The Role of CAR-T Cell Therapy in *Mantle Cell Lymphoma*

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MANTLE CELL LYMPHOMA: NOW and BEYOND
Rome, Donna Camilla Savelli Hotel

Mantle Cell Lymphoma: Where does CAR-T cell therapy fit?

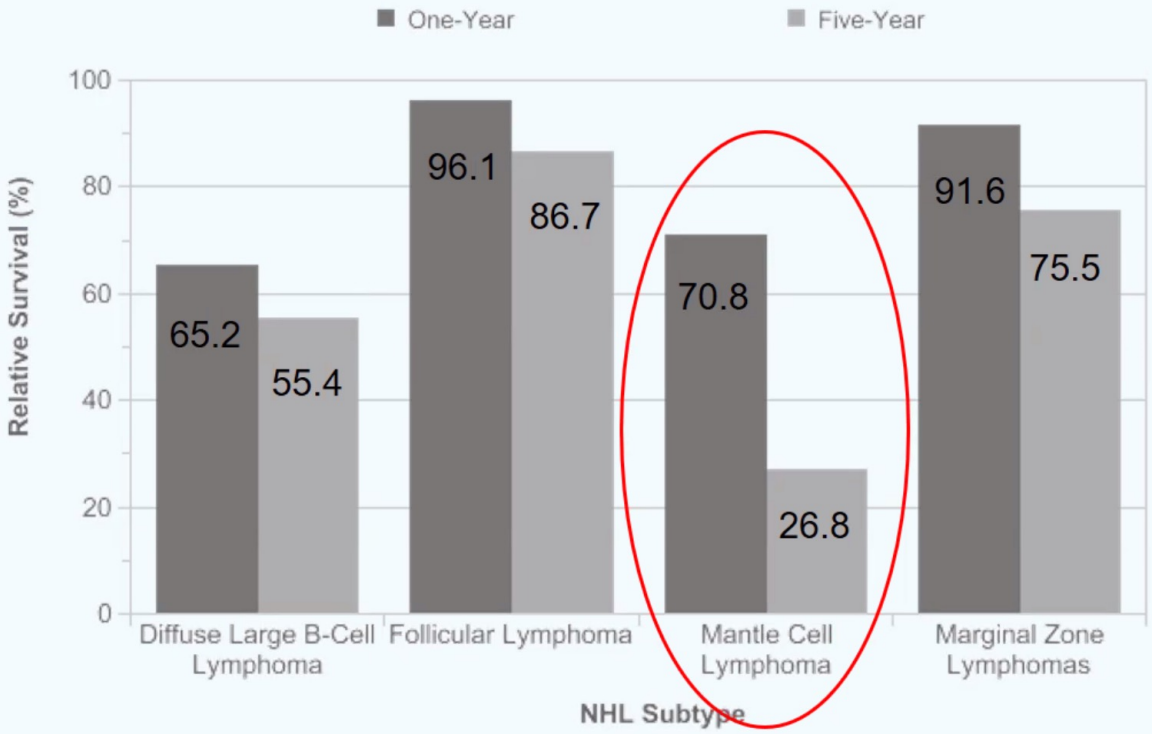
"I don't know yet, but we will all find out soon as the larger clinical trials mature…"

Mantle Cell Lymphoma: Now and Beyond
November 8, 2019

Mantle Cell Lymphoma: Role of CAR-T Cells
Stephen J. Schuster, M.D.

Mantle Cell Lymphoma: A Continuing Challenge

One- and Five-Year Relative Survival (%), All Ages, 2004 - 2011

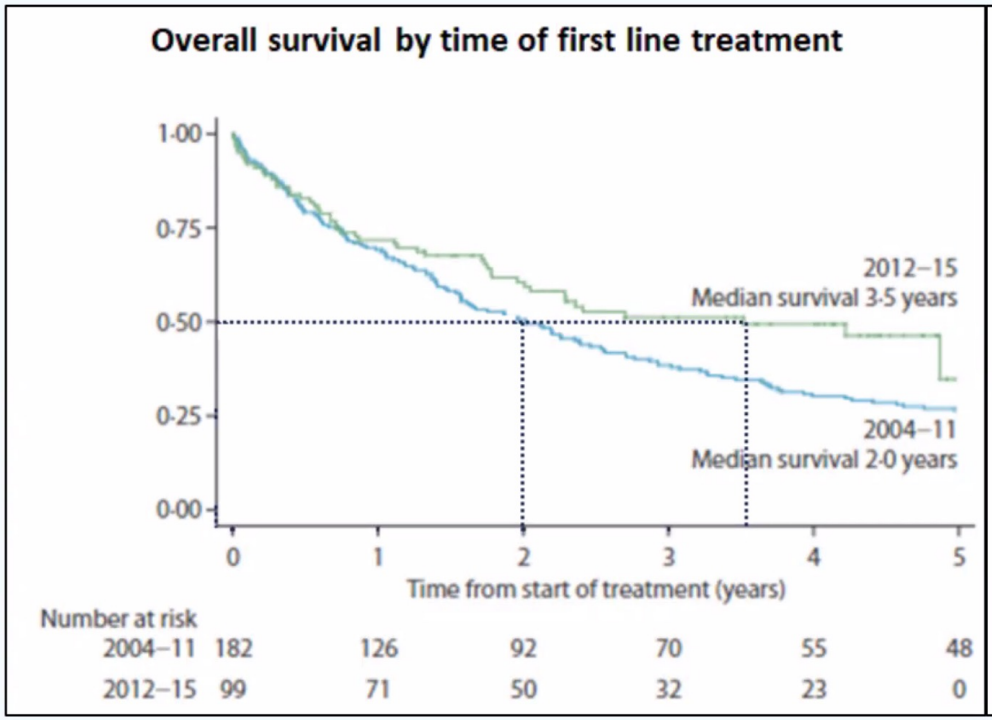


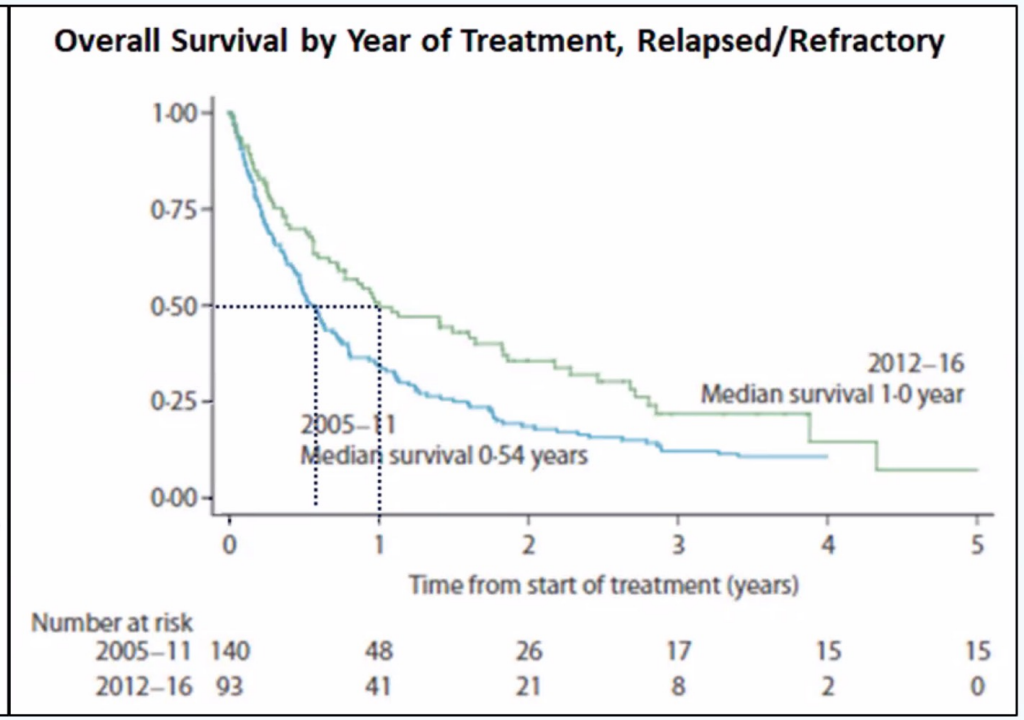
Haematological Malignancy Research Network (HMRN)

CANCER RESEARCH UK

http://info.cancerresearchuk.org/cancerstats/faqs/#How

Mantle Cell Lymphoma: Impact of Newer Therapies, 2012 - 15



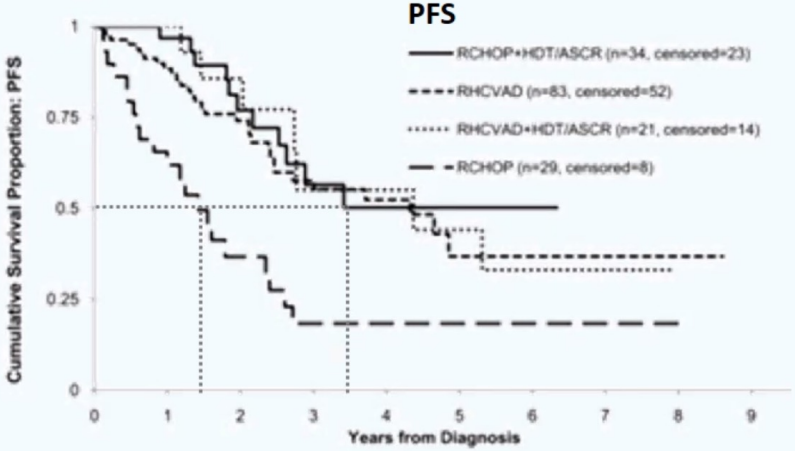


Smith A, *et al.* Br J Haematol. 2018 Apr; 181(2): 215–228.

MCL Outcomes: Conventional Immunochemotherapies

NCCN Oncology Outcomes Database: Age <65 [1]

PFS



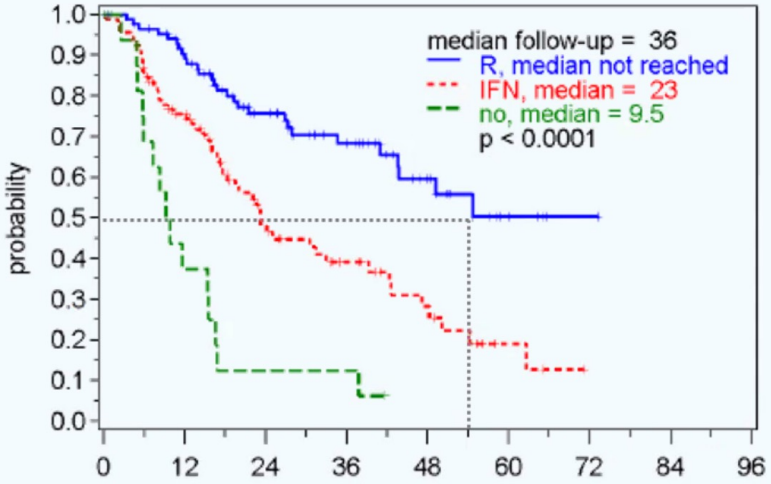
Median follow-up: 33 months	
3-year PFS:	
R-HCVAD	58%
R-CHOP + HDT/ASCT	56%
R-HCVAD + HDT/ASCT	55%
R-CHOP	18%

Selected Nonintensive Regimens [2]

PFS

Regimen	First Author	mPFS (months)
R-CHOP	Kluin-Nelemans	26
R-FC		28
Bendamustine rituximab	Rummel	35.4
R-CHOP		22.1
R-CHOP + RIT	Smith	34.2

DOR after R-CHOP by Maintenance [3]



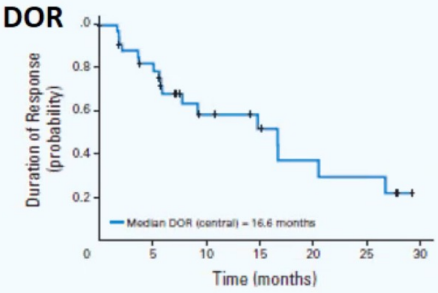
[1] LaCasce *et al.* Blood. 2012; 119(9): 2093-2099.
[2] Cheah *et al.* J Clin Oncol. 2016; 34:1256-1269.
[3] Kluin-Nelemans *et al.* NEJM. 2012; 367:520-531

Relapsed or Refractory MCL Outcomes: Newer Agents

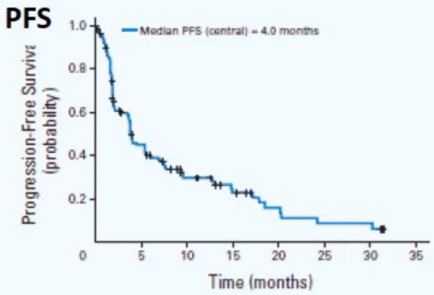
Lenalidomide

ORR: 28% (7.5% CR)

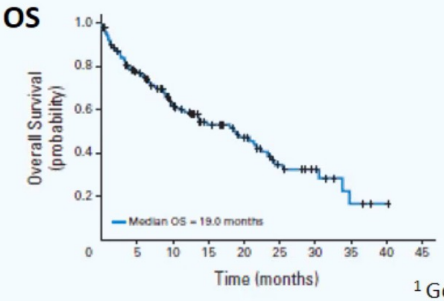
DOR



PFS



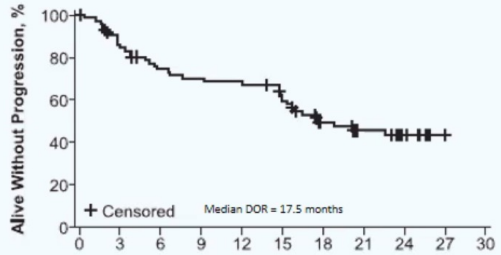
OS



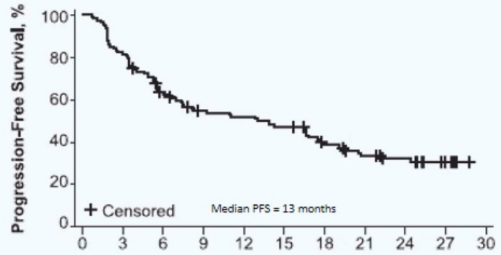
Ibrutinib

ORR: 67% (23% CR)

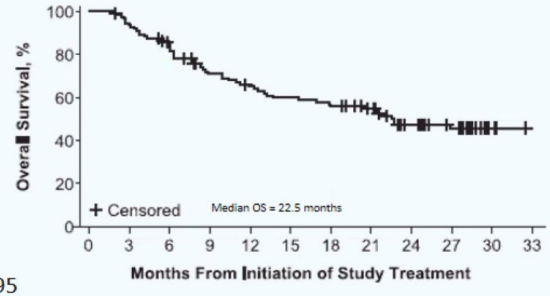
Duration of Response



Progression-Free Survival



Overall Survival



[1] Goy *et al.* J Clin Oncol. 2013; 31:3688-3695
[2] Wang *et al.* Blood. 2015;126(6):739-745

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]

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Wang M, *et al. J Clin Oncol*. 2022; JCO2102370. doi:10.1200/JCO.21.02370

Journal of Clinical Oncology®

Original Reports

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 Kharat, MD[16]; Mac 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]; Joana Kloos, MD[20]; and Patrick M. Reagan, MD[20]

PURPOSE Brexucabtagene autoleucel (KTE-X19) autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy is approved for the treatment of relapsed/refractory mantle cell lymphoma (MCL). Outcomes after a 3-year follow-up in the pivotal ZUMA-2 study of KTE-X19 in relapsed/refractory MCL are reported, including for subgroups by prior therapy (bendamustine and type of Bruton tyrosine kinase inhibitor [BTKi]) or high-risk characteristics.

METHODS Patients with relapsed/refractory MCL (one to five prior therapies, including prior BTKi exposure) received a single infusion of KTE-X19 (2×10^6 CAR T cells/kg).

RESULTS After a median follow-up of 35.6 months, the objective response rate among all 68 treated patients was 91% (95% CI, 81.8 to 96.7) with 68% complete responses (95% CI, 55.2 to 78.5); medians for duration of response, progression-free survival, and overall survival were 28.2 months (95% CI, 13.5 to 47.1), 25.8 months (95% CI, 9.6 to 47.6), and 46.6 months (95% CI, 24.9 to not estimable), respectively. Post hoc analyses showed that objective response rates and ongoing response rates were consistent among prespecified subgroups by prior BTKi exposure or high-risk characteristics. In an exploratory analysis, patients with prior bendamustine benefited from KTE-X19, but showed a trend toward attenuated T-cell functionality, with more impact of bendamustine given within 6 versus 12 months of leukapheresis. Late-onset toxicities were infrequent; only 3% of treatment-emergent adverse events of interest in ZUMA-2 occurred during this longer follow-up period. Translational assessments revealed associations with long-term benefits of KTE-X19 including high-peak CAR T-cell expansion in responders and the predictive value of minimal residual disease for relapse.

CONCLUSION These data, representing the longest follow-up of CAR T-cell therapy in patients with MCL to date, suggest that KTE-X19 induced durable long-term responses with manageable safety in patients with relapsed/refractory MCL and may also benefit those with high-risk characteristics.

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ASSOCIATED CONTENT
Data Supplement
Protocol

Author affiliations and support information (if applicable) appear at the end of this article.
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INTRODUCTION

Despite recent therapeutic advances in mantle cell lymphoma (MCL), most treatments provide limited duration responses, indicating high unmet need for novel therapies.[1,2] In patients who discontinue the Bruton tyrosine kinase inhibitor (BTKi) ibrutinib because of progressive disease or intolerance, reports indicate that the median overall survival (OS) ranges from 2.5 to 14.2 months.[3-12] MCL prognosis depends on MCL risk factors, with important high-risk factors including blastoid variant,[13,14] high Ki-67 proliferation index (PI),[15] tumor protein p53 gene (*TP53*) mutation[16] or high P53 expression,[17] and disease progression within 24 months after initial diagnosis (POD24).[18,19] Patients with these characteristics have limited treatment options and poor outcomes, with a median OS of 6.6 months to 4 years after initial therapy.[7,18,20] In addition, treatments in previous lines may affect outcomes with subsequent therapies; for example, bendamustine-containing treatments may be associated with reduced T-cell number and function, potentially affecting cellular therapies.[21]

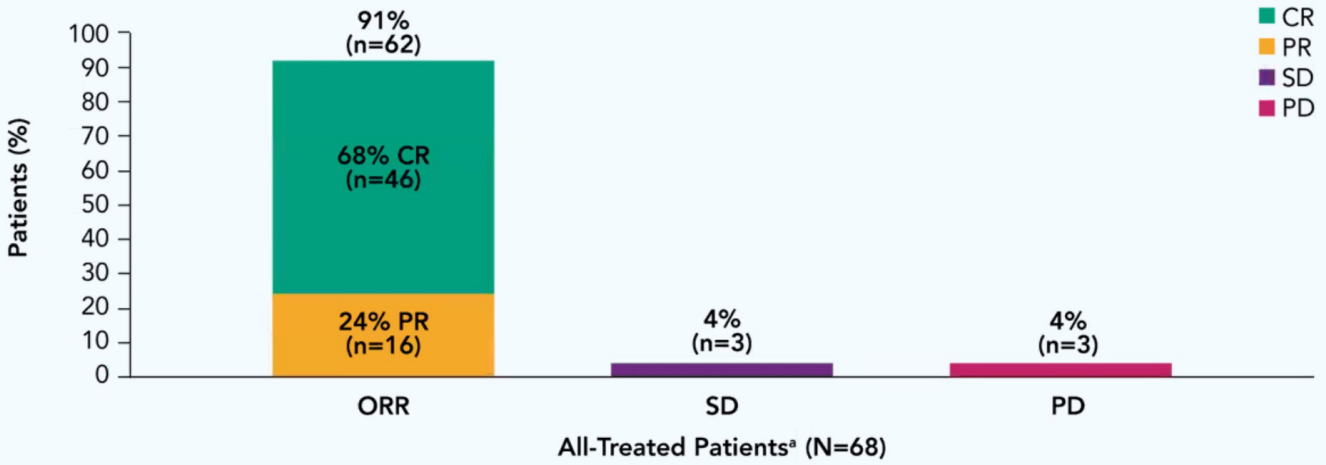
ZUMA-2 (ClinicalTrials.gov identifier: NCT02601313) is a pivotal, single-arm, multicenter, phase II trial of the autologous anti-CD19 chimeric antigen receptor (CAR) T-cell therapy brexucabtagene autoleucel (KTE-X19) in patients with heavily pretreated MCL that was relapsed/

SCAN ME

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

ascopubs.org/doi/full/10.1200/JCO.21.02370

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)

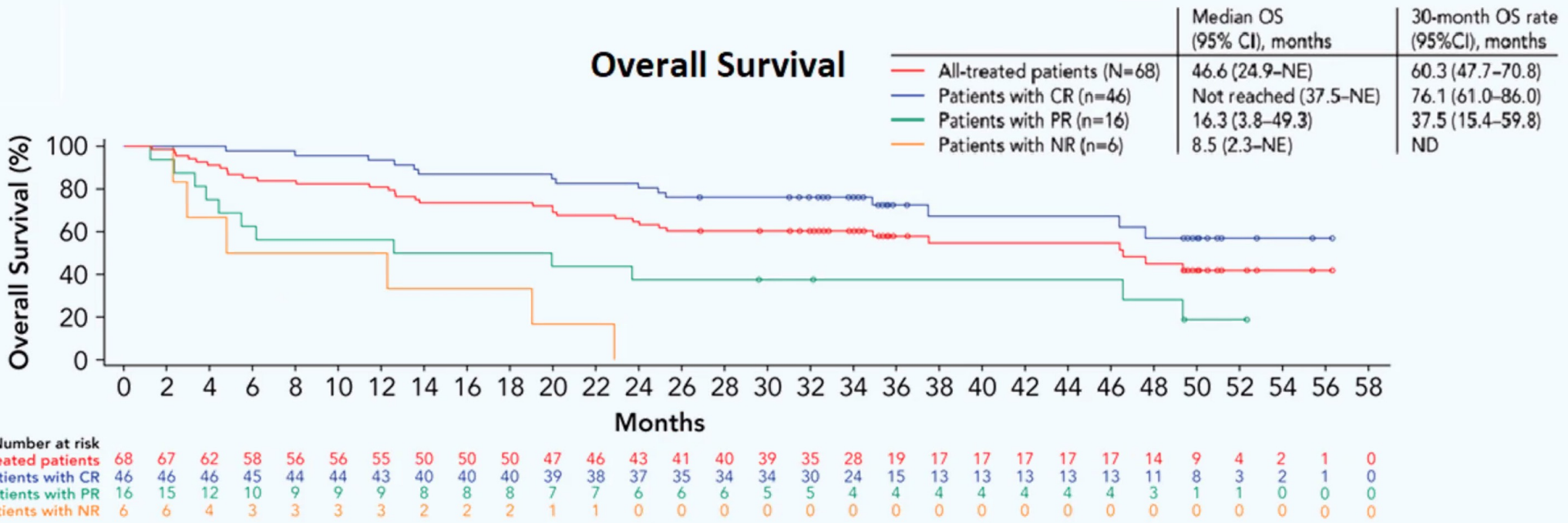
With 3-years of follow-up, these data demonstrate that a single infusion of KTE-X19 resulted in high response rates and durable responses in R/R MCL.

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.

Wang M, *et al. J Clin Oncol*. 2022; JCO2102370. doi:10.1200/JCO.21.02370

Overall Survival in All Treated Patients: 3-Year Follow Up (N=68)



Median OS among all 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-free survival.

Wang M, *et al. J Clin Oncol*. 2022; JCO2102370. doi:10.1200/JCO.21.02370

KTE-X19 CAR-T Therapy in R/R MCL: CRS and Neurotoxicity

Cytokine Release Syndrome and Neurologic Events among All 68 Treated Patients.*

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Symptom of cytokine release syndrome	Gr. ≥3: 15%					
Any	62 (91)	20 (29)	32 (47)	8 (12)	2 (3)	0
Pyrexia	62 (91)	15 (22)	40 (59)	7 (10)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	14 (21)	1 (1)	0
Hypoxemia	23 (34)	1 (1)	10 (15)	8 (12)	4 (6)	0
Neurologic event Gr. ≥3: 31%	43 (63)	13 (19)	9 (13)	15 (22)	6 (9)	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Confusional state	14 (21)	3 (4)	3 (4)	8 (12)	0	0
Aphasia	10 (15)	3 (4)	4 (6)	3 (4)	0	0

* Shown are events of any grade that occurred in at least 15% of the patients and events of grade 3 or higher that occurred in at least 4% of the patients. Cytokine release syndrome was graded according to Lee et al.[21] The severity of neurologic events and symptoms of cytokine release syndrome were graded with the use of the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Wang M, *et al. N Engl J Med* 2020;382:1331-42.

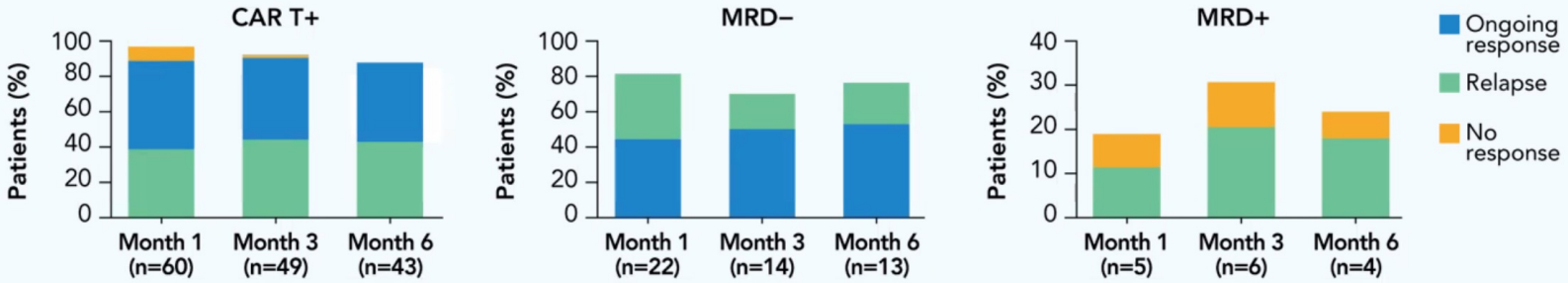
Overall AEs and AEs Occurring Since the Primary Analysis Report

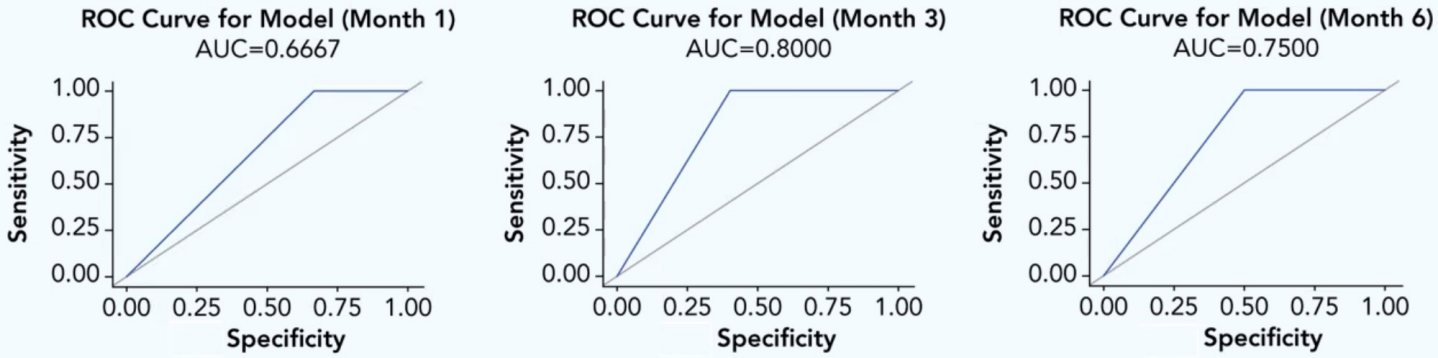
	All-Treated Patients (N=68)				
	Overall AEs Occurring Since Infusion	AEs Occurring Since the Primary Analysis Report			
		Any Grade	Grade 3	Grade 4	Grade 5
AEs, n (%)					
Any	68 (100)	18 (26)	4 (6)	7 (10)	3 (4)
Any KTE-X19–related	66 (97)	9 (13)	2 (3)	6 (9)	0
Serious AEs, n (%)					
Any	48 (71)	8 (12)	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 Lee et al. 2014; 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.

Wang M, *et al. J Clin Oncol*. 2022; JCO2102370. doi:10.1200/JCO.21.02370

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)

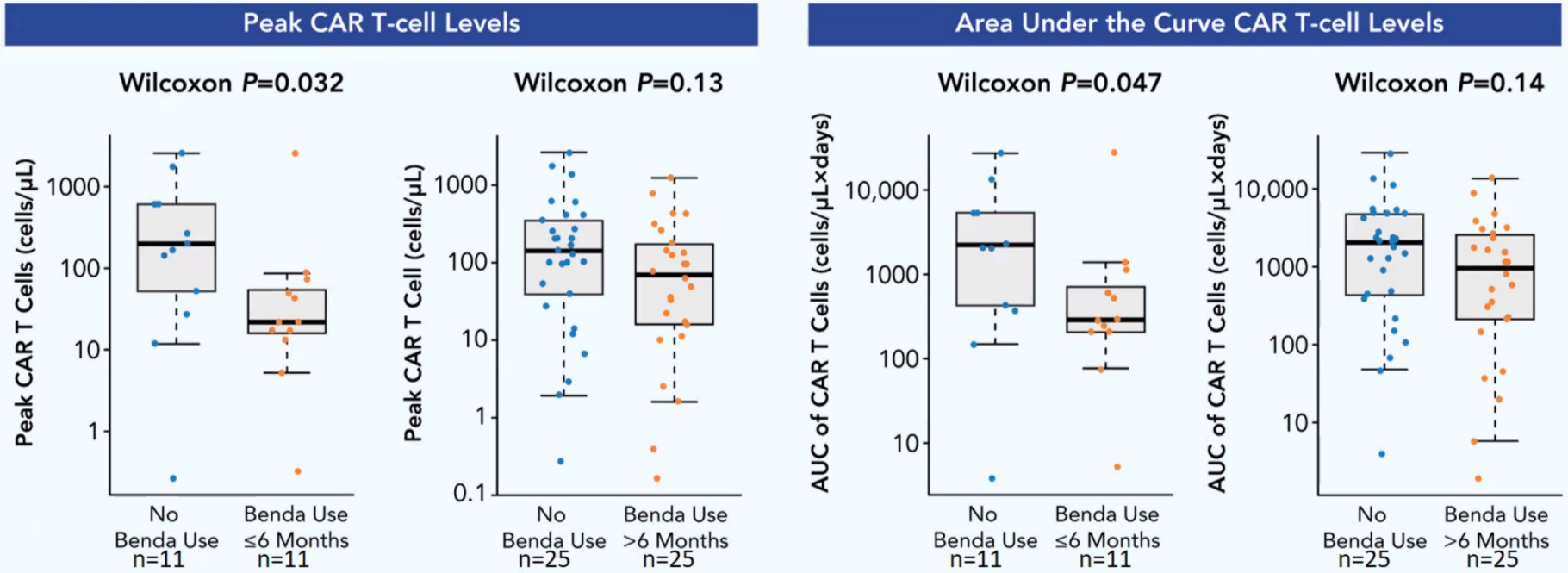
DOR, PFS, and OS were not reached in patients with MRD-negativity at 6 months, suggesting MRD-negativity may predict for a longer response duration. However, sample size of this exploratory analysis was limited, further investigation is warranted.

Median follow-up 35.6 months.

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

Wang M, *et al. J Clin Oncol*. 2022; JCO2102370. doi:10.1200/JCO.21.02370

Comparison of Pharmacokinetics After Propensity Score Matching of Patients With or 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 within 6 months of CAR-T infusion compared to patients with no prior bendamustine exposure

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.

Wang M, *et al. J Clin Oncol*. 2022; JCO2102370. doi:10.1200/JCO.21.02370

Safety and Preliminary Efficacy in Patients with Relapsed/Refractory Mantle Cell Lymphoma Receiving Lisocabtagene Maraleucel in Transcend NHL 001

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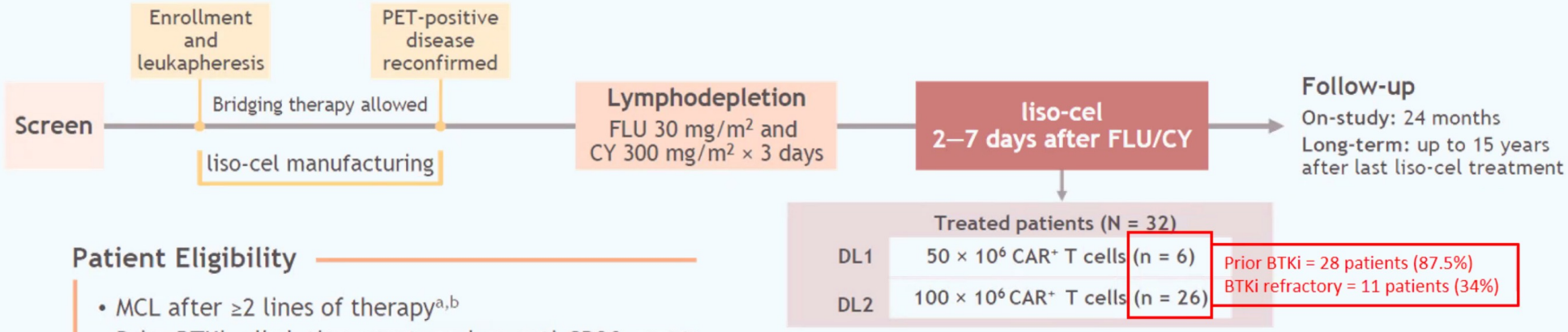
[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Northwestern University, Feinberg School of Medicine, Robert H. Lurie Comprehensive Cancer Center, Chicago, IL; [3]City of Hope National Medical Center, Duarte, CA; [4]Massachusetts General Hospital Cancer Center, Boston, MA; [5]University of Colorado Cancer Center, Aurora, CO; [6]University of Nebraska Medical Center, Omaha, NE; [7]Fred Hutchinson Cancer Research Center, Seattle, WA; [8]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA; [9]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA; [10]Levine Cancer Institute, Atrium Health, Charlotte, NC; [11]University of Alabama at Birmingham, Birmingham, AL; [12]Immunotherapy Program, Northside Hospital Cancer Institute, Atlanta, GA; [13]Juno Therapeutics, a Bristol-Myers Squibb Company, Seattle, WA; [14]Bristol-Myers Squibb Company, Princeton, NJ; [15]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX

Palomba M L, …..Wang M, *et al. Blood* 2020; 136 (Supplement 1): 10–11.

TRANSCEND NHL 001 Study Design: MCL Cohort



Patient Eligibility

- MCL after ≥2 lines of therapy[a,b]
- Prior BTKi, alkylating agent, and an anti-CD20 agent[c]
- Prior HSCT allowed (autologous/allogeneic)
- Secondary CNS lymphoma allowed
- ECOG PS of 0–2[d]
- CrCl >30 mL/min/1.73 m²
- LVEF ≥40%
- No lower threshold for ALC, ANC, platelets, or hemoglobin

End Points

Primary

- AEs, DLTs, ORR by IRC per Lugano classification

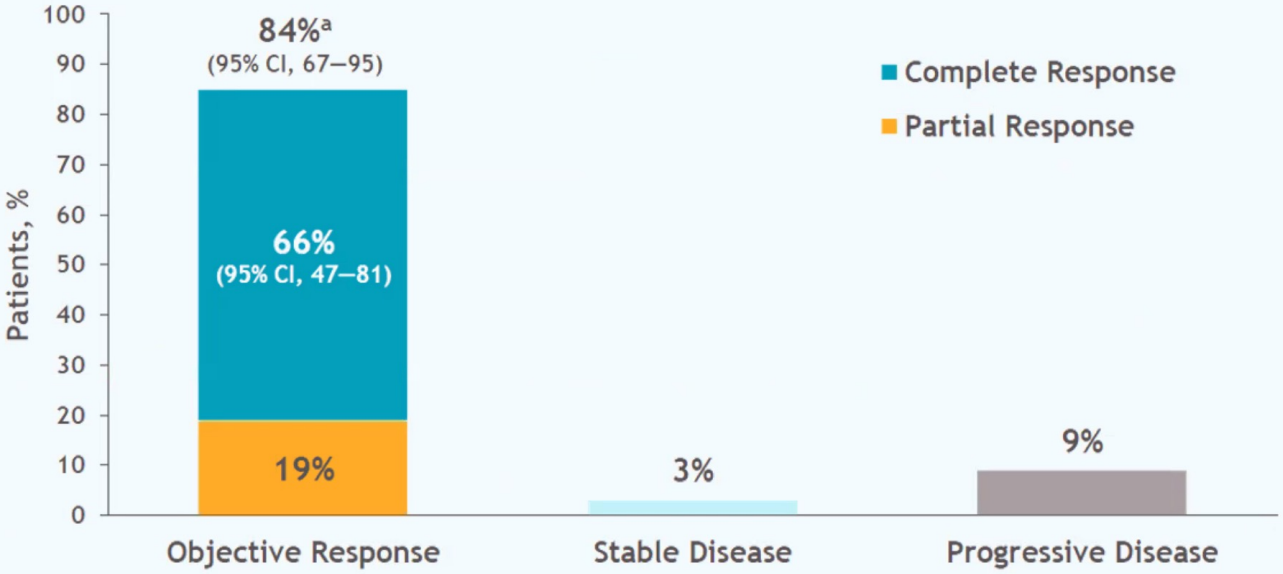
Secondary

- CR rate by IRC, duration of response, PFS, OS, cellular kinetics, HRQoL, number of ICU days

[a]Confirmed cyclin D1 expression or evidence of t(11;14). [b]The original protocol allowed enrollment of patients with R/R disease after ≥1 line of prior MCL therapy but was later amended to require ≥2 lines of prior therapy. [c]The original protocol did not include a requirement for prior treatment; this requirement was added in an amendment. [d]The original protocol allowed enrollment of patients with ECOG PS of 2 but was later amended to allow only patients with ECOG PS of 0–1.
ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CY, cyclophosphamide; DL, dose level; DLT, dose-limiting toxicity; FLU, fludarabine; IRC, independent review committee.

Palomba M L, …..Wang M, *et al. Blood* 2020; 136 (Supplement 1): 10–11.

Best Overall Response by Investigator Assessment



- Median on-study follow-up: 5.9 (range, 0.4–24.8) months
- Median time to first CR or PR: 0.95 (range, 0.9–2.0) months

- ORR and CR rate, respectively, for patients with high-risk features:
  - Ki67 ≥30% (n = 23): 83% and 65%
  - Blastoid morphology (n = 13): 77% and 54%
  - *TP53* mutations (n = 7): 100% and 57%

[a]Based on 32 patients treated; one patient was not evaluable and is not shown in the figure.

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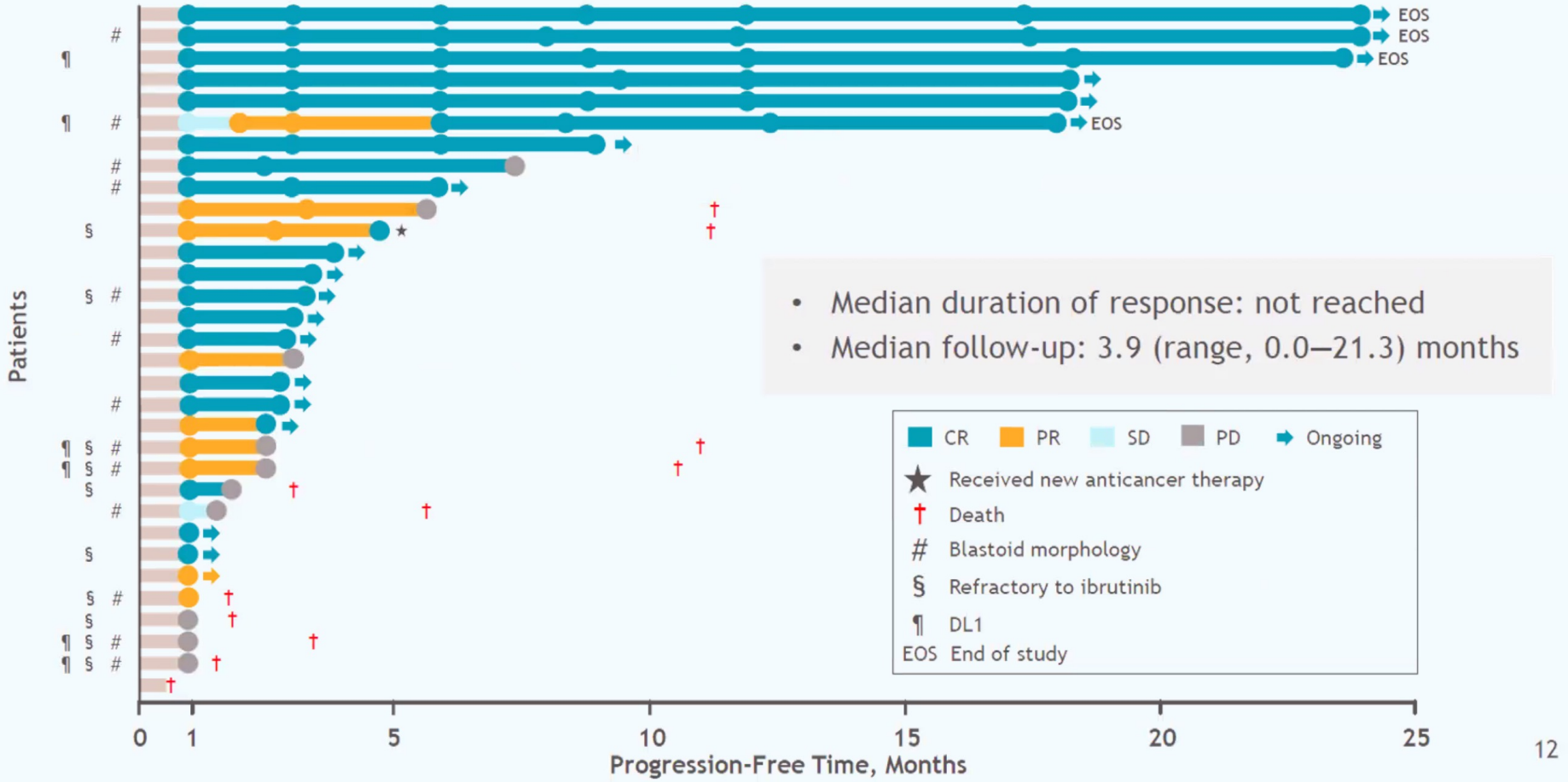
Patient Responses over Time



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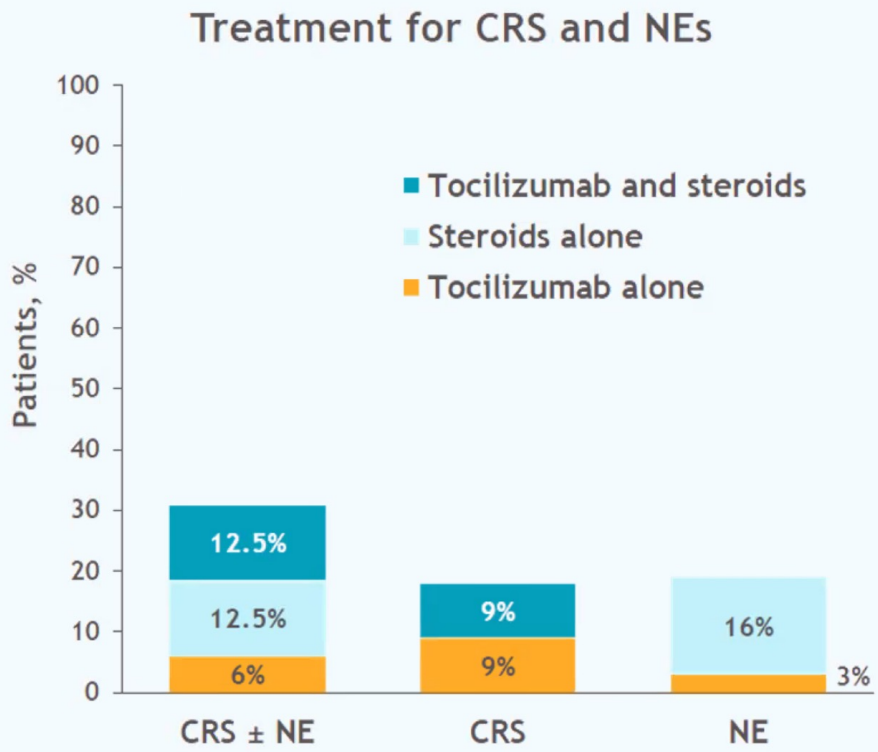
Patient Incidence and Management of CRS and NEs

	All liso-cel–Treated Patients (N = 32)
CRS or NE, n (%)	
Any grade	19 (59)
Grade ≥3	5 (16)
CRS	
Any grade, n (%)	16 (50)
Grade ≥3, n (%)	1 (3)
Time to onset, median (range), days	6 (2–10)
Time to resolution, median (range), days	4 (2–9)
NE	
Any grade, n (%)	11 (34)
Grade ≥3, n (%)	4 (12.5)
Time to onset, median (range), days	8 (2–25)
Time to resolution, median (range), days	4 (1–27)
ICU admissions, n (%)	3 (9)
CRS and/or NE	3 (9)
Other reasons	0



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Molte Grazie

Questions & Comments