ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA
DIPARTIMENTO DI
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POLICLINICO DI
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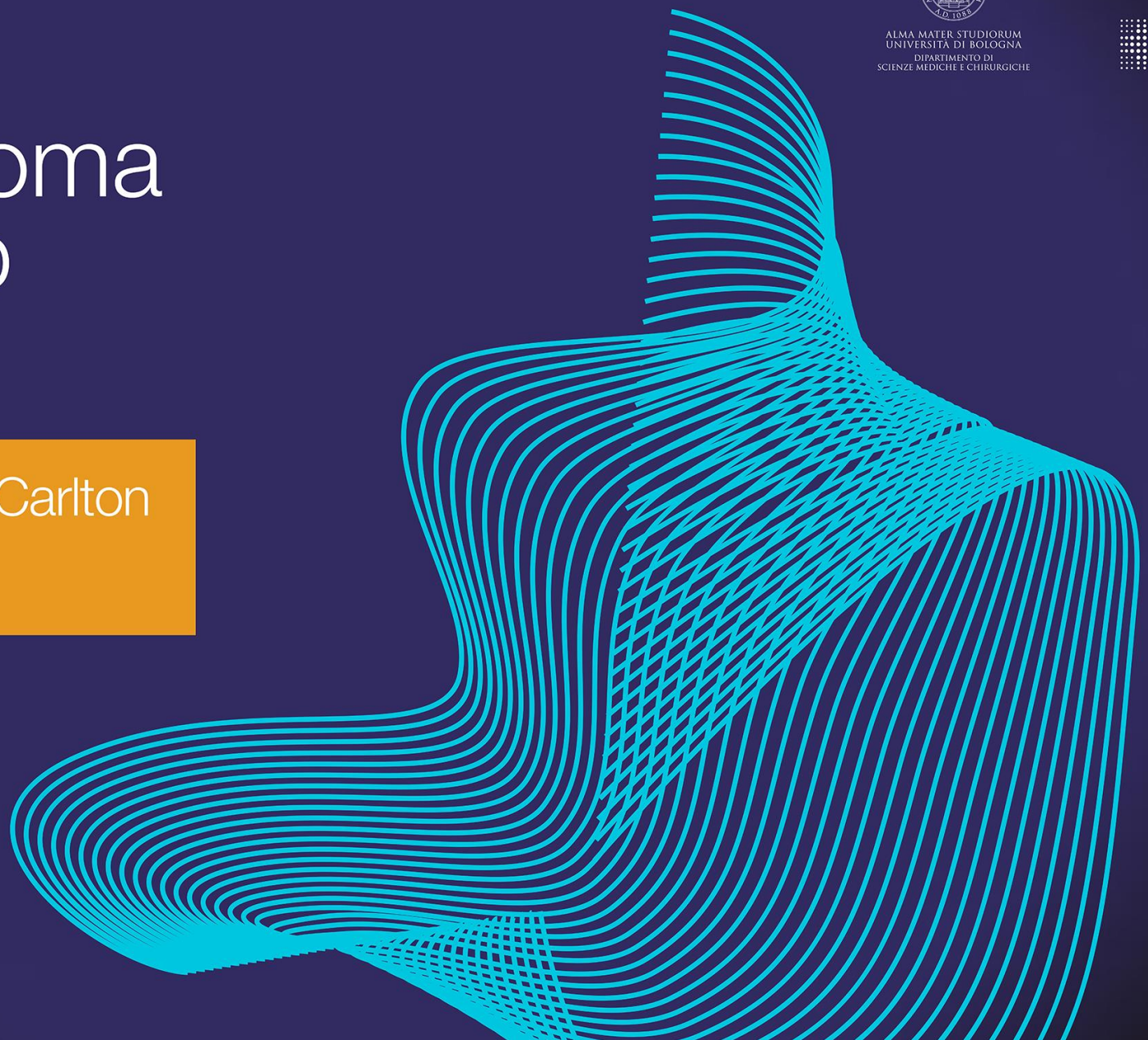
SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Aggressive Lymphoma Workshop



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President: **Pier Luigi Zinzani**

Disclosures of Dr. Michael Wang

Research Support	Consultancy	Honoraria
Acerta Pharma, AstraZeneca, BeiGene, BioInvent, Celgene, Genmab, Genentech, Innocare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics, VelosBio, Vincerx	AbbVie, Acerta Pharma, ADC Therapeutics America, Amphista Therapeutics Limited, AstraZeneca, Be Biopharma, BeiGene, BioInvent, Deciphera, DTRM Biopharma (Cayman) Limited, Genentech, InnoCare, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Lilly, Merck, Miltenyi Biomedicine, Milken Institute, Oncternal, Parexel, Pepromene Bio, Pharmacyclics, VelosBio	AbbVie, Acerta Pharma, AstraZeneca, Bantam Pharmaceutical, BeiGene, BioInvent, Bristol Myers Squibb, CAHON, Dava Oncology, Eastern Virginia Medical School, Genmab, i3Health, IDEOlogy Health, Janssen, Kite Pharma, Leukemia & Lymphoma Society, Medscape, Meeting Minds Experts, MD Education , MJH Life Sciences, Merck, Moffit Cancer Center, Nurix, Oncology Specialty Group, OncLive, Pharmacyclics, Physicians Education Resources (PER), Practice Point Communications (PPC), Scripps, Studio ER Congressi, WebMD

