d] n (%)	45 (52)	29 (34)
Neutropenia,[d,e] n (%)	74 (86)	73 (85)
Anemia,[d] n (%)	49 (57)	22 (26)
Serious infection,[d] n (%)	21 (24)	20 (23)
Hypogammaglobulinemia,[d] n (%)	7 (8)	0

- Grade ≥3 CRS and ICANS occurred in 6% and 21% of patients, respectively
- Median (range) time to onset and duration of CRS events was 4 (1-12) and 6 days (1-36), respectively
- Median (range) time to onset and duration of ICANS was 7 (1-31) and 7 days (1-122), respectively
- No cases of replication-competent retrovirus or brexu-cel–related secondary malignancies were reported

[a] CRS events are graded per the revised grading system proposed by Lee et al 2014.[1] [b] Neurologic events are identified based on Topp et al 2015. [c] ICANS events are graded per the ASTCT ICANS grading (Lee et al 2019).[2] [d] All other events are graded per CTCAE version 4.03. [e] Includes neutropenia, neutrophile count decreased and febrile neutropenia.

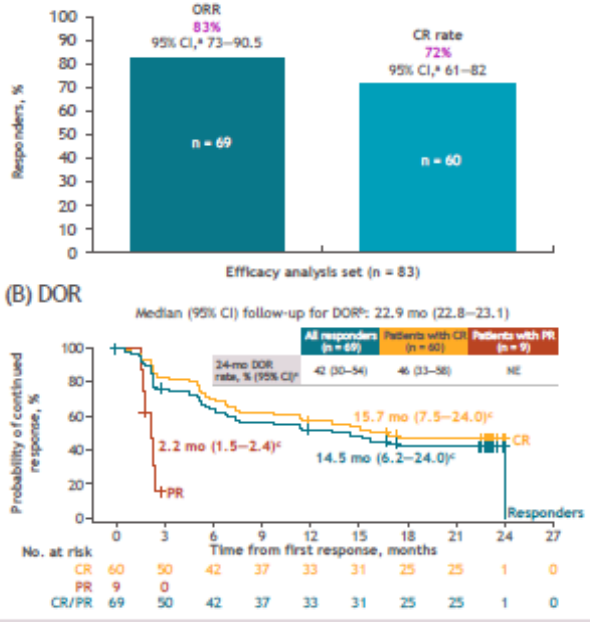
1. Lee DW, et al. Blood. 2014;124(2):188-95. 2. Lee DW, et al. Biol Blood Marrow Transplant. 2019(4):625-638.

AE, adverse event; CRS, cytokine release syndrome; ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE, Common Terminology Criteria for Adverse Events; ICANS, immune effector cell-associated neurotoxicity syndrome; TEAE, treatment-emergent adverse event.

Lisocabtagene Maraleucel in Patients With Relapsed or Refractory Mantle Cell Lymphoma: Results From the Final Analysis of the Mantle Cell Lymphoma Cohort of the Open-label, Phase 1, Seamless Design, Multicenter TRANSCEND NHL 001 Study

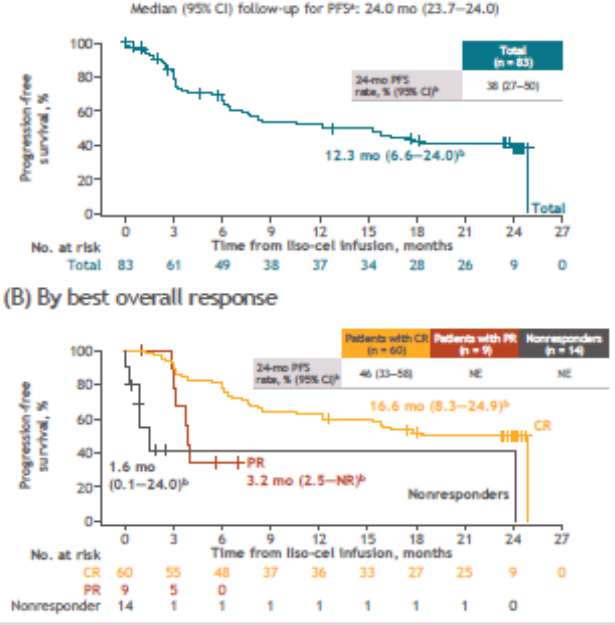
Liso-cel continued to show clinically meaningful and durable disease control with high efficacy, including unchanged response rates, durable responses (Figure 3), and sustained PFS (Figure 4) and OS (Figure 5), consistent with primary analysis results[1]

