LA RIVOLUZIONE NEL MONDO DEL
LINFOMA MANTELLARE!

Milano, Hilton Milan Hotel
27 gennaio 2025

Responsabili Scientifici
Paolo Corradini, Pier Luigi Zinzani

Come selezionare il paziente appropriato

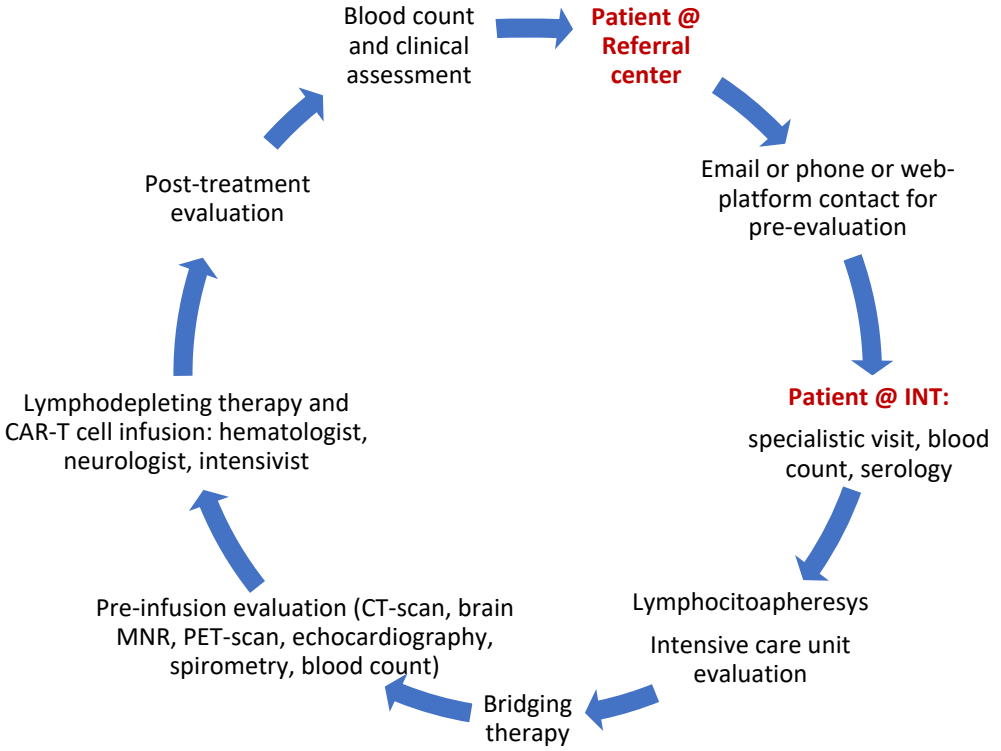
Annalisa Chiappella

Ematologia, Fondazione IRCCS Istituto Nazionale dei Tumori, Milano

Disclosures of Annalisa Chiappella

Company name	Lecture fee/Educational activities	Advisory board	Other
Abbvie		X	
Eli Lilly	X		
Gilead-Sciences	X	X	
Hoffmann-La Roche		X	
Incyte		X	
Jannsen-Cilag	X		
Novartis	X		

The patient's journey: INT experience



The selection of the patient is a crucial time-point

Patient selection is primarily guided by the AIFA approved indications

- **Age ≥ 18 years**
- **Relapsed/refractory after 2 prior lines of therapy (including antiCD20 mAb and anthracycline or bendamustine chemo, and iBTKs)**
- ECOG Performance Status 0,1
- HBV/HCV/HIV active infection → no use
- CNS involvement → **selected cases**
- Previous allo-SCT → **selected cases**
- Adequate renal (eGFR > 60 ml/min), hepatic, pulmonary or cardiac function (LVEF >50%)
- Prior anti-CD19 therapy → repeat biopsy to prove the presence of CD19
- **ANC > 1000, Hb > 8, PLTS > 75.000, ALC >100**

Outline of the discussion: patient selection

- Clinical characteristics
  - Age
  - CNS involvement
  - CAR-HEMATOTOX
  - Refractoriness to iBTKs
  - Bendamustine exposure
- Biological features
  - High-risk MCL

Outline of the discussion: patient selection

- Clinical characteristics
  - Age
  - CNS involvement
  - CAR-HEMATOTOX
  - Refractoriness to iBTKs
  - Bendamustine exposure
- Biological features
  - High-risk MCL

Patient selection: age

GERIATRIC ONCOLOGY (L BALDUCCI, SECTION EDITOR)

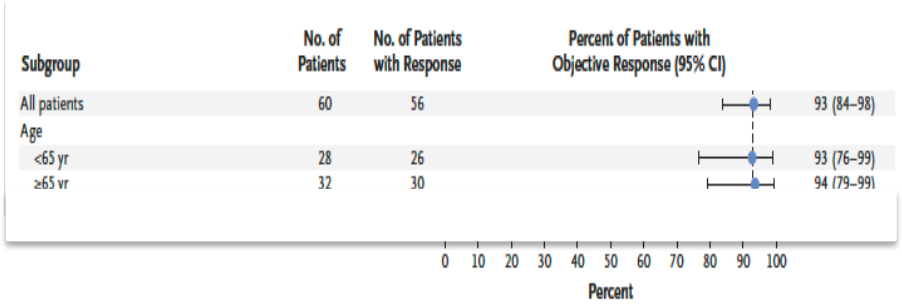
CAR T-Cell Therapy in the Older Person: Indications and Risks

Geoffrey Shouse[1] · Alexey V. Danilov[1,2] · Andy Artz[1]

