Predictors of Toxicity and Response to CAR T-cell Therapy in Multiple Myeloma

Doris K. Hansen, MD
H. Lee Moffitt Cancer Center & Research Institute
Department of Blood & Marrow Transplant & Cellular Immunotherapy

October 18th, 2025
Cell Coast Conference
Tampa, FL

MOFFITT CANCER CENTER

Disclosures

Research funding

- Bristol Myers Squibb/Celgene, Janssen, Adaptive Biotechnologies, Kite Pharma, and Karyopharm
- Additional funding from Pentecost Myeloma Research Center, Myers Foundation, Schulze, and M-CARES awards (pilot grants) via Moffitt Cancer Center
- NCI/R01CA281756-01A1

Consultancy

- Bristol Myers Squibb, Janssen, Legend Biotech, Karyopharm, Kite Pharma, AstraZeneca, and Pfizer

Objectives

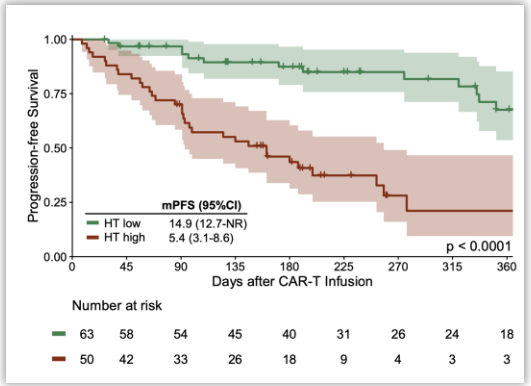
- Discuss development of a pre-apheresis predictive model for BCMA CAR-T (SCOPE-MM)
- Discuss predictors of toxicity, particularly NINT, and durable response
- Discuss talquetamab as a bridge to BCMA CAR-T

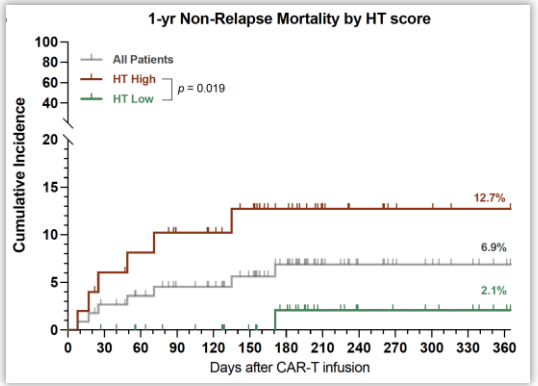
Can we predict which RRMM patient will respond or develop toxicity to BCMA CAR-T?

CAR-HEMATOTOX Score:

- ❖ Entity agnostic; validated in relapsed myeloma
- ❖ Predicts toxicity and survival in RRMM after CAR-T at lymphodepletion

Features	0 Point	1 Point	2 Points
Platelets [G/l]	> 175	75-175	< 75
ANC [per ul]	> 1200	< 1200	-
Hemoglobin [g/dl]	> 9.0	< 9.0	-
CRP [mg/dl]	< 3.0	> 3.0	> 2000
Ferritin [ng/ml]	< 650	650-2000	> 2000



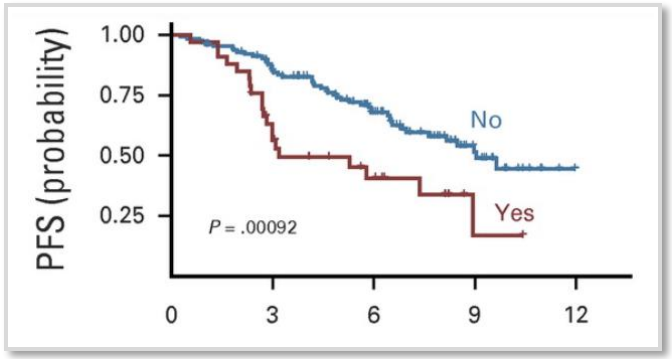


MyCARe Model:

- ❖ Built on RRMM cohort with myeloma-specific variables
- ❖ Predicts survival in RRMM after CAR-T at lymphodepletion

TABLE 2. Multivariable Modeling of Early Relapse/Progression

Factor	HR	95% CI	*P*	Score
EMD or PCL present	1.92	1.30 to 2.82	<.001	1
High-risk cytogenetics	1.95	1.31 to 2.92	.001	1
Ferritin > NL (sex-/age-adjusted)	1.59	1.07 to 2.37	.02	1
Lenalidomide refractoriness	1.69	1.02 to 2.82	.04	1
MyCARe risk				
Low (score 0-1)	Ref			
Intermediate (score 2-3)	3.27	1.87 to 5.72	<.001	
High (score 4)	7.89	4.21 to 14.79	<.001	