Figure 3. Response rate (A) and DOR (B) in the efficacy analysis set



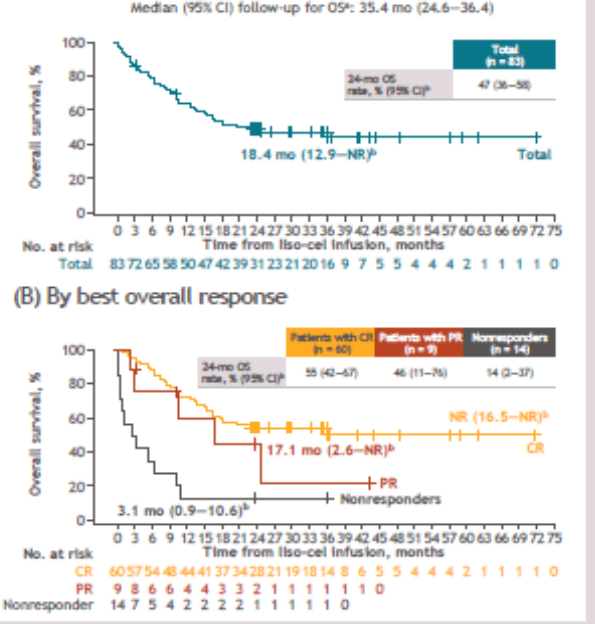
All percentages are rounded to whole numbers except those with ".5%". Data on KM curves are expressed as median (95% CI). *Two-sided 95% exact Clopper-Pearson CIs; [a]Reverse KM was used to obtain median follow-up and its 95% CI; [c]KM method was used to obtain 2-sided 95% CIs. NE, not evaluable.

Figure 4. PFS in the efficacy analysis set



Data on KM curves are expressed as median (95% CI).
*Reverse KM was used to obtain median follow-up and its 95% CI; [b]KM method was used to obtain 2-sided 95% CIs.

Figure 5. OS in the efficacy analysis set



Data on KM curves are expressed as median (95% CI).
*Reverse KM was used to obtain median follow-up and its 95% CI; [b]KM method was used to obtain 2-sided 95% CIs.
NR, not reached.

Table 4. AESIs in the TE period (liso-cel–treated set)

	TE period[a] (n = 88)
CRS,[b] n (%)	
Any grade	54 (61)
Grade ≥ 3	1 (1)
NEs,[c] n (%)	
Any grade	27 (31)
Grade ≥ 3	8 (9)
Grade ≥ 3 infections, n (%)	13 (15)
Tumor lysis syndrome, n (%)	2 (2)
Infusion-related reaction, n (%)	2 (2)
Prolonged cytopenias,[d] n (%)	35 (40)
Grade ≥ 3 decreased hemoglobin at Day 29 visit	4 (5)
Grade ≥ 3 decreased neutrophils at Day 29 visit	21 (24)
Grade ≥ 3 decreased platelets at Day 29 visit	28 (32)

[a]Occurring ≤ 90 days after liso-cel infusion; AEs occurring after the initiation of subsequent anticancer treatment or liso-cel retreatment were not considered TEAEs; [b]CRS was graded using the Lee 2014 criteria[3]; [c]NEs were defined as investigator-identified neurologic AEs related to liso-cel; [d]Prolonged cytopenias were defined as grade ≥ 3 laboratory result of anemia, neutropenia, or thrombocytopenia not resolved at the Day 29 study visit.
AESI, adverse event of special interest.