Disease	Median age at diagnosis	% Diagnosed at age > 65 years	Adverse prognosis with older age?
Diffuse large B cell lymphoma	66	54%	YES
Mantle cell lymphoma	68	71%	YES
Follicular lymphoma	63	47%	YES
Multiple myeloma	69	74%	YES
B-cell acute lymphoblastic leukemia	17	14%	YES

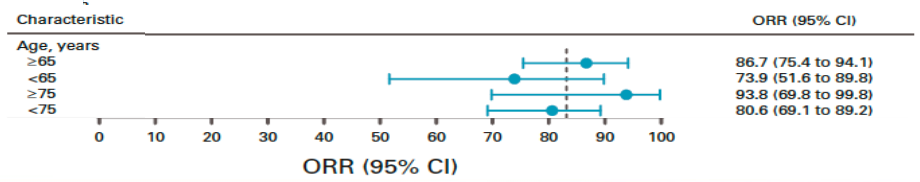
Zuma-2

Characteristic	Patients
Median age (range) — yr	65 (38–79)



Transcend NHL-001; MCL

Characteristic	Liso-Cel–Treated Set (N = 88)
Age, years	
Median (range)	68.5 (36-86)
≥65, No. (%)	64 (73)
≥75, No. (%)	18 (20)



Shouse G, et al. Curr Oncol Rep 2022; Wang M, et al. N Engl J Med 2020; Wang M, et al. J Clin Oncol 2024.

Suggested approach to older adults being considered for CART

Older adult patient (age ≥65) with hematologic malignancy being considered for CART

Assessments

- Review available disease-specific prognostic information
- Consider geriatric assessment (GA) inclusive of cognition screen.
- Assess risks for CART toxicities especially neurotoxicity, but also including CRS and infection

Interventions

- Educate family and caregivers
- Formulate early cytokine release syndrome intervention plan to mitigate risk of toxicity
- Functionally optimize patients utilizing pre-CART and post-CAR-T physical and occupational therapy
- Define expert team at your center to facilitate supportive care for neurotoxicity (e.g., occupational therapy, neurology, psychiatry, palliative care, etc.)
- Consider alternative therapies for patients deemed high risk of poor outcomes

Shouse G, et al. Curr Oncol Rep 2022.

Patient selection: CNS involvement

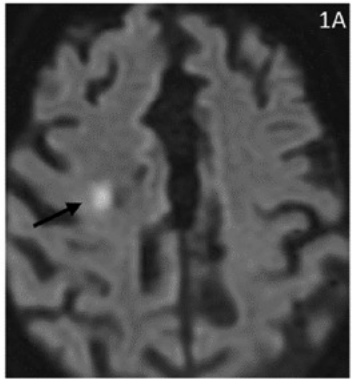
Efficacy and safety of brexucabtagene autoleucel CAR T-cell therapy with BTK inhibitors in the treatment of relapsed mantle cell lymphoma with central nervous system involvement

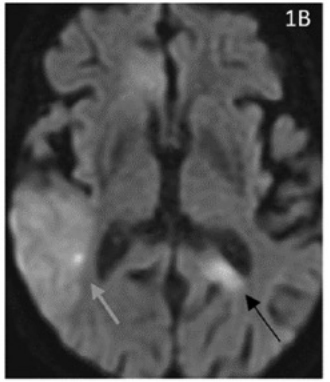
Anath C. Lionel[a#], Ashwath Gurumurthi[a#], Ahmed Fetooh[a], Rami Eldaya[b], Sairah Ahmed[a], Swaminathan P. Iyer[a], Loretta J. Nastoupil[a], Jason Westin[a], Ranjit Nair[a], Luis Fayad[a], Luis Malpica[a], Sudhakar Tummala[c], Christopher Flowers[a], Sattva S. Neelapu[a], Michael L. Wang[a] and Preetesh Jain[a]

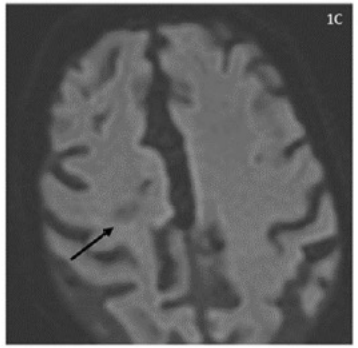
[a]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [b]Department of Neuroradiology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [c]Department of Neuro-oncology, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

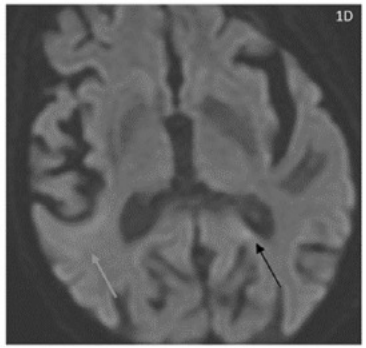
4 patients:
2 treated with acalabrutinib + brexu-cel
2 treated with Zanubrutinib + brexu-cel

CR at day 30: 100%
Last follow-up;
3 in persistent CR (6mo,9mo,22mo)
one died do to progressive disease