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

- Michael L. Wang, MD[1]; Javier Munoz, MD, MS, FACP[2]; Andre Goy, MD[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, FACP[8]; Ian W. Flinn, MD, PhD[9]; David B. Miklos, MD, PhD[10]; John M. Pagel, MD, PhD, DSc[11]; Marie José Kersten, MD, PhD[12]; Roch Houot, MD, PhD[13]; Amer Beitinjaneh, MD[14]; Weimin Peng, PhD[15]; Xiang Fang, PhD[15]; Rhine R. Shen, PhD[15]; Rubina Siddiqi, PhD[15]; Ioana Kloos, MD[15]; Patrick M. Reagan, MD[16]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Banner MD Anderson Cancer Center, Gilbert, AZ, USA; [3]John Theurer Cancer Center, Hackensack University, Hackensack, NJ, USA; [4]Moffitt Cancer Center, Tampa, FL, USA; [5]Dana-Farber Cancer Institute, Boston, MA, USA; [6]Cleveland Clinic Foundation, Cleveland, OH, USA; [7]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [8]Texas Oncology, Dallas, TX, USA; [9]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [10]Stanford University School of Medicine, Stanford, CA, USA; [11]Swedish Cancer Institute, Seattle, WA, USA; [12]Amsterdam UMC, University of Amsterdam, Amsterdam, Cancer Center Amsterdam, The Netherlands, on behalf of HOVON/LLPC; [13]CHU Rennes, Université Rennes, INSERM & EFS, Rennes, France; [14]University of Miami, Miami, FL, USA; [15]Kite, a Gilead Company, Santa Monica, CA; and [16]University of Rochester Medical Center, Rochester, NY, USA

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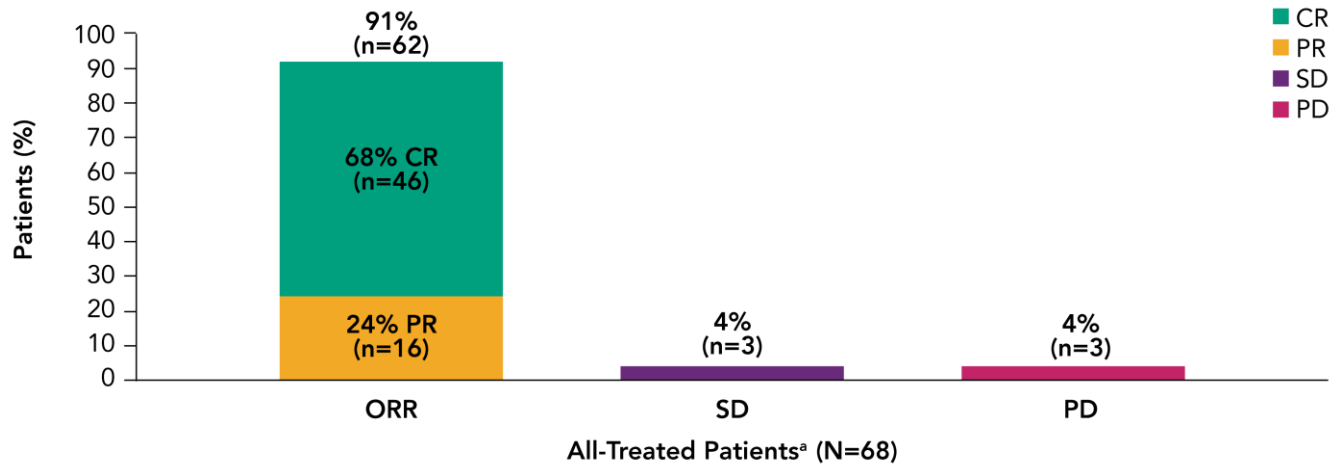
Objective Response Rate (ORR) in All Treated Patients (N=68)



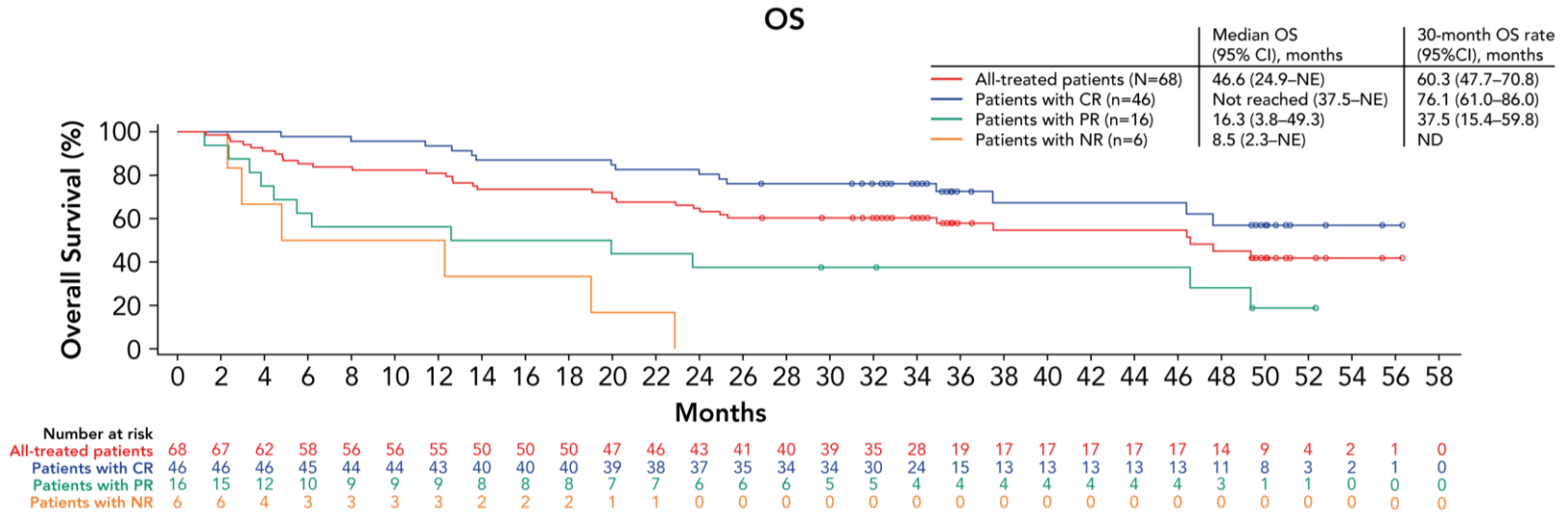
- After a median follow-up of 35.6 months (range, 25.9-56.3), the ORR (CR + partial response [PR]) was 91% (95% CI, 81.8-96.7), with a 68% CR rate (95% CI, 55.2-78.5) and a median DOR of 28.2 months (95% CI, 13.5-47.1)
- In the ITT population, ORR was 84% (95% CI, 73.4-91.3), with a 62% CR rate (95% CI, 50.1-73.2)

With 3-years of follow-up, these data demonstrate that a single infusion of KTE-X19 resulted in high rates of durable responses in R/R MCL.