- Rates of grade ≥ 3 CRS, NEs, infections, and prolonged cytopenias in the TE period remained low, consistent with the primary analysis[1] (Table 4)

Table 5. SPMs (liso-cel–treated set)

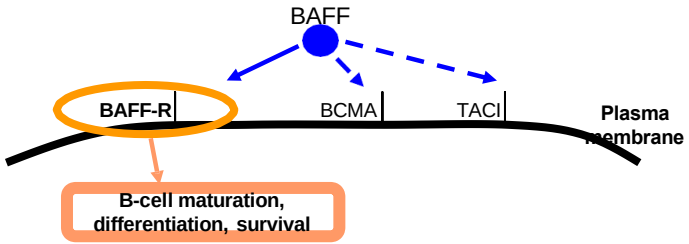
	Liso-cel–treated set[a] (n = 88)
SPM, n (%)[b]	16 (18)
Basal cell carcinoma	5 (6)
Squamous cell carcinoma/squamous cell carcinoma of skin	5 (6)
Myelodysplastic syndrome	2 (2)
Prostate cancer/prostate cancer metastatic	2 (2)
Acinar cell carcinoma of the pancreas	1 (1)
Invasive ductal breast carcinoma	1 (1)
Lung adenocarcinoma	1 (1)
Small cell lung cancer	1 (1)

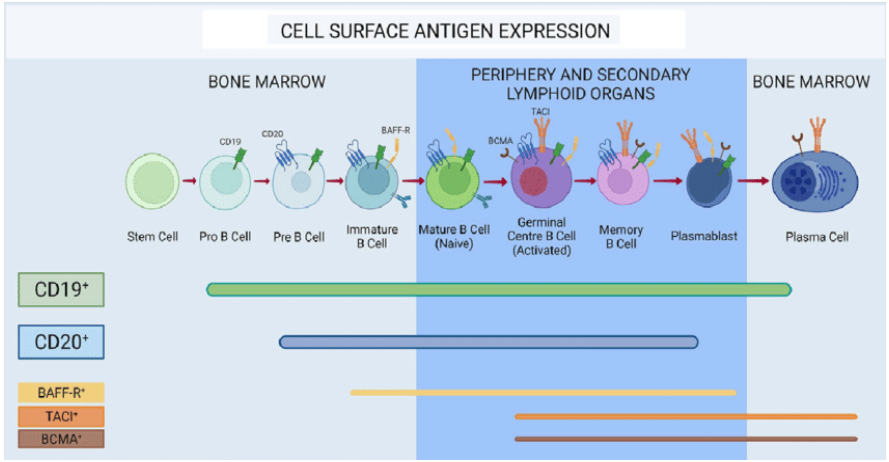
[a]Includes events reported on or after liso-cel infusion, including during the LTFU study; [b]Some patients had > 1 SPM.

- The total incidence of SPMs at any time on study was 18% with no T-cell malignancies (Table 5)
- Since the primary analysis, 1 additional patient had an SPM of myelodysplastic syndrome considered related to LDC in the post-TE period

BAFF-R is a First-in-Class Target for B-Cell Malignancies

- ***BAFF-R signaling is required for B-Cell differentiation and survival,*** may be less prone to downregulation by tumors
- ***Specifically targets more mature B-cells***, sparing earlier populations.
- Broadly expressed across ***all B-cell malignancies***





Panagiotis K. *et al.*, *The Canadian Journal of Neurological Sciences* (2022)

BAFF-R expression in B-cell malignancies

B-cell malignancy cases (%)	Total BAFF-R–positive
Hairy cell leukemia	10/10 (100)
Chronic lymphocytic leukemia	21/21 (100)
Mantle cell lymphoma	7/7 (100)
Follicular lymphoma	13/16 (81)
Diffuse large B-cell lymphoma	14/18 (78)
Marginal zone lymphoma	10/11 (91)

Rodig S. J., *et al.*, *Human Pathology* (2005)
Qin H. *et al.*, *Clinical Cancer Research (2018)*