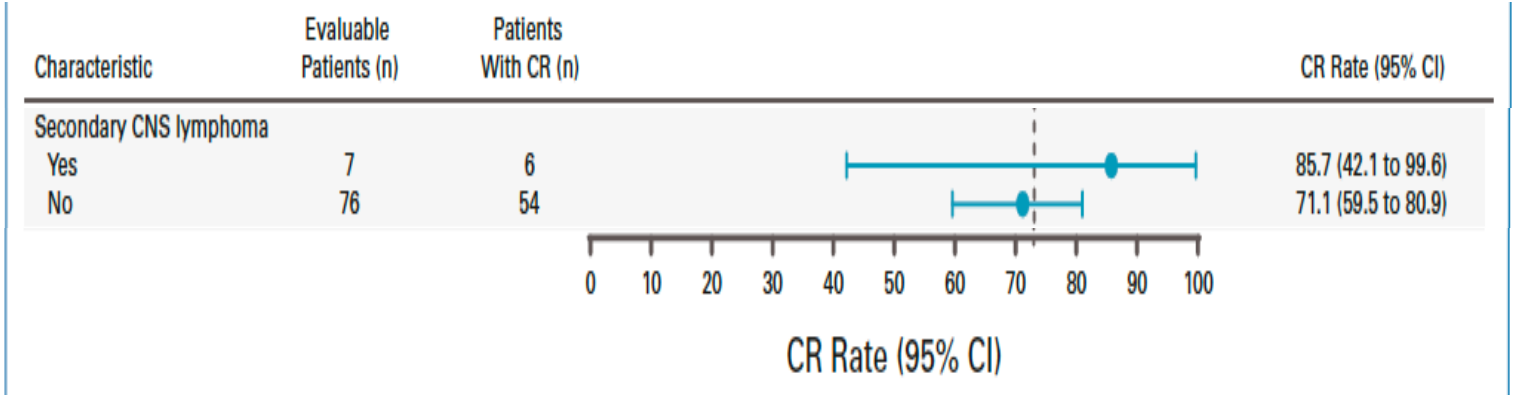




Lionel AC, et al. Leuk Lymph 2024.

Patient selection: CNS involvement

TRANSCEND NHL-001: TRANSCEND-MCL included seven patients with secondary CNS lymphoma treated with liso-cel. Among these patients, response rates (ORR, 85.7%; CR rate, 85.7%) were comparable with the overall population.

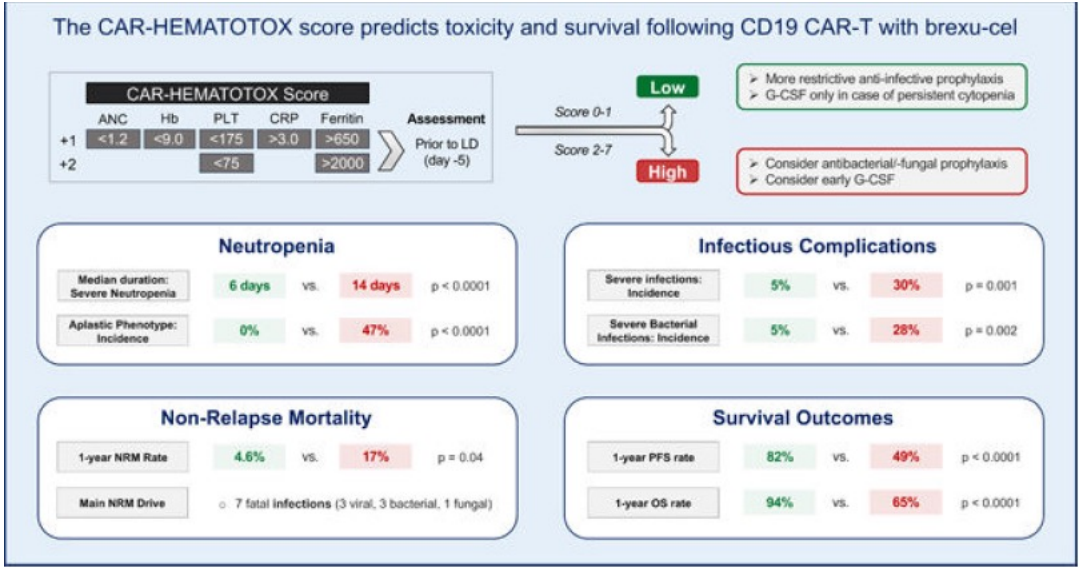


Wang M, et al. J Clin Oncol 2024.

Patient selection: CAR-HEMATOTOX

The CAR-HEMATOTOX score identifies patients at high risk for hematological toxicity, infectious complications, and poor treatment outcomes following brexucabtagene autoleucel for relapsed or refractory MCL

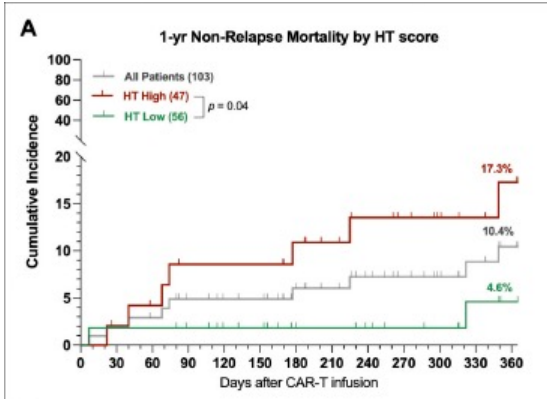
Kai Rejeski[1,2,3], Yucai Wang[4], Omar Albanyan[5], Javier Munoz[6], Pierre Sesques[7], Gloria Iacoboni[8], Lucia Lopez-Corral[9,10], Isabelle Ries[11], Veit L. Bücklein[1,2], Razan Mohty[5], Martin Dreyling[1], Aliyah Baluch[12], Bijal Shah[13], Frederick L Locke[5], Georg Hess[11], Pere Barba[8], Emmanuel Bachy[7], Yi Lin[4], Marion Subklewe[1,2,3,†], Michael D. Jain[5,†]