Assessed by an IRRC according to the Lugano Classification.[1] [a] Since the previous report,[2] 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; DOR, duration of remission; IRRC, Independent Radiology Review Committee; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

1. Cheson BD, et al. J Clin Oncol. 2014;32:3059-3068. 2. Wang M, et al. *Blood*. 2020;136(suppl 1):20-22.

Overall Survival (OS) in All Treated Patients (N=68)



- The median progression-free survival (PFS) was 25.8 months, as shown in the full poster
- In the ITT population (data not shown), the median PFS was 24.0 months and the median OS was 47.4 months

Median OS among treated patients was 46.6 months and was not reached among those who achieved CR.

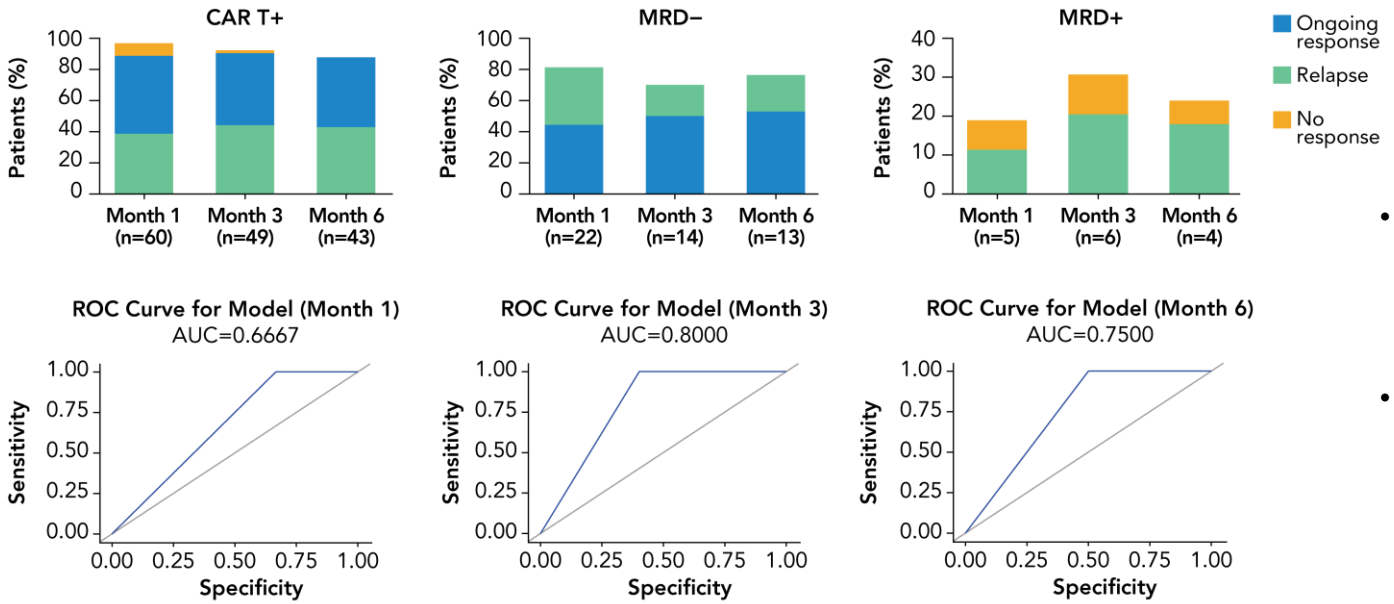
Median follow-up 35.6 months.
CR, complete remission; mo, month; NE, not estimable; NR, no response; OS, overall survival; PFS, progression-frere survival.

Overall AEs and AEs Occurring Since the Primary Analysis Report

	All-Treated Patients (N=68)				
	Overall AEs Occurring Since Infusion	AEs Occurring Since the Primary Analysis Report			
		Any Grade	Grade 3	Grade 4	Grade 5
AEs, n (%)					
Any	68 (100)	18 (26)	4 (6)	7 (10)	3 (4)
Any KTE-X19–related	66 (97)	9 (13)	2 (3)	6 (9)	0
Serious AEs, n (%)					
Any	48 (71)	8 (12)	4 (6)	0	3 (4)
Serious KTE-X19–related	37 (54)	2 (3)	2 (3)	0	0
CRS or neurologic events, n (%)	63 (93)	2 (3)	1 (1)	0	0
CRS[a]	62 (91)	0	0	0	0
Neurologic events	43 (63)	2 (3)	1 (1)[b]	0	0
Serious neurologic event	22 (32)	1 (1)	1 (1)[b]	0	0
Cytopenias, n (%)					
Thrombocytopenia	50 (74)	2 (3)	0	2 (3)	0
Neutropenia	59 (87)	8 (12)	1 (1)	7 (10)	0
Anemia	47 (69)	3 (4)	2 (3)	0	0
Infection, n (%)					
Any	36 (53)	7 (10)	3 (4)	0	1 (1)
Serious	21 (31)	4 (6)	3 (4)	0	1 (1)
COVID-19 associated viral	0	0	0	0	0
Non–COVID-19 associated viral	11 (16)	3 (4)	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[1]; 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. [a]CRS events were graded per revised Lee et al. 2014 grading system[12]; all other AEs were graded per Common Terminology Criteria for Adverse Events version 4.03. [b]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. 1. Wang M, et al. N Engl J Med. 2020;382:1331-1342.