BAFF-R CAR T Clinically Validated Construct has Potential to Address Unmet Needs in Oncology and Autoimmune Diseases

BAFF-R CAR is 2nd generation CAR

- Humanized BAFF-R scFv
- Containing 4-1BB and TCR signaling domains

PeproMene's Lead Asset BAFF-R CAR-T (PMB CT01) Lead Indication is B-Cell NHL followed by expansion into treating Autoimmune Diseases

Targeting B-Cell Malignancies

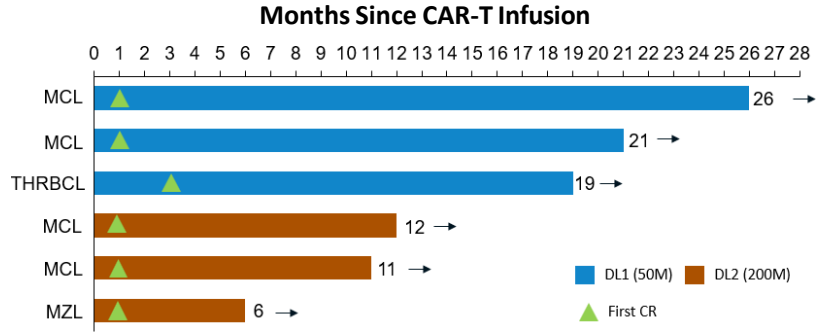
- Address therapy resistance in R/R disease
- Eliminate malignant B-cell proliferation via targeted MoA

Targeting B-Cell Driven Autoimmune Disease

- Selective targeting to reduce autoreactive B-cells
- Potential for long-lasting disease control
- Reduced toxicity compared to B-cell depletion that targets all B-cell stages

BAFF-R CAR-T cells (PMB-CT01) has demonstrated 100% CRs with Durable Responses and Favorable Safety Profile among the first patients treated

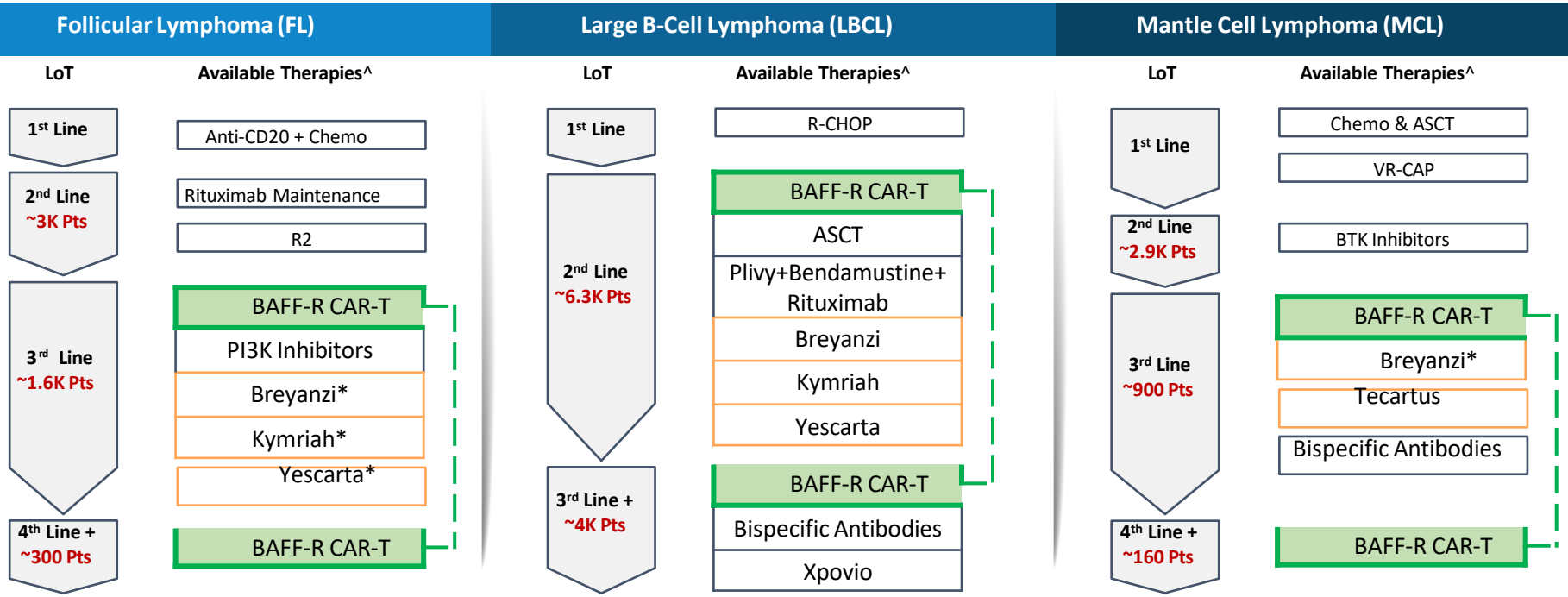
Dose/Patient	Pt. 1	Pt. 2	Pt. 3	Pt. 4	Pt. 5	Pt. 6
CAR-T Dose	50 M	50 M	50 M	200 M	200 M	200 M
Demographics / Characteristics						
Age at Infusion	56	75	41	63	72	75
Sex	M	M	M	M	M	M
Diagnosis	MCL	MCL	THRBCL	MCL	MCL	MZL
Stage at Baseline	IV	IV	III	IV	IV	IIA
Prior Therapy Exposure						
# Prior Lines	4	10	3	3	4	1
Prior CD19 CAR-T	Yes	Yes	No	No	Yes	No
Prior HCT	No	No	Yes	No	No	No
CD19 Expression	Yes	Yes	No	Yes	Yes	Yes