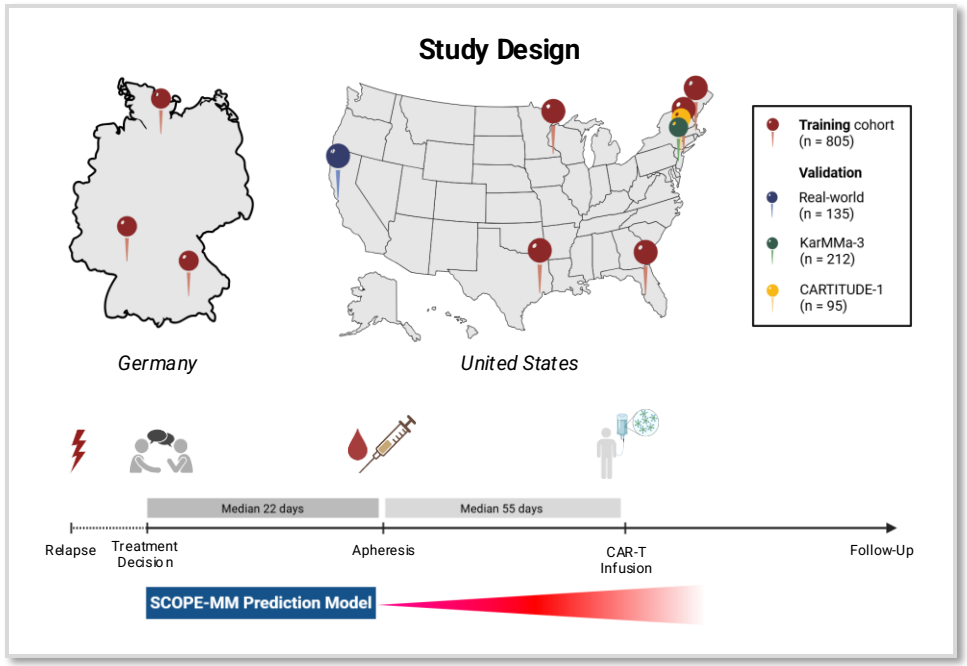


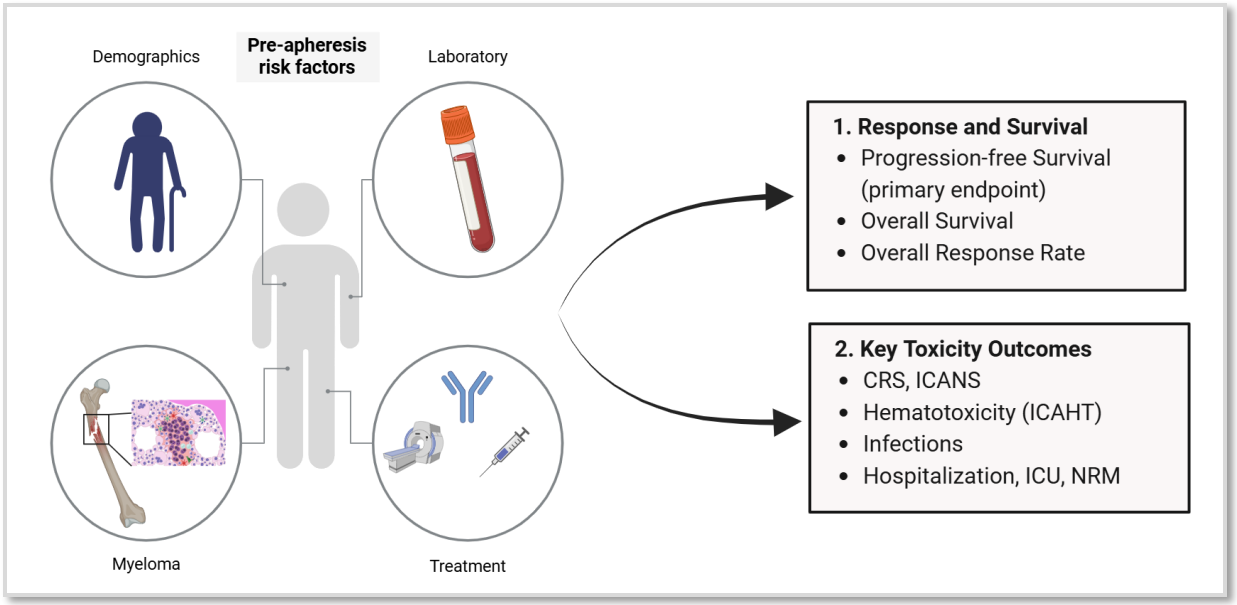
Rejeski et al. Blood 2021 | Rejeski & Hansen et al. J Hematol Oncol 2023 | Gagelmann et al. JCO 2024

SCOPE-MM: Main Study Objectives, Study Design and Data Collection

Study Aims:

1. To identify **early predictors** of CAR-T response and toxicity in RRMM patients.
2. To develop a **risk stratification model at a pre-apheresis** time point that is product-agnostic and can identify high-risk candidates for toxicity and adverse treatment outcomes.



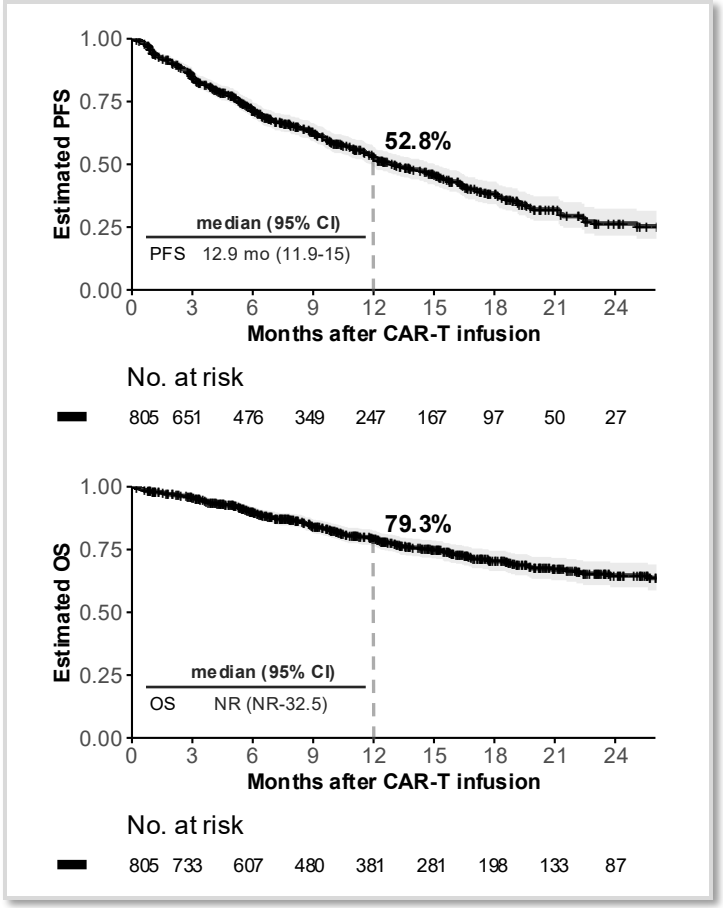


Training Cohort of 805 real-world patients

The training cohort showed classic features of a RRMM patient population, including a high prevalence of **EMD lesions** and **high-risk cytogenetics**, and being **heavily pre-treated and penta-refractory**.

	Entire cohort (n = 805)	Ide-cel (n = 514)	Cilta-cel (n = 291)
Demographic Features			
Age – years (range)	63 (31-88)	66 (34-88)	63 (31-86)
Sex, female – %	43.5	42.4	45.4
Race, Black/Hispanic – %	16.9	18.2	14.6
Country, USA – %	82.7	81.3	85.2
Disease Features			
History of EMD – %	31.8	30.8	33.4
Cytogenetics – %	63.2	59.9	68.8
BM Plasma Cells >50% – %	18.5	19.2	17.3
Serum LDH at pre-apheresis (U/l) – median (IQR)	215 (181-259)	218 (181-259)	209 (180-257)
Albumin at pre-apheresis (g/dL) – median (IQR)	3.9 (3.6-4.2)	3.9 (3.5-4.1)	4.0 (3.7-4.2)
Beta-2-microglobulin (mg/L) – median (IQR)	3 (2.3-4.2)	3.1 (2.3-4.5)	2.8 (2.2-3.9)
Treatment-related Features			
Median lines of prior therapy excl. bridging – median (IQR;range)	5 (4-7;1-20)	5 (4-7;2-20)	5 (4-6;1-14)
Penta-refractory status – %	30.4	32.7	26.3
Prior BCMA Exposure – %	11.9	13.8	8.6
Bridging Therapy – %	78.1	77.8	78.7

The **overall response rate was 81.3%**, with a median PFS of 12.9 months and a median OS that was not reached.

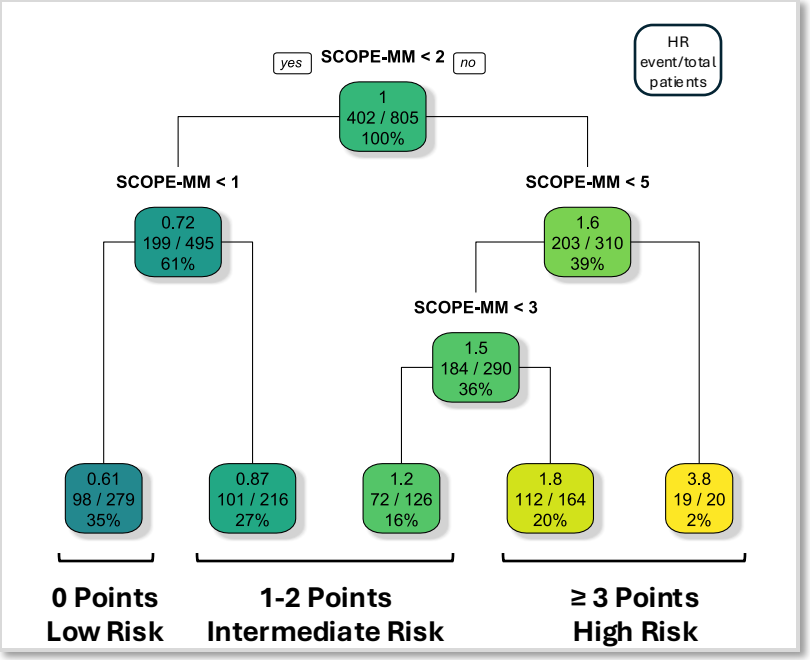


Rejeski, Cordas dos Santos et al. *Under Review*

The final model:
Stratification of CAR-T Outcomes at Pre-Apheresis Evaluation in Multiple Myeloma (SCOPE-MM)

Risk groups were defined using **partitioning models** based on similar hazard ratios.

We developed the **point-based, weighted SCOPE-MM model**, assigning one point each for BMPC ≥50%, history of EMD, and serum LDH above the upper limit of normal, and two points each for high pre-apheresis CAR-HEMATOTOX score and prior BCMA exposure.

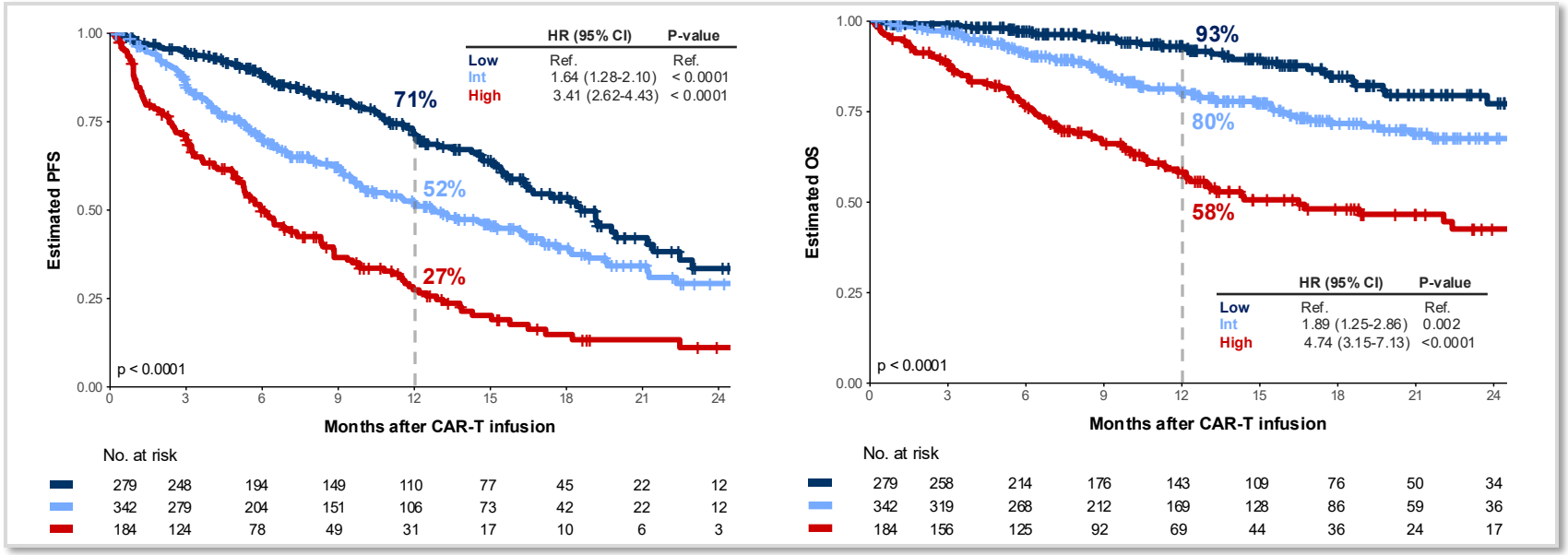


CAR-HEMATOTOX Components	
Platelets [G/l]	0-2 points
ANC [G/l]	0-1 points
Hgb [g/dl]	0-1 points
CRP [mg/dl]	0-1 points
Ferritin [ng/ml]	0-2 points
High-Risk	**≥ 3 points**

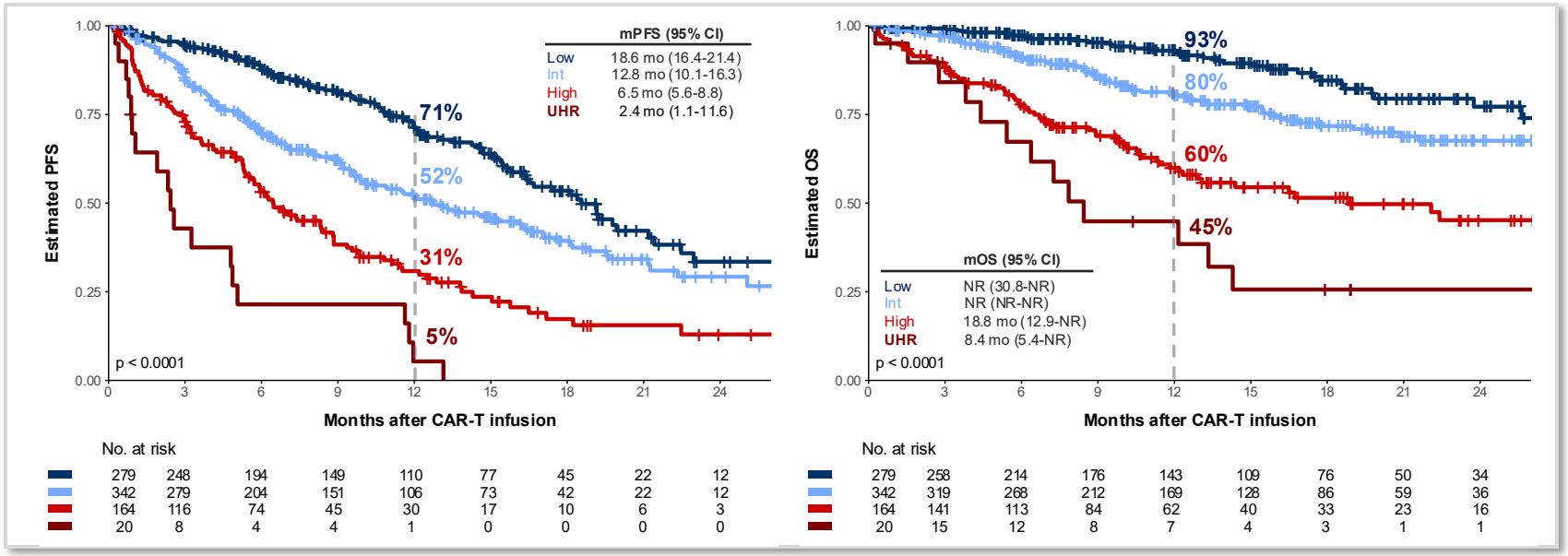
SCOPE-MM Components	Points		
	0	+1	+2
CAR-HEMATOTOX Category*	**Low Risk**	-	**High Risk**
Prior BCMA Exposure	**No**	-	**Yes**
BMPC ≥ 50%	**No**	**Yes**	-
History of EMD	**No**	**Yes**	-
Serum LDH >ULN	**No**	**Yes**	-
SCOPE-MM Low		0 points	
SCOPE-MM Intermediate		1-2 points	
SCOPE-MM High		≥ 3 points	

SCOPE-MM stratifies for survival and identifies ultra-high-risk patients with poor outcomes

The **three-tiered SCOPE-MM model** (low, intermediate, high risk) clearly stratified patients with respect to IMWG response criteria, progression-free survival, and overall survival.

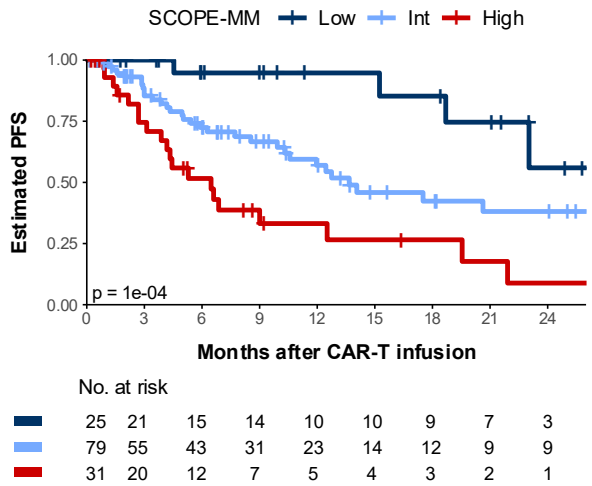


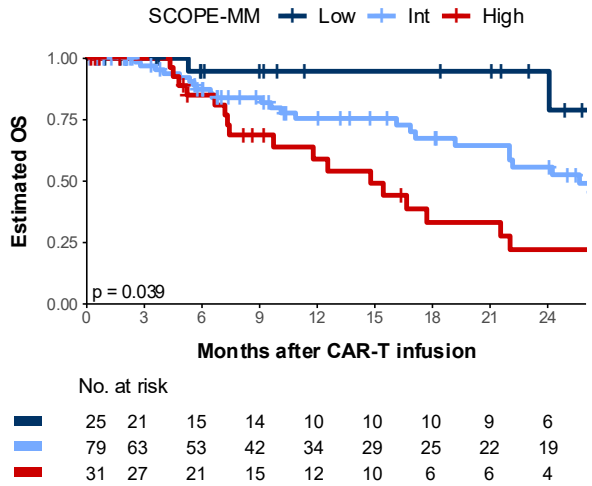
Extending to a **four-tiered model**, the model identified a minor **ultra-high-risk group of 2.5% of patients** (UHR, >5 points) characterized by particularly poor outcomes, with a median PFS of 2.4 months and a median OS of 8.4 months.



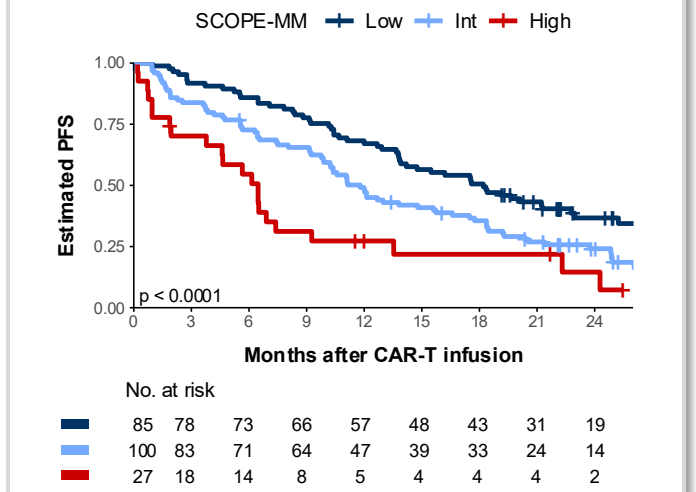
Broad external validation: SCOPE-MM discriminates for survival in a second real-world cohort and in the CAR-T treated patients of the KarMMa-3 and CARTITUDE-1 trials

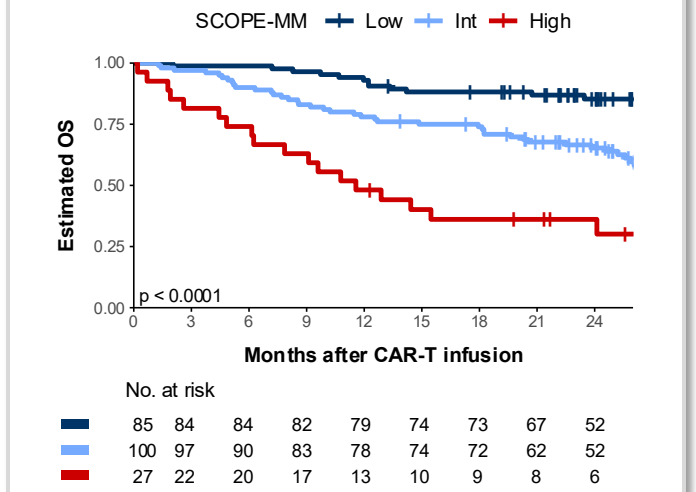
Real-world cohort



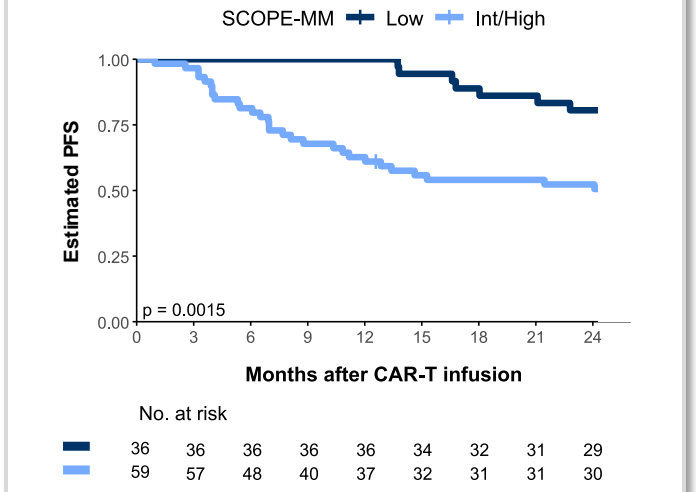


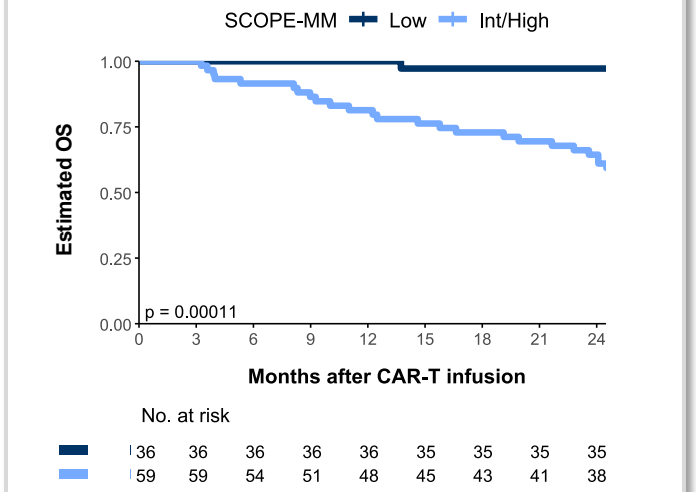
KarMMa-3*





CARTITUDE-1*

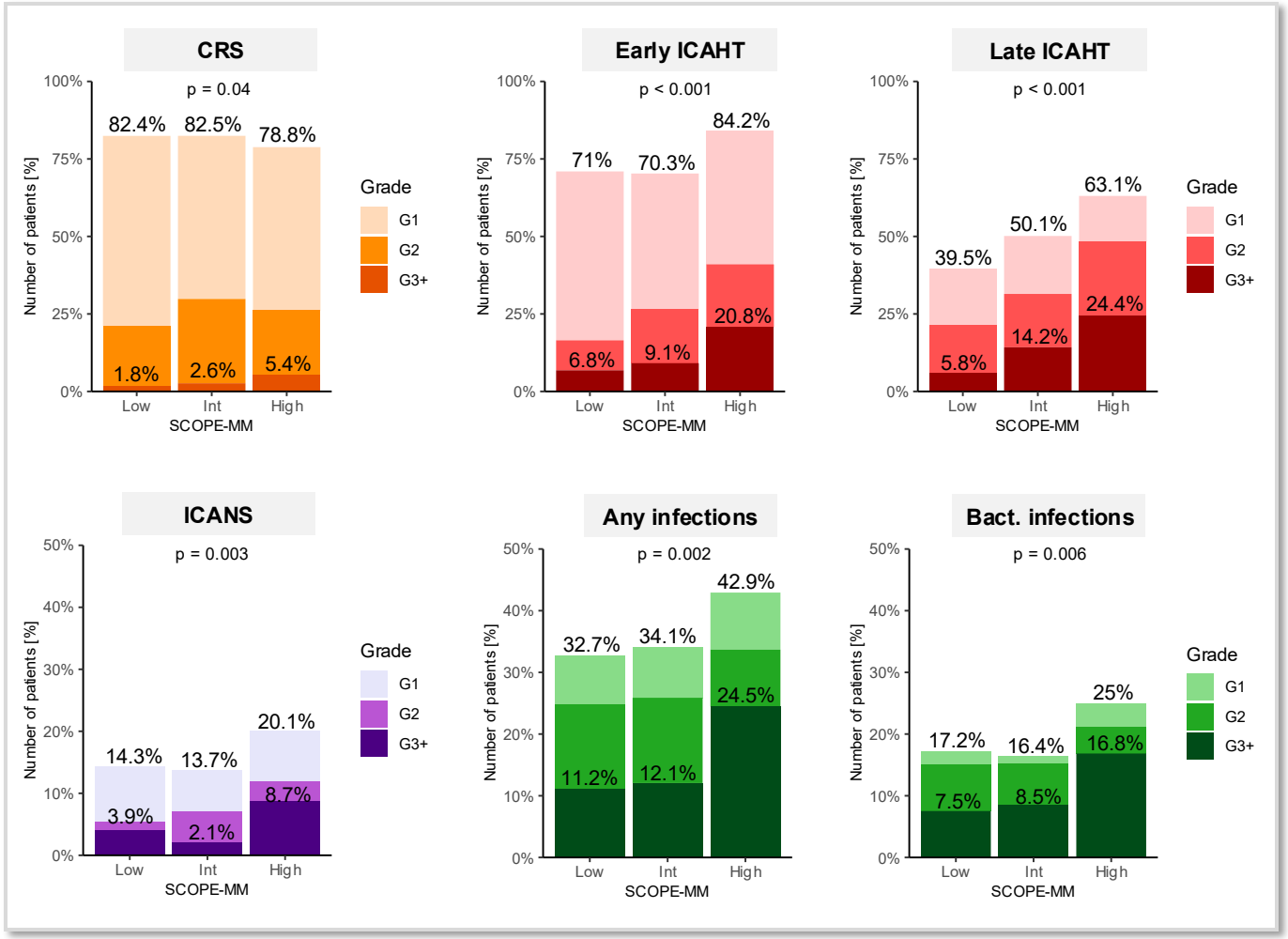




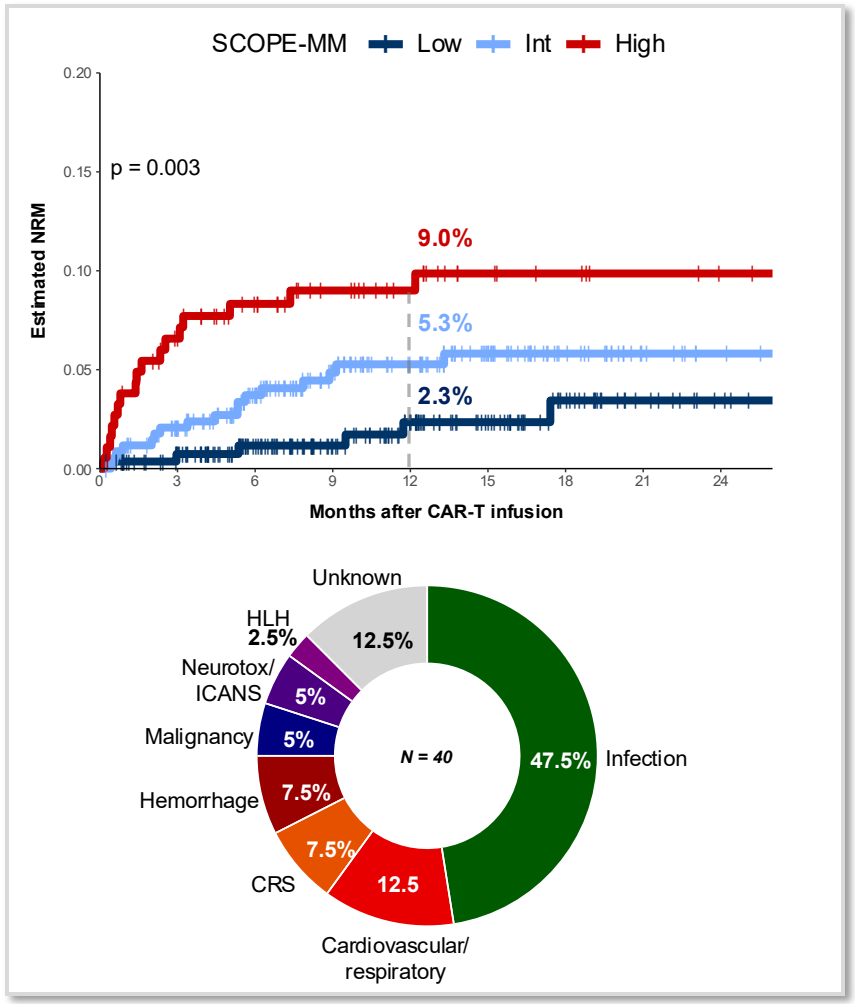
*Data analysis and visualization provided by BMS and Janssen | Rejeski, Cordas dos Santos et al. *Under Review*

SCOPE-MM is associated with CAR-T toxicities and non-relapse mortality

CAR-T-related toxicities*: cytokine release syndrome (CRS), hematotoxicity (ICAHT), neurotoxicity (ICANS), and infections

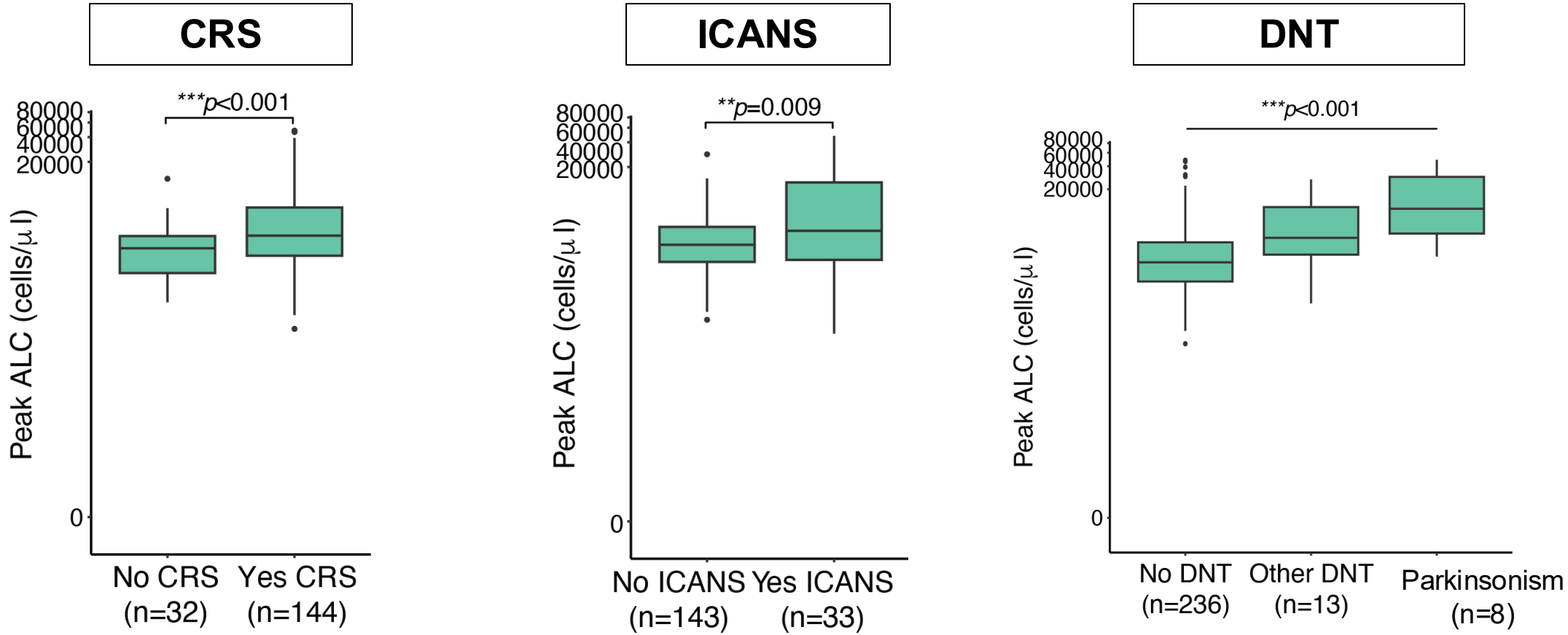


Non-relapse mortality (NRM) and cause of death



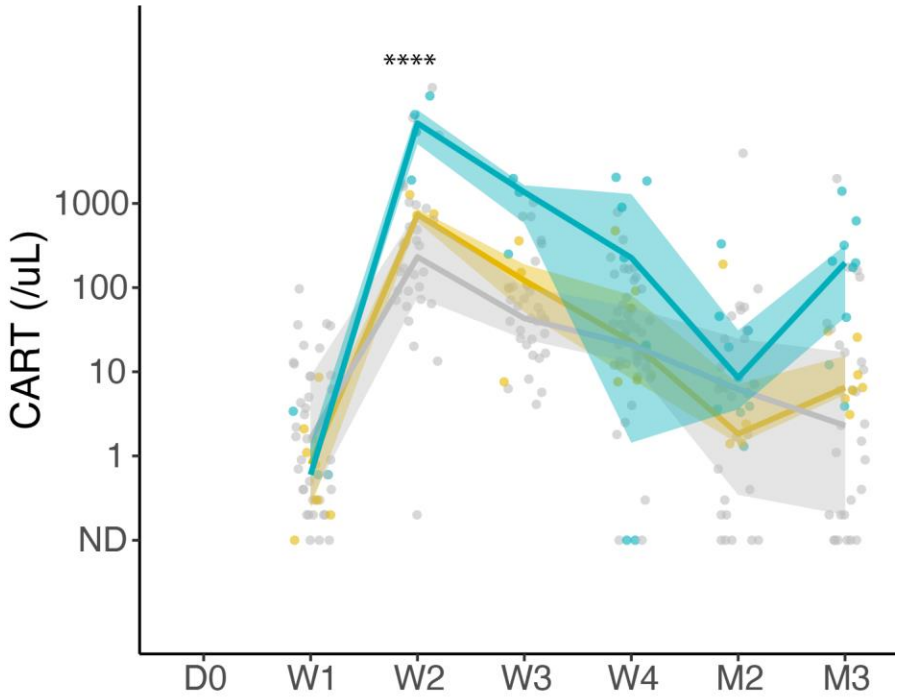
*Grading according to Lee et al. BBMT (2019), Rejeski et al. Blood (2023)

Cilta-cel: Peak ALC is associated with increased risk of CRS, ICANS, and DNT

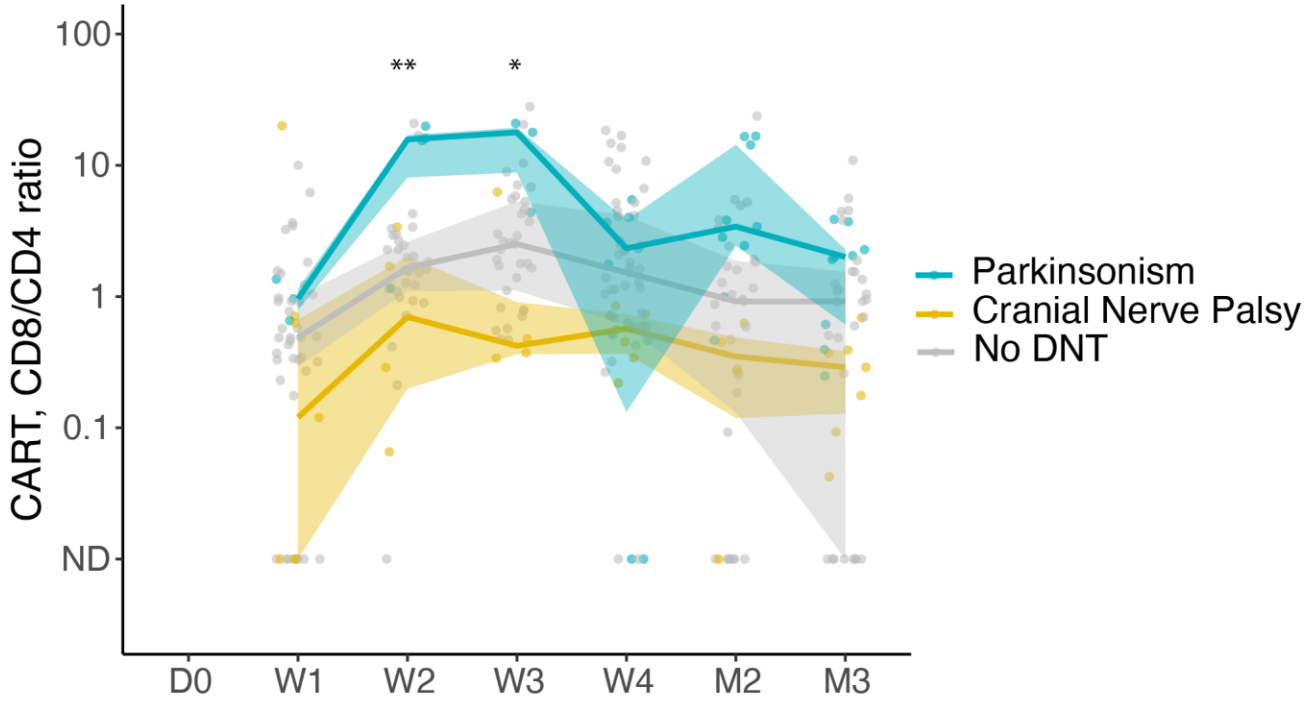


Peak ALC was higher in patients developing CRS, ICANS and DNT, particularly Parkinsonism

Cilta-cel: Patients with Parkinsonism show highest CAR-T expansion with elevated CD8/CD4 Ratio

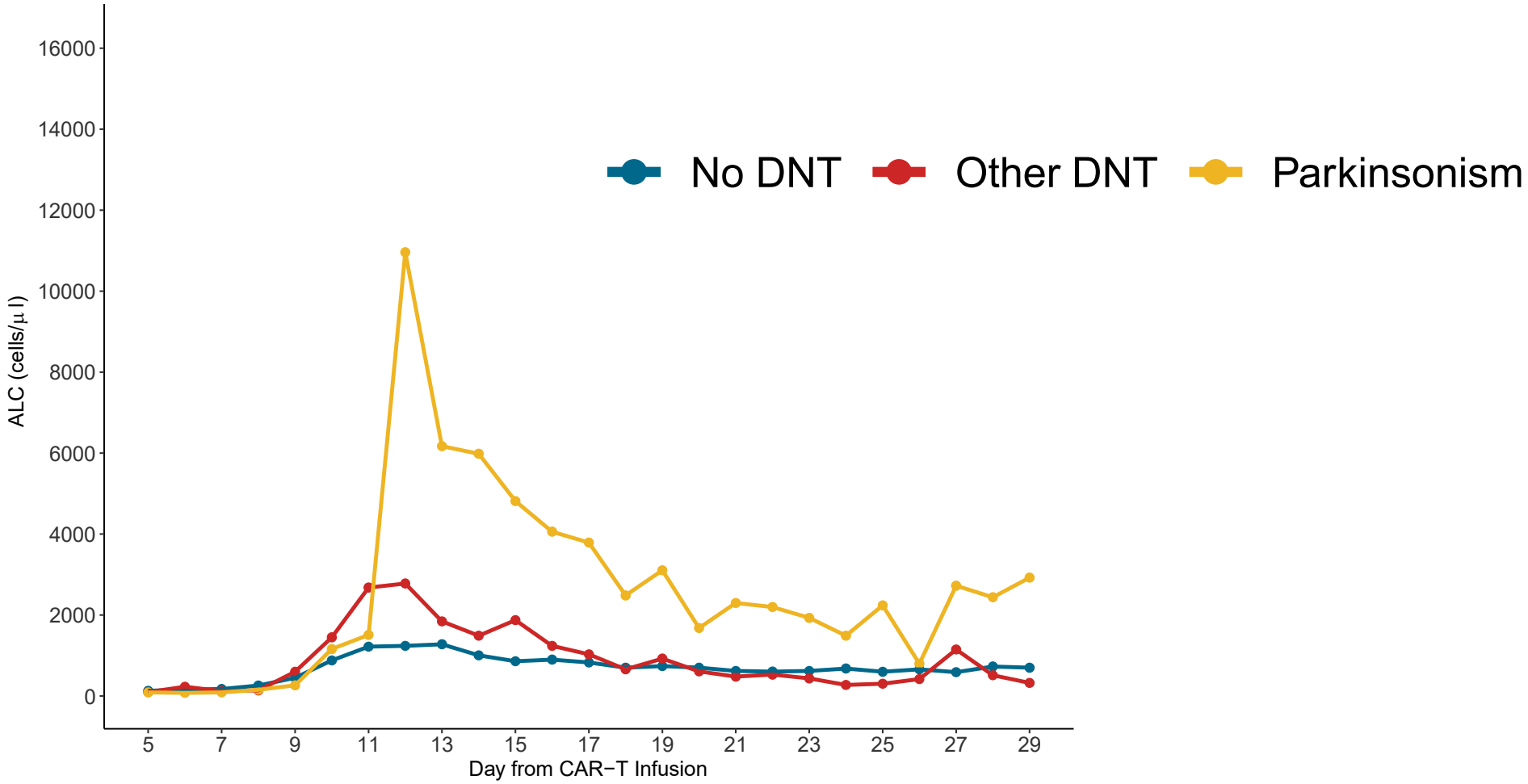


CAR T-cell expansion by FC



CD8/CD4 CAR-T ratio

Cilta-cel: Longitudinal evaluation of ALC reveals rapid peak CAR-T expansion in patients with Parkinsonism



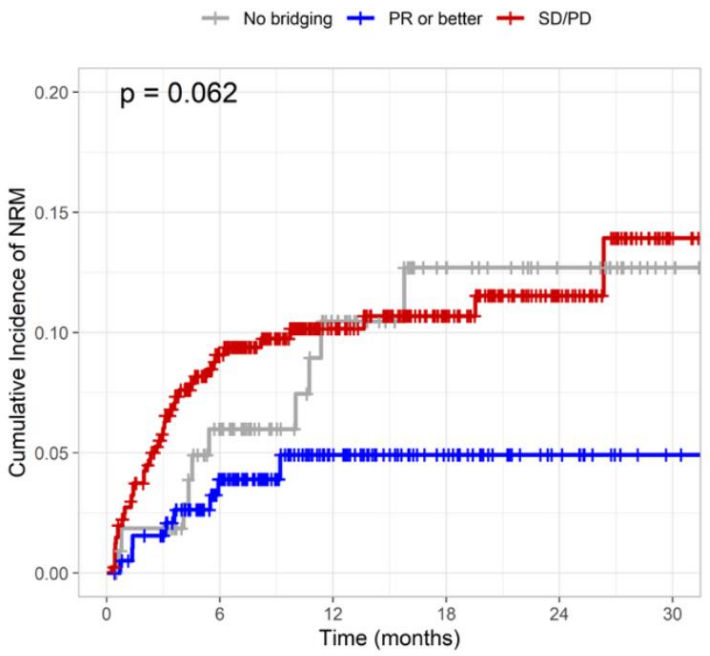
Effective bridging therapy (BT) can mitigate the risk of CAR-T toxicity and reduce risk of non-relapse mortality (NRM)

Non-response to BT

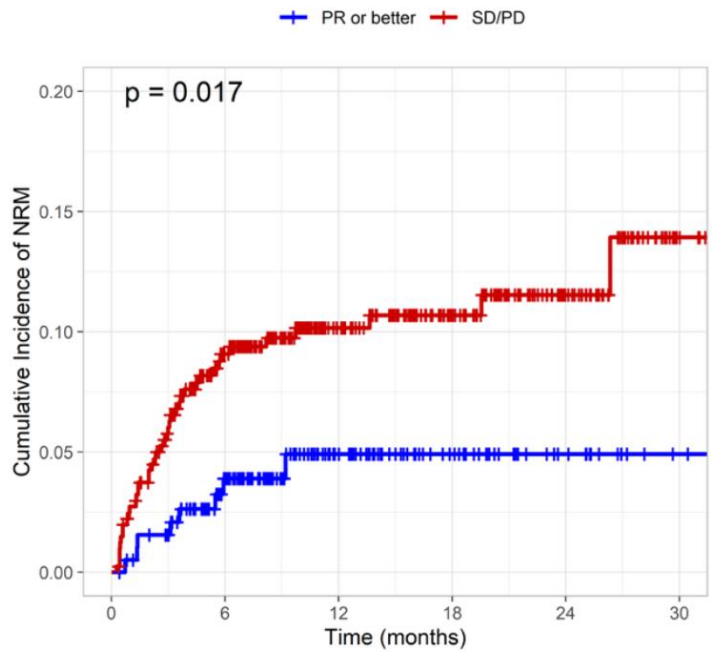
Response to bridging and NRM; 33%: PR or better response to BT

- ❖Increased immune-mediated toxicity (Parkinsonism, IEC-colitis)
- ❖High non-relapse mortality
- ❖Decreased CAR-T efficacy

All cilta-cel patients, N=761



Patients receiving bridging (86%)

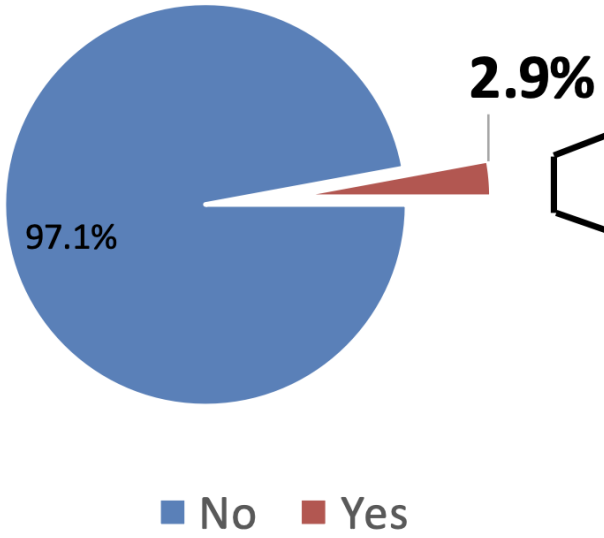


Please do not share unpublished data

Unpublished data from U.S. Multiple Myeloma Immunotherapy Consortium submitted to ASH 2025

Non-response to bridging therapy with cilta-cel: 10 times higher risk of developing Parkinsonism

Parkinsonism with SOC Cilta-cel
22 cases of 761 (2.9%)



Risk of Parkinsonism in non-responders vs responders to bridging (PR or better):
5% vs 0.5% (p<0.05)

Of 22 cases of Parkinsonism, 21 (95%) patients did not respond to bridging, even though post CAR-T response rate was 91% and CR rate of 68%

Please do not share unpublished data

Unpublished data from U.S. Multiple Myeloma Immunotherapy Consortium submitted to ASH 2025

Talquetamab: an effective bridging therapy pre-BCMA CAR-T in late relapse

Heavily pretreated, median 5 pLOT

N=134, 119 with CAR-T infusion (cilta-cel: 98)

- ❖ HR cytogenetics: 44%
- ❖ Extramedullary disease: 41%
- ❖ Median talquetamab exposure: 23 days

Talquetamab

- ❖ ORR: 71%, CR: 19%

CAR-T

- ❖ ORR: 88%, CR: 54%

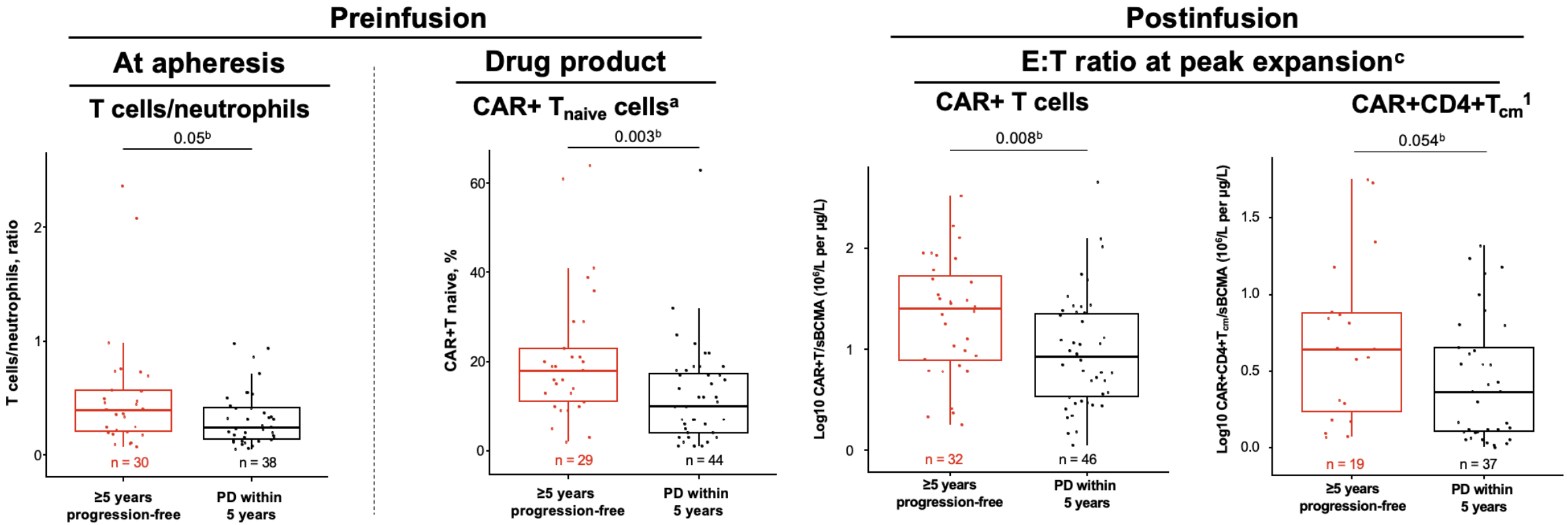
Toxicity	All grades (%)	Grade 3 and 4 (%)
CRS	68	2
ICANS	6	1
IEC-HS	0	-
Delayed Neurotoxicity	1.5 (2): CN palsy	-
Infections	18	5
Severe cytopenia (day + 60)	5	5

No cases of Parkinsonism, Guillan Barre or other NT. NRM 4%, mostly due to infections
60% showed complete resolution of on-target off tumor toxicities

Please do not share unpublished data

Dhakal B. Blood 2025 (in press)

Long-term response to cilta-cel: Better T cell fitness and CAR-T expansion



Long-term disease control: better immune fitness with more naïve T cells in CAR-T products
Higher E:T ratio with total CAR-T cells and more CD4+ CAR-T cells with central memory phenotype at peak expansion

CAR+ T_{naive} cells were defined as CD95-CD27+CD45RO-. [b]2-sided nominal *P* values unadjusted for multiplicity were provided for descriptive purposes. [c]E:T ratio was defined as maximal CAR-positive T-cell levels normalized by pre-infusion serum sBCMA levels.

Conclusion

- The SCOPE-MM score is the first **pre-apheresis, clinically actionable risk model** for patients with RRMM undergoing BCMA CAR-T
- The SCOPE-MM score is **clinically valuable and product-agnostic**. For this reason, the **IMWG Immunotherapy Committee recommends** use of the score for risk stratification in both clinical trials and real-world studies
- **Early application of SCOPE-MM** can change practice by identifying high-risk patients who may benefit from intensified bridging therapy or combination strategies and pre-emptive toxicity mitigation strategies
- **Higher cilta-cel expansion** and **ALC** associate with increased risk of neurotoxicity including ICANS and **delayed neurotoxicity**. Rapid peak CAR-T expansion is observed in patients with Parkinsonism
- **Effective bridging therapy** reduces toxicity and improves efficacy including **talquetamab** for heavily pretreated patients
- **Long term** disease control with cilta-cel associates with better **T cell fitness** and **CAR-T expansion**

Acknowledgements

Omar Castaneda
Ariel Grajales-Cruz
Ciara L. Freeman
Rebecca Gonzalez
Syed Hamza Bin Waqar
Michael Jain
Frederick Locke
Melissa Alsina
Kenneth Shain
Rachid Baz
Brandon Blue
Fabiana Perna
Lauren Peres
Laura Oswald

All patients and their families!

Marion Subklewe
Sebastian Theurich
Michael von Bergwelt
Wajma Shahbaz
Tobias Tix

Hamburg
Winfried Alsdorf
Katja Weisel

DFCI:
Omar Nadeem
Shonali Midha
Adam Sperling
Nikhil Munshi

MSKCC:
Bruno Costa
Sridevi Rajeeve
Roni Shouval
Sham Mailankody
Saad Usmani

Susan Geyer
Katharine Dooley
A.D. Menezes Silva
Corraes
Saurabh Chhabra
Lisa Hwa
Christenson
Ricardo Parrondo
Vincent Rajkumar
Genevieve Spiess
Haily Stephens

Janssen
Nikoletta Lendvai
Quanlin Li
Nitil Patel

Stanford
Surbhi Sidana
Hitomi Hosoya
Lekha Mikkilineni
Masooma Rana

Heidelberg
Jan Frenking
Mirco Friedrich
Marc S. Raab

BMS
Tim Campbell
Yun Li

MD Anderson:
Krina Patel
Christen Dillard
Mahmoud Gaballa
Oren Pasvolsky
Saurabh Chhabra

TUM
Florian Bassermann
Judith Hecker
Anna Purcarea