MRD Detection at 3 and 6 Months Predicts Relapse

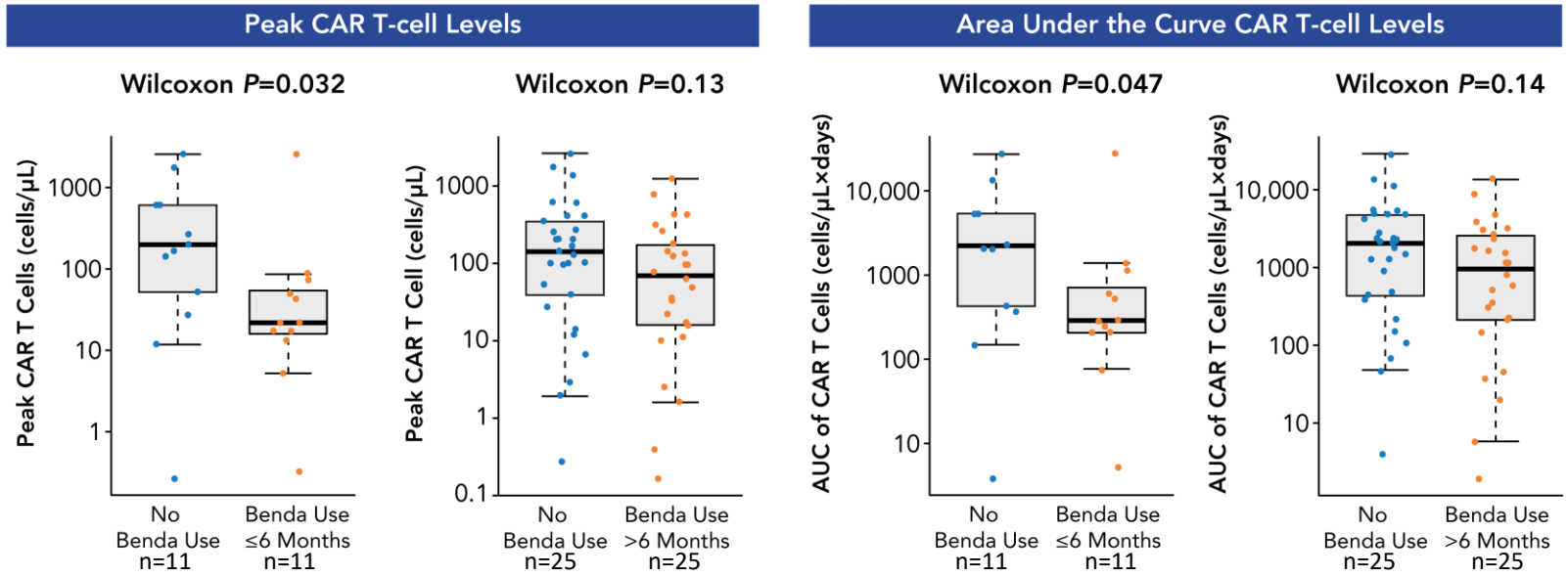


- MRD-negative status at Months 1, 3, and 6 was associated with durable response
- ROC MRD at Months 3 and 6 is predictive of relapse potential (AUC 0.80 and 0.75, respectively)

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. However, sample size of this exploratory analysis was limited, further investigation is warranted.

Median follow-up 35.6 months.
AUC, area under the curve; CAR, chimeric antigen receptor; MRD, minimal residual disease; ROC, receiver operating characteristics.

Comparison of Pharmacokinetics After Propensity Score Matching of Patients With and Without Prior Bendamustine Exposure



- An exploratory analysis using propensity score matching (1:1) found peak and area under the curve CAR T-cell levels were significantly lower in patients with prior bendamustine use within 6 months of CAR T-cell infusion compared to patients with no prior bendamustine use

Patients may benefit from longer time spans between prior bendamustine and cell therapy, though further analyses are warranted.

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

US Lymphoma CAR T Consortium Experience of Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma in Standard-of-Care Practice

Background

- Brexucabtagene autoleucel (brexu-cel) was approved by the US FDA for relapsed or refractory MCL based on the pivotal ZUMA-2 study.
- Brexu-cel demonstrated high response rates (ORR 91%, CR 68%) in ZUMA-2, and 3-year follow-up demonstrated durable responses, with a median PFS of 25.8 months and a median OS of 46.6 months.
- Patients treated in clinical trials often differ from those treated in standard-of-care practice.
- We report the pattern of use, safety, and efficacy of brexu-cel in standard-of-care practice among centers in the US Lymphoma CAR-T Consortium.