CRS/ICANS of Any Grade During the DLT Period

	B-NHL (n=6)		Total
CRS (Grade 1)	50M: 3	200M: 3	**6**
Neurotox/ICANS (Grade 1)	50M: 2	200M: 0	**2**

PMB-CT01 Has the Potential to Be Used Either as an Alternative to, or Following CD19 CAR-T



- Recent clinical successes and real-world data have led to the **earlier adoption of CAR-T therapies in the treatment of B-cell malignancies**

Notes: **Assumes all R/R patients treated; ^Additional treatment options available; *Available after 2+ lines of systemic therapy; Abbreviations: ASCT: Autologous Stem Cell Transplant; LoT: Line of Therapy; R2: Lenalidomide and Rituximab; Sources: NCCN (2024); NIH; Semin Hematol. (2023); Mayo Clinic (2024); ASCO Post (2024); OncLive (2024); AACR (2017); Cancers (2023); Adv Ther. (2022); (see notes for source details)

CD19-Targeted CAR-T Potential Utilization

Annual U.S. Incident Patients**

PMB-CT01 Will be First in Class and Have First-Mover Advantage

Clinical Stage BAFF-R-Targeting Therapies

NOVARTIS	luminary therapeutics	诗健生物 Escugen	Mayo Clinic
Ianalumab	LMY-920	ESG206	MC10029
Anti-BAFF-R IgG1 mAb	Auto-BAFF-ligand CAR-T	Anti-BAFF-R mAb	Auto-BAFF-R CAR-T
Phase 3	Phase 1	Phase 1	Phase 1
Autoimmune; NHL (Ph1)	Autoimmune; R/R NHL; R/R Myeloma	B-Cell Lymphoid Malignancies	B-Cell Hematologic Malignancies

Few Clinical Stage Competitors

- Only **a few players** actively developing therapies
- Field remains relatively uncrowded, allowing for **first-mover advantages**

Potential for Increased Toxicity

- **Uncertainty around BAFF ligand-targeting approaches**, as they often hit multiple targets
- **Non-specific targeting** raises concerns for increased toxicity

Untested or Inefficient Constructs

- Several assets have little to no data regarding their **affinity, specificity**, or **clinical efficacy**
- **mAbs are less efficient** than CAR-T therapies

Thank You