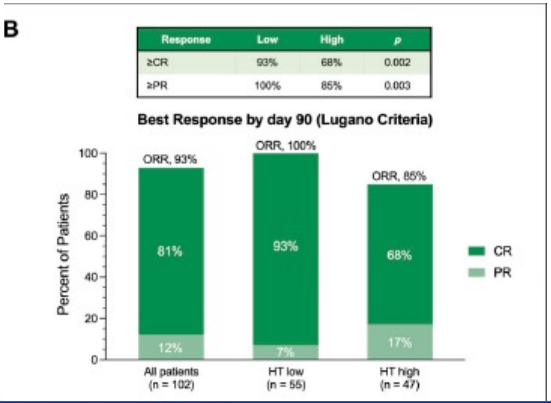


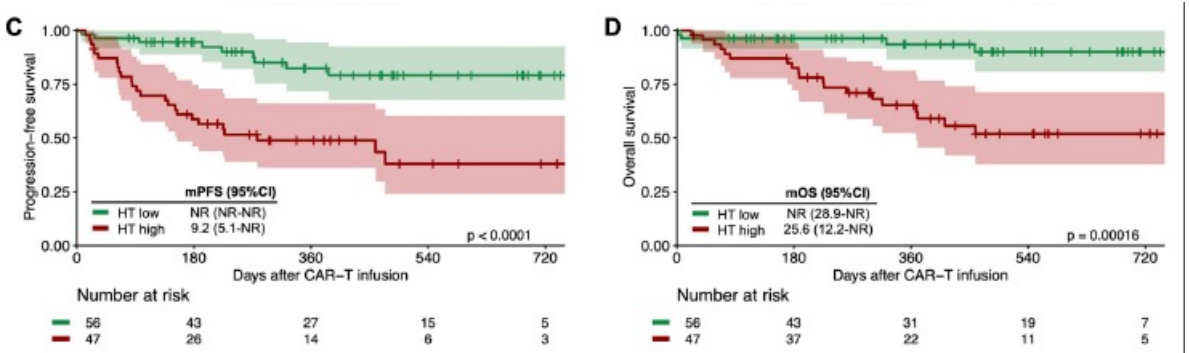
- High HT scores were independently associated with severe hematotoxicity, infections, and poor PFS/OS.
- Infections and hematotoxicity are common after brexu-cel and contribute to NRM.
- **The baseline HT score identified patients at increased risk of poor treatment outcomes.**

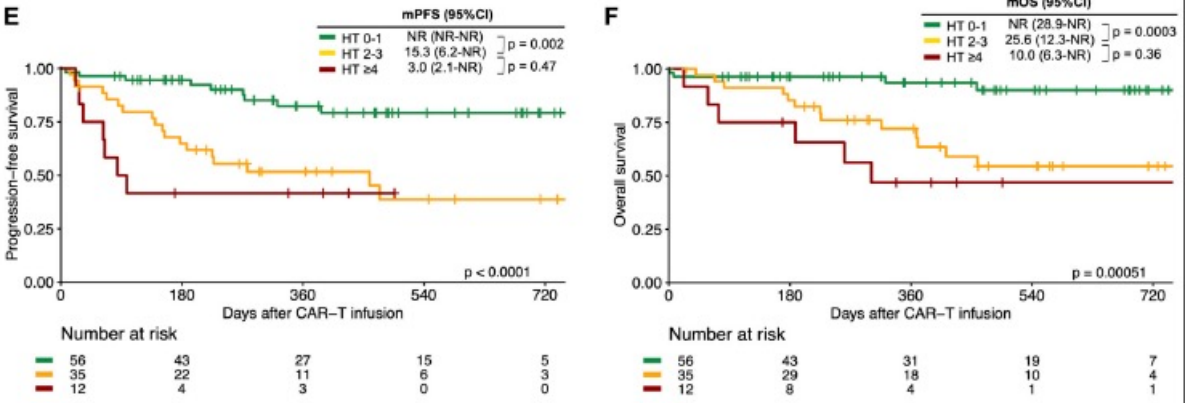
Rejeski K, et al. Am J Hematol 2023.

Patient selection: CAR-HEMATOTOX







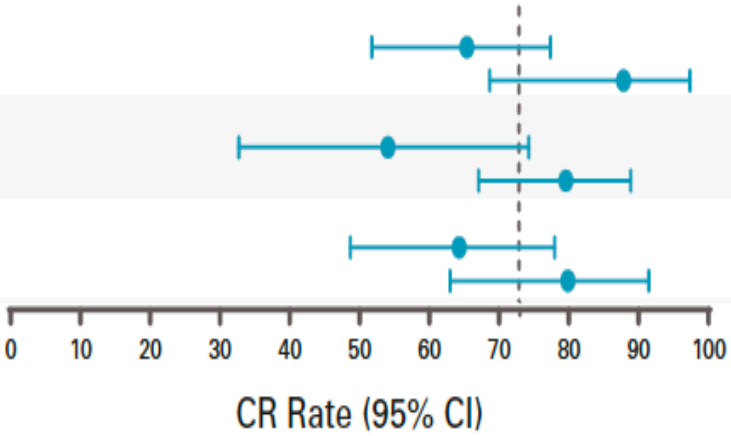


Rejeski K, et al. Am J Hematol 2023.