Key ZUMA-2 Eligibility Criteria

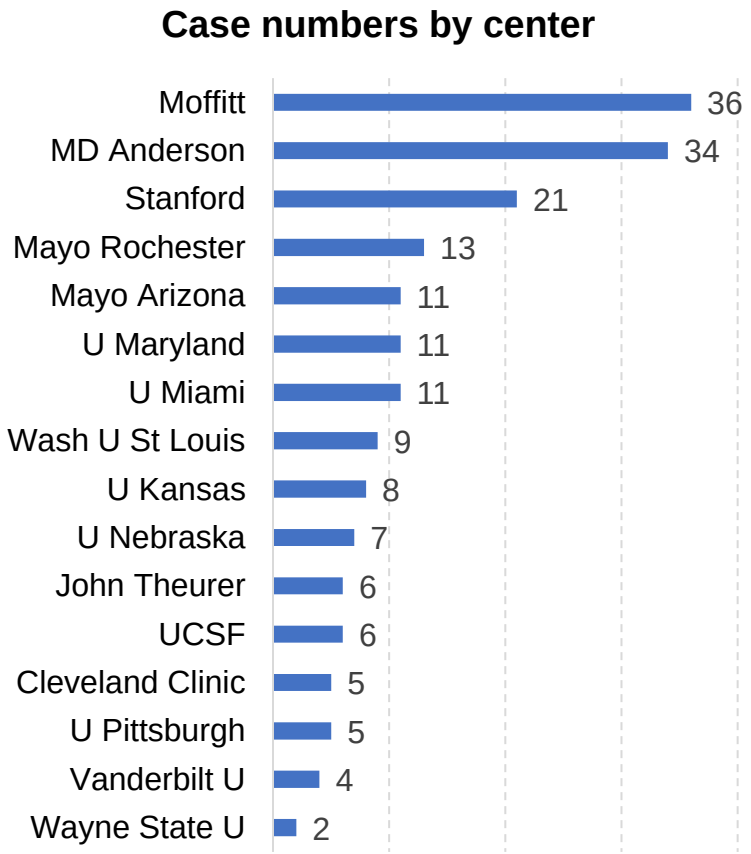
- 1-5 lines of prior therapy, must have included:
  - ✓ Anti-CD20
  - ✓ Anthracycline or bendamustine
  - ✓ Ibrutinib or acalabrutinib
- No CNS involvement
- ECOG PS<2
- Adequate blood counts
- Adequate hepatic and renal function, e.g., CrCl ≥60
- No significant comorbidities

ZUMA-2 Bridging Therapy

- Corticosteroid
- Ibrutinib
- Acalabrutinib

Methods

- Sixteen centers participated in this retrospective study.
- Patients who underwent leukapheresis by December 2021 with an intent to manufacture brexu-cel were included.
- Baseline clinical characteristics, bridging therapy, adverse events after brexu-cel infusion, and post-infusion outcome data were collected.
- Eligibility for ZUMA-2 was retrospectively determined based on characteristics at the time of leukapheresis.
- Duration of response, PFS, and OS were analyzed using the Kaplan-Meier method.



Brexu-Cel RWE: Patient characteristics

Variable	Number	Variable	Number
Age, median (range)	67 (34-89)	**Prior therapies**	
Sex, male	128 (76%)	Total lines, median (range)	3 (1-10)
ECOG PS ≥2	18 (11%)	Prior anthracycline or bendamustine	150 (89%)
Simplified MIPI		Prior bendamustine	85 (51%)
Intermediate risk (4-5)	87 (52%)	Prior cytarabine	88 (52%)
High risk (6-11)	26 (15%)	Prior AutoSCT	47 (28%)
Ki-67 ≥30%	118/152 (78%)	Prior rituximab maintenance	78 (46%)
Ki-67 ≥50%	86/152 (57%)	Prior BTKi	144 (86%)
Blastoid/pleomorphic	68 (40%)	BTKi-refractory n=128, BTKi-intolerant n=10	
***TP53* mutation or deletion**	61/126 (48%)	Prior lenalidomide	32 (19%)
Complex karyotype	31/111 (28%)	Prior venetoclax	54 (32%)
Stage III-IV	151 (90%)	**POD24**	87 (52%)
CNS involvement	16 (10%)	**Disease status before CAR T**	
Bone marrow involvement	65/118 (55%)	Relapsed after last line	94 (56%)
Bulky disease (≥10 cm)	24 (14%)	Refractory to last line	74 (44%)

Brexu-Cel RWE: ZUMA-2 ineligibility and bridging therapy

Reasons for ZUMA-2 ineligibility	Number (%)
Any reason	**129 (77%)**
ZUMA-2 ineligible solely due to being BTKi- and/or anthracycline-/bendamustine-naïve	26 (15%)
ZUMA-2 ineligible due to disease status (R/R after 5 lines of therapy, AlloSCT or anti-CD19 CAR cell therapy, CNS or cardiac involvement) **or clinically significant comorbidities**	**103 (61%)**
Top reasons	
Creatinine clearance <60 mL/min	33 (20%)
No prior BTKi	24 (14%)
Prior lines of therapy >5	19 (11%)
No prior anthracycline/bendamustine	18 (11%)
ECOG PS ≥2	18 (11%)
CNS involvement by lymphoma	16 (10%)
Significant cardiac disease <12 months	13 (8%)
Platelet <50,000/µL	11 (7%)
ANC <1000/µL	9 (5%)
Clinically significant pleural effusion	9 (5%)
Another active malignancy within 3 years	9 (5%)

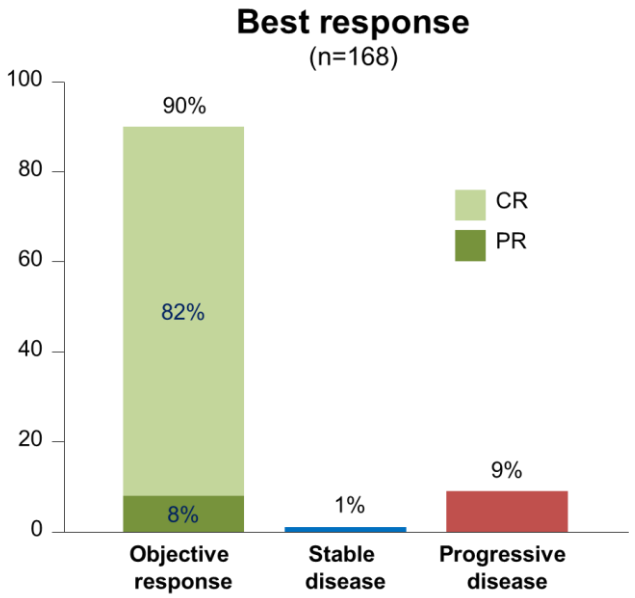
Bridging therapy	Number
BTKi-based	30
Venetoclax ± CD20	8
BTKi + Venetoclax-based	16
(R-)Chemo ± Steroid	35
(R-)Chemo + Radiation ± Steroid	5
Lenalidomide-based	6
Radiation ± Steroid ± CD20	10
Steroid and/or steroid	4
Total	**114 (68%)**
Response to bridging therapy	
CR	5 (6%)
PR	26 (30%)
SD	25 (28%)
PD	32 (36%)
Not assessed/unknown	26

Brexu-Cel: AEs of interest

CRS and ICANS Incidences				
	CRS, n (%)	**ICANS, n (%)**	CRS in ZUMA-2 (%)	NE in ZUMA-2 (%)
Total	151 (90%)	103 (61%)	91%	63%
Maximum grade				
1-2	138 (82%)	49 (29%)	76%	32%
3-4	12 (7%)	54 (32%)	15%	31%
5	1 (1%)			
Management of CRS and/or ICANS				
Tocilizumab	129 (77%)		59%	26%
Tocilizumab doses, median (range)	2 (1-4)			
Steroid	116 (69%)		22%	38%
Anakinra	28 (17%)			
Siltuximab	5 (3%)			

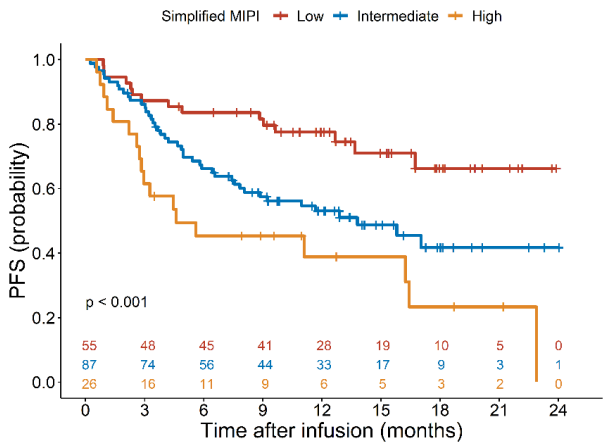
Cytopenia and infection	Day 30, n (%)	Day 90, n (%)
Hemoglobin < 8 g/dL	13/164 (8%)	8/146 (5%)
Platelet < 50,000/µL	70/164 (43%)	16/146 (11%)
ANC < 1000/µL	54/164 (33%)	27/146 (18%)
ANC < 500/µL	23/164 (14%)	9/146 (6%)
Infections	Days 0-30: 35/168 (21%)	Days 31-90: 19/164 (12%)

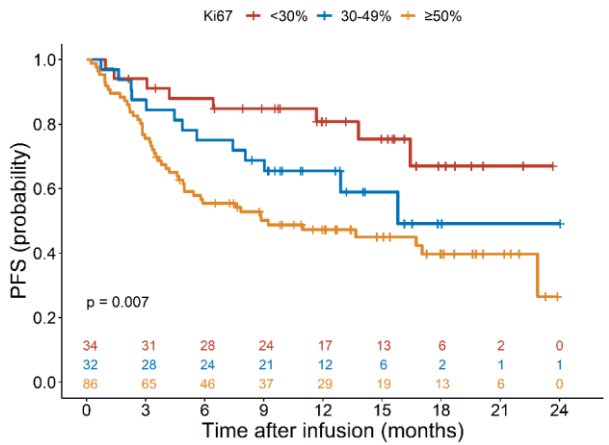
Brexu-Cel RWE: Response rate

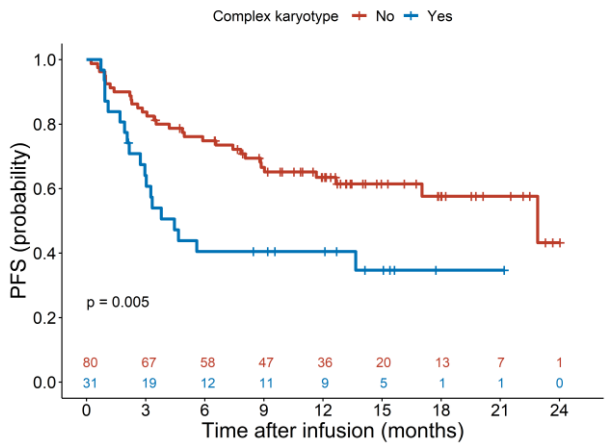


Subgroup	ORR (95% CI)	CR rate (95% CI)
All (n=168)	90 (84-94)	82 (75-88)
Blastoid/pleomorphic		
No (n=100)	90 (82-95)	82 (73-89)
Yes (n=68)	90(80-96)	82 (71-91)
***TP53* aberration**		
No (n=65)	91 (81-97)	88 (77-95)
Yes (n=61)	89 (78-95)	72 (59-83)
Complex karyotype		
No (n=80)	86 (77-93)	81 (71-89)
Yes (n=31)	87 (70-96)	74 (55-88)
Ki67 proliferation index		
<30% (n=34)	91 (76-98)	91 (76-98)
30-49% (n=32)	97 (84-100)	84 (67-95)
≥50% (n=86)	88 (80-94)	78 (68-86)
Simplified MIPI risk group		
Low risk (n=55)	95 (85-99)	91 (80-97)
Intermediate risk (n=87)	90 (81-95)	82 (72-89)
High risk (n=26)	81 (61-93)	65 (44-83)
POD24		
No (n=81)	94 (86-98)	89 (80-95)
Yes (n=87)	86 (77-93)	76 (65-84)
CNS involvement		
No (n=152)	91 (85-95)	83 (76-89)
Yes (n=16)	81 (54-96)	75 (48-93)
BTKi history		
BTKi-naïve (n=24)	96 (79-100)	88 (68-97)
BTKi-exposed (n=144)	89 (83-94)	81 (74-87)
BTKi-refractory (n=128)	89 (82-94)	80 (73-87)
BTKi-intolerance (n=10)	80 (44-97)	80 (44-97)
BTKi-sensitive (n=6)	100 (54-100)	100 (54-100)
ZUMA-2 eligibility		
Eligible (n=39)	90 (76-97)	85 (69-94)
Ineligible (n=129)	90 (83-95)	81 (74-88)
Ineligible due to BTKi- or anthracycline/bendamustine-naïve (n=26)	96 (80-100)	96 (80-100)
Ineligible due to disease status or comorbidities (n=103)	88 (81-94)	78 (68-85)
Bridging therapy		
No (n=54)	93 (82-98)	81 (69-91)
Yes (n=114)	89 (81-94)	82 (74-89)

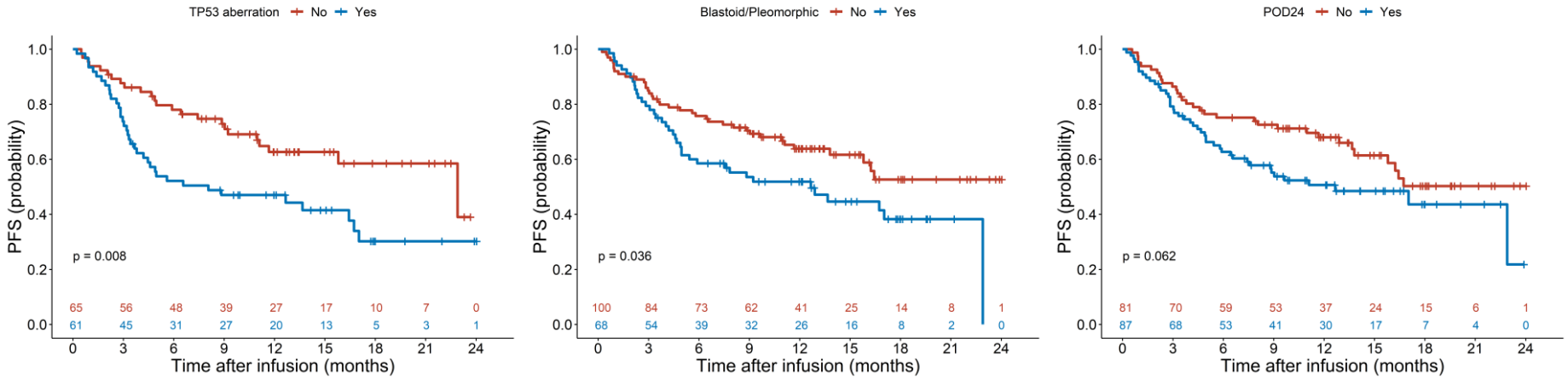
Brexu-Cel RWE: PFS by subgroup



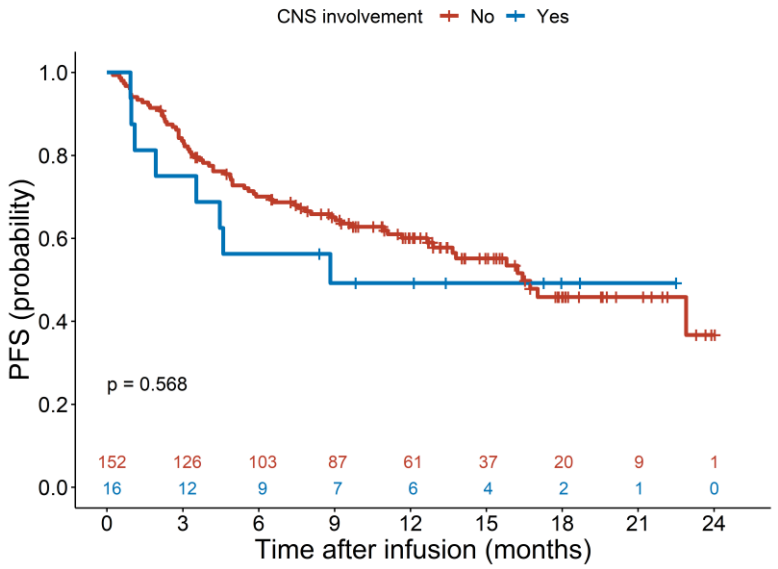


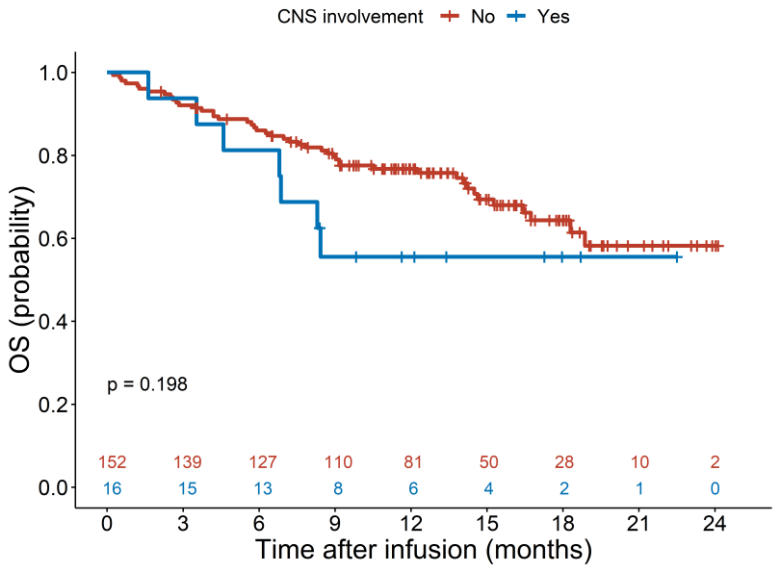


Brexu-Cel RWE: PFS by subgroup

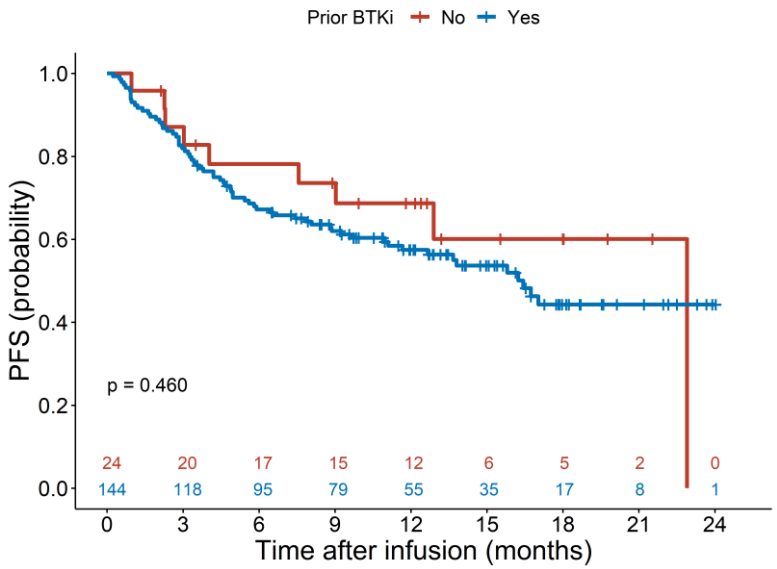


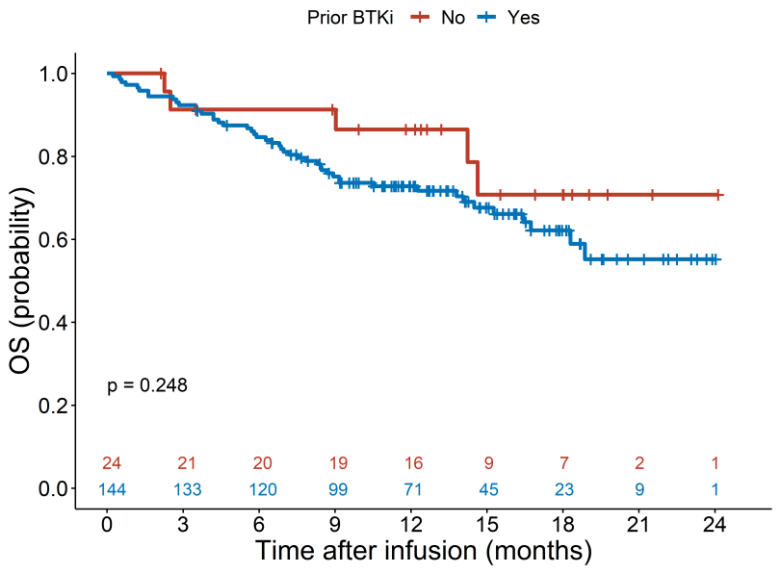
Brexu-Cel RWE: Feasibility in patients with CNS involvement



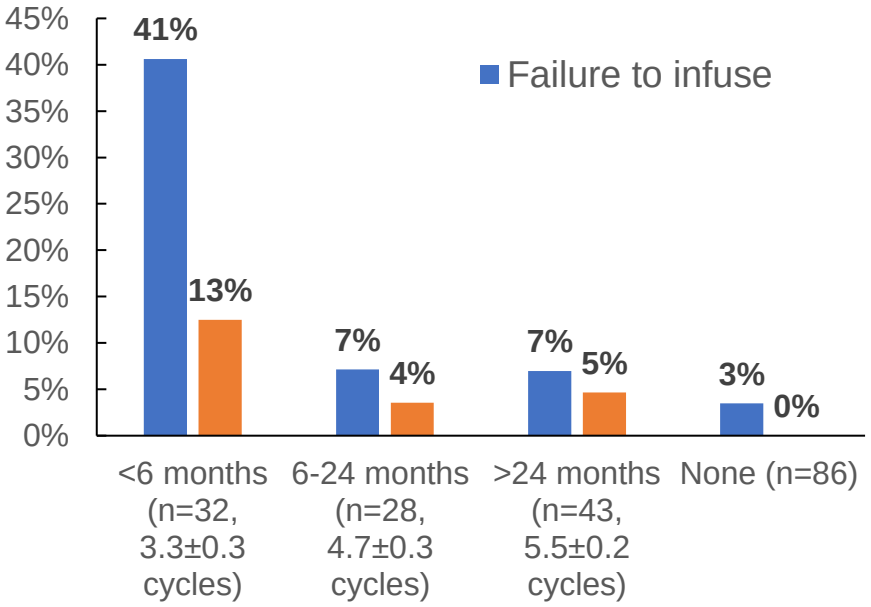


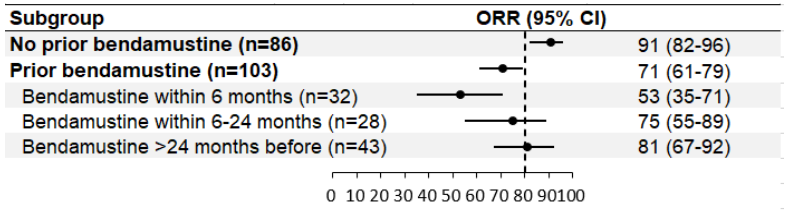
Brexu-Cel RWE: Impact of prior BTKi

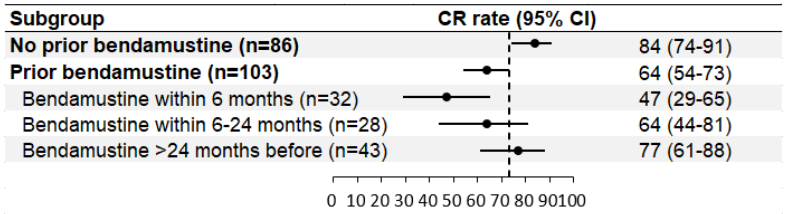




Brexu-Cel RWE: Impact of prior bendamustine exposure







Summary

- Real-world data of brexu-cel in standard-of-care appear comparable to ZUMA-2 data, but long-term follow-up is needed.
- Disease intrinsic high-risk features may still be associated with inferior outcomes in the setting of CAR-T.
- Recent bendamustine exposure is associated with inferior outcomes of CAR-T.