Patient selection: Refractoriness to iBTKs

TRANSCEND NHL-001

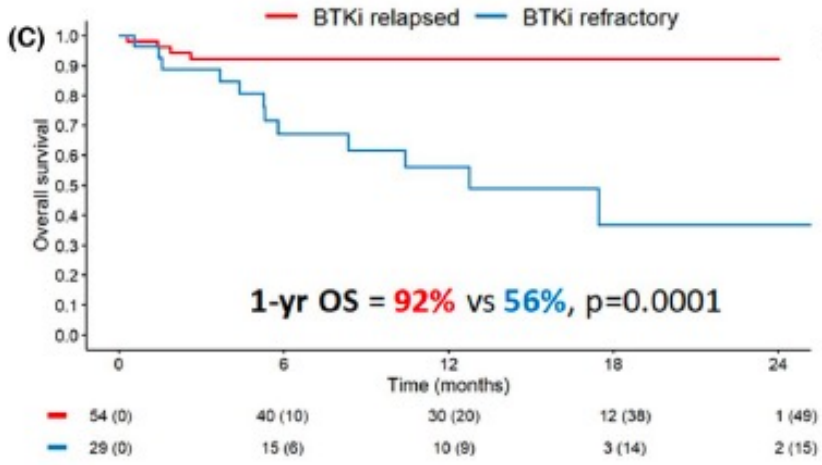
Characteristic	Evaluable Patients (n)	Patients With CR (n)	CR Rate (95% CI)
Response to last therapy			
Refractory	58	38	65.5 (51.9 to 77.5)
Relapsed	25	22	88.0 (68.8 to 97.5)
Chemotherapy response			
Refractory	24	13	54.2 (32.8 to 74.4)
Sensitive	59	47	79.7 (67.2 to 89.0)
Previous BTKi exposure			
Refractory to BTKi	45	29	64.4 (48.8 to 78.1)
Not refractory to BTKi	35	28	80.0 (63.1 to 91.6)

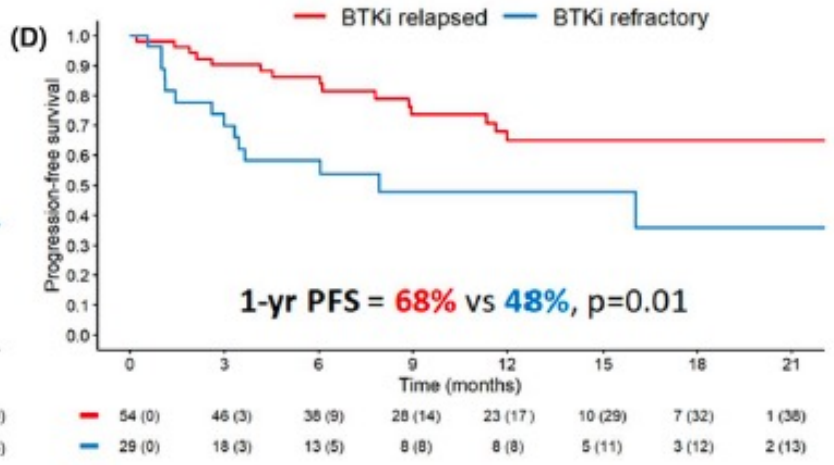


Wang M, et al. J Clin Oncol 2024.

Patient selection: Refractoriness to iBTKs

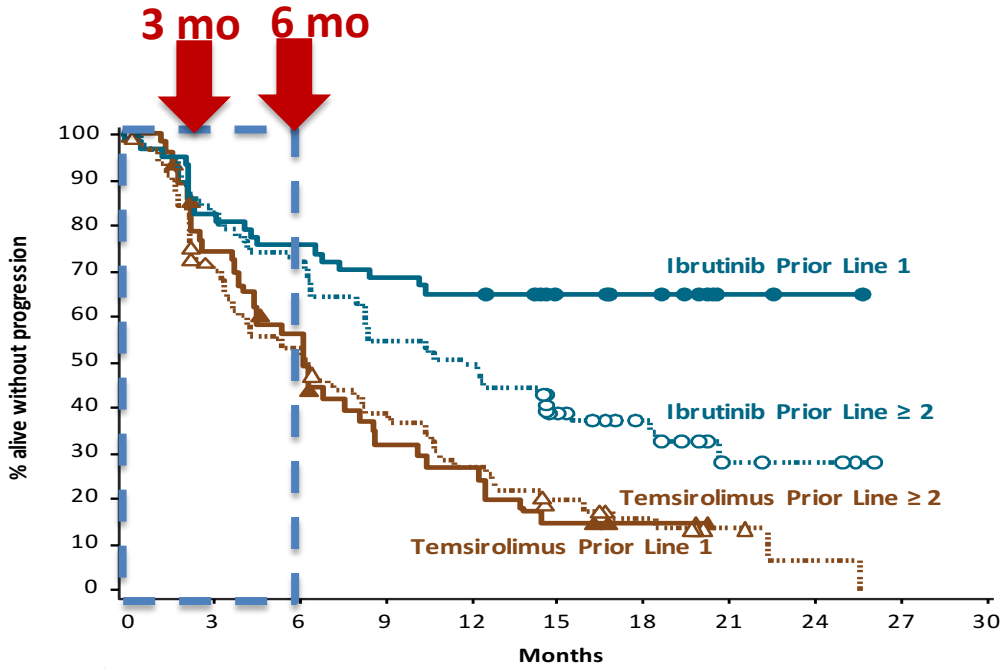
Real Life: CART-SIE Italian experience





Stella F, et al. Br J Hematol 2024.

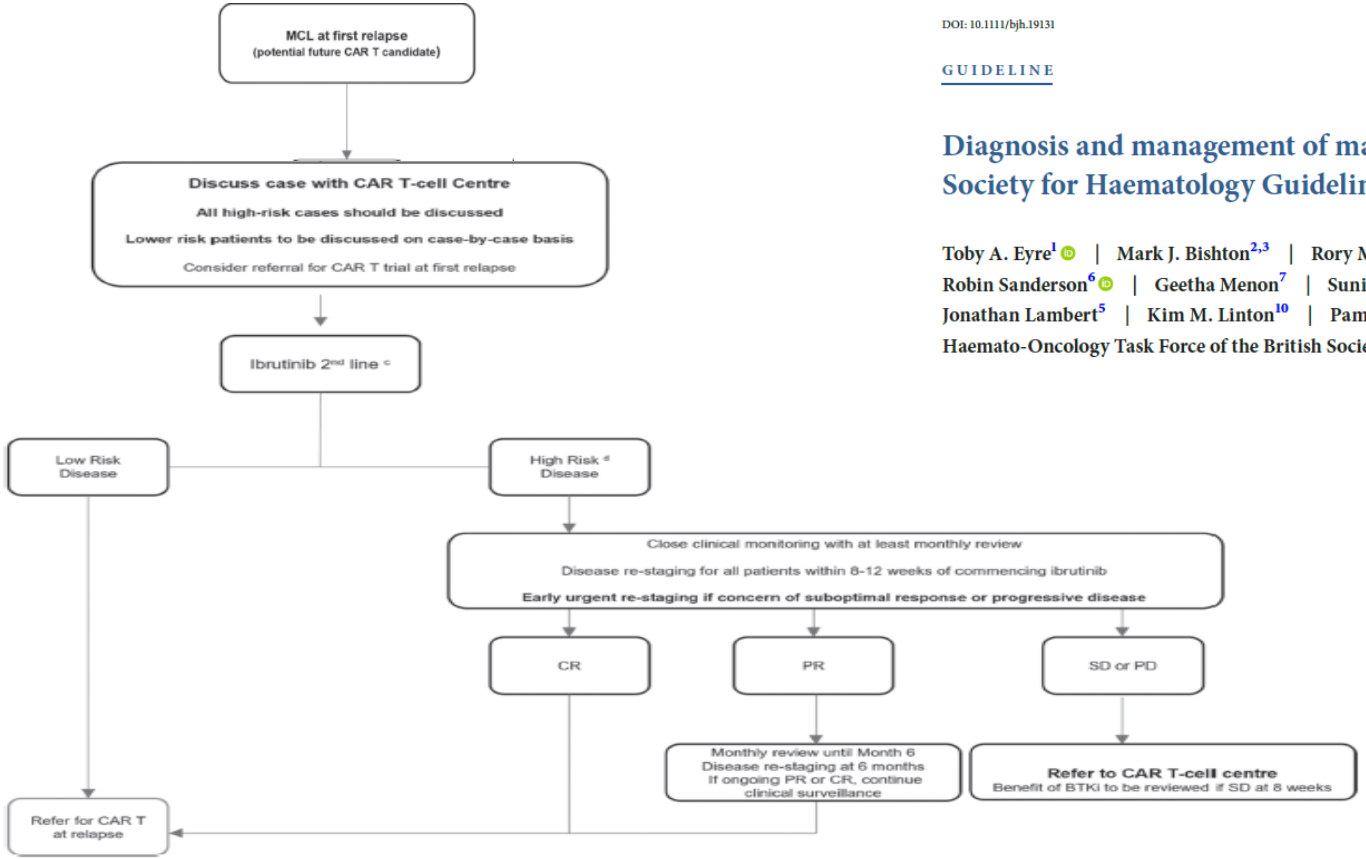
Early referral: identification of patients refractory to iBTKs



Patients at risk

Ibr 1 prior	57	47	43	39	37	21	19	3	2	0	0
Tem 1 prior	50	33	24	13	11	6	4	0	0	0	0
Ibr ≥2 prior	82	67	58	44	40	24	15	5	3	0	0
Tem ≥2 prior	91	60	45	32	22	13	7	3	1	0	0

Eyre T, et al. Blood 2015.



DOI: 10.1111/bjh.19131

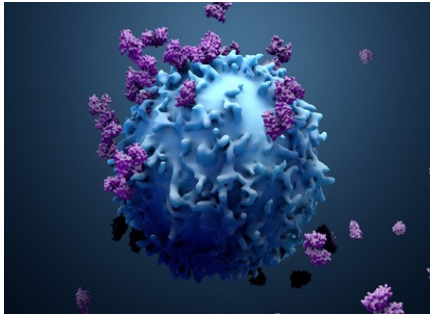
GUIDELINE

Diagnosis and management of mantle cell lymphoma: A British Society for Haematology Guideline

Toby A. Eyre[1] | Mark J. Bishton[2,3] | Rory McCulloch[4] | Maeve O'Reilly[5] | Robin Sanderson[6] | Geetha Menon[7] | Sunil Iyengar[8] | David Lewis[9] | Jonathan Lambert[5] | Kim M. Linton[10] | Pamela McKay[11] | on behalf of the Haemato-Oncology Task Force of the British Society for Haematology

Eyre TA, et al. Br J Hematol 2023.

Phase II study PRIMACART. PI: Prof. Paolo Corradini



PRIMACART

STUDIO DI FASE II PER VALUTARE L'EFFICACIA DELLA TERAPIA A CELLULE CAR-T CON KTE-X19 IN PAZIENTI CON LINFOMA MANTELLARE RECIDIVATO/REFRATTARIO CON OTTENUTA REMISSIONE PARZIALE IN CORSO DI TERAPIA DI SALVATAGGIO CON IBRUTINIB

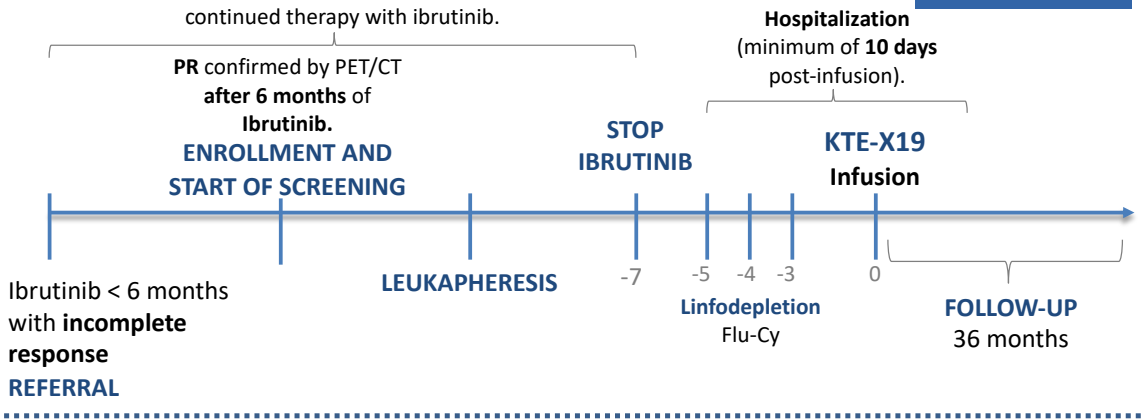
Primary Objective: CR at 90 days after infusion of KTE-X19.

Secondary Objectives: CR at 6 months; PFS/OS at 1, 2, and 3 yrs; DOR, NRM; AEs; biological study.

2 centers:

- Fondazione IRCCS Istituto Nazionale dei Tumori, Milano
- Istituto di Ematologia L.A. Seragnoli, Bologna

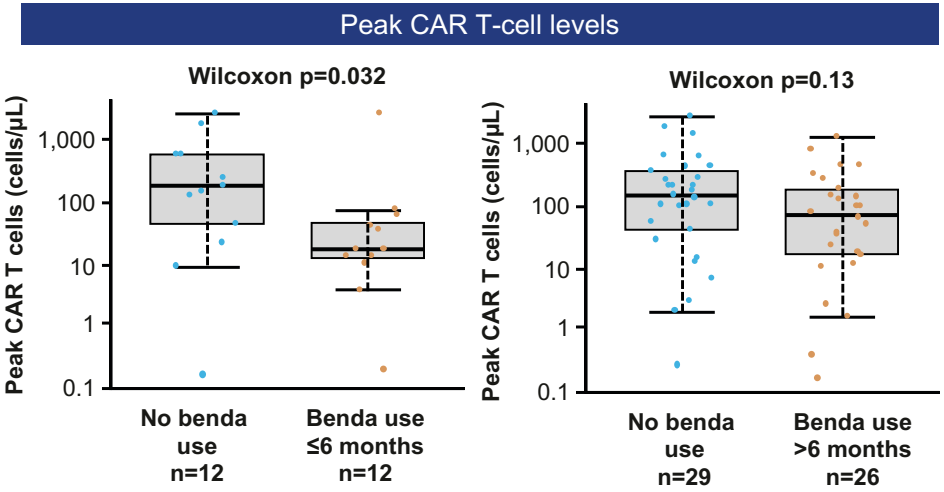
20 PATIENTS



Patient selection: Bendamustine exposure

ZUMA-2 study cessation of bendamustine prior to leukapheresis.

54% of patients in ZUMA-2 received prior bendamustine
Median time from last bendamustine exposure to brexucabtagene autoleucel infusion was 20.9 months

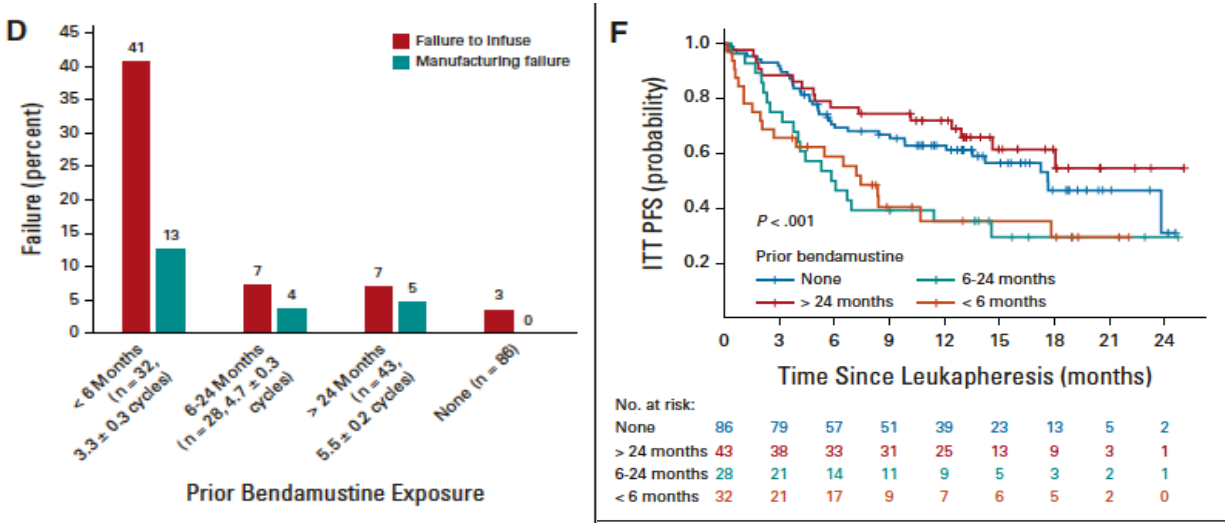


	Benda use ≤6 months vs. no benda use[a]		Benda use >6 months vs. no benda use[b]	
Efficacy, n (%)	Benda use ≤6 months (n=11)	No benda use (n=11)	Benda use >6 months (n=25)	No benda use (n=25)
ORR	9 (81.8)	11 (100)	21 (84.0)	25 (100.0)
CR rate	6 (54.5)	9 (81.8)	15 (60.0)	20 (80.0)
Ongoing response at 18 months	2 (18.2)	4 (36.4)	8 (32.0)	13 (52.0)

Patients treated with brexu-cel could benefit from longer time spans between prior bendamustine and CAR T therapy.

Wang M, et al. N Engl J MED 2020.

Patient selection: Bendamustine exposure



Subgroup	CR Rate (95% CI)
No prior bendamustine (n = 86)	84 (74 to 91)
Prior bendamustine (n = 103)	64 (54 to 73)
Bendamustine within 6 months (n = 32)	47 (29 to 65)
Bendamustine within 6-24 months (n = 28)	64 (44 to 81)
Bendamustine > 24 months before (n = 43)	77 (61 to 88)

Wang Y, et al. J Clin Oncol 2023.

Outline of the discussion: patient selection

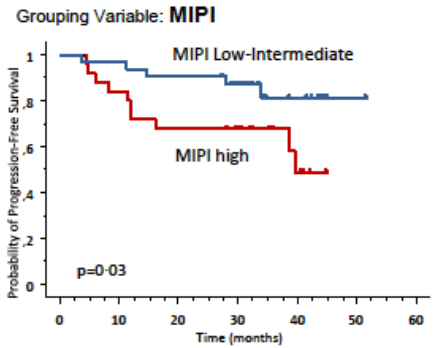
- Clinical characteristics
  - Age
  - CNS involvement
  - CAR-HEMATOTOX
  - Refractoriness to iBTKs
  - Bendamustine exposure
- Biological features
  - High-risk MCL

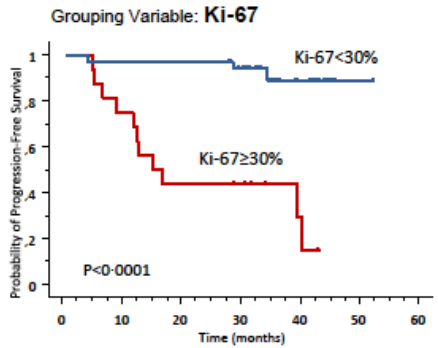
Patient selection: High-risk MCL

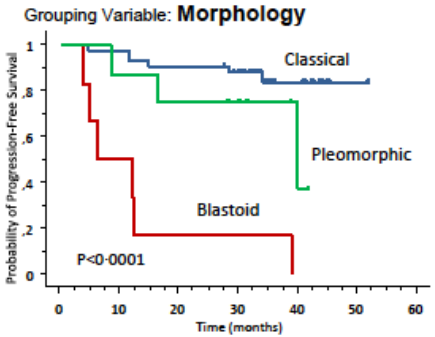
Rituximab, bendamustine, and low-dose cytarabine as induction therapy in elderly patients with mantle cell lymphoma: a multicentre, phase 2 trial from Fondazione Italiana Linfomi

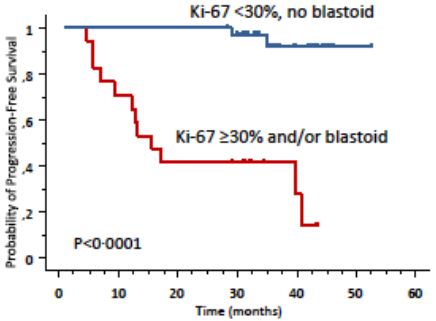
Carlo Visco, Annalisa Chiappella, Luca Nassi, Caterina Patti, Simone Ferrero, Daniela Barbero, Andrea Evangelista, Michele Spina, Annalia Molinari, Luigi Rigacci, Monica Tani, Alice Di Rocco, Graziella Pinotti, Alberto Fabbri, Renato Zambello, Silvia Finotto, Manuel Gotti, Angelo M Carella, Flavia Salvi, Stefano A Pileri, Marco Ladetto, Giovannino Ciccone, Gianluca Gaidano, Marco Ruggeri, Maurizio Martelli, Umberto Vitolo

Lancet Haematol 2016









Visco C et al, Lancet Haematol 2016.

Patient selection: High-risk MCL

Leukemia (2021) 35:787–795
https://doi.org/10.1038/s41375-020-01013-3

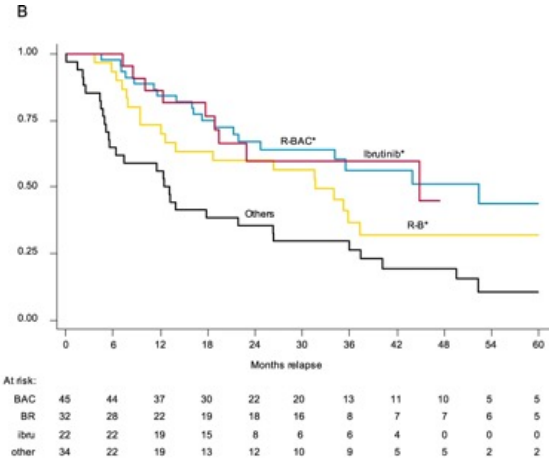
ARTICLE

Lymphoma

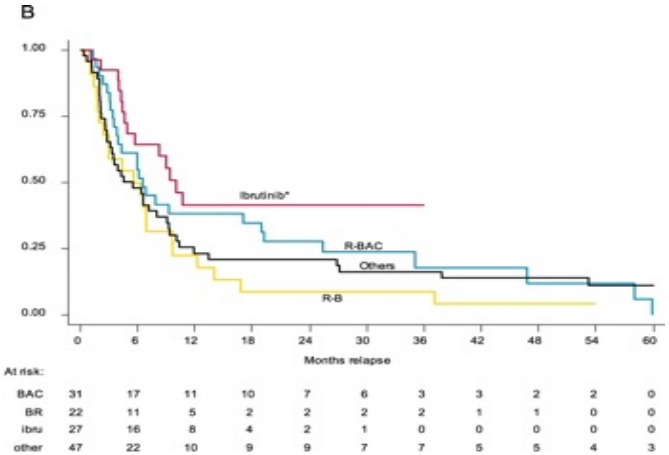
Outcomes in first relapsed-refractory younger patients with mantle cell lymphoma: results from the MANTLE-FIRST study

Carlo Visco[1] · Alice Di Rocco[2] · Andrea Evangelista[3] · Francesca Maria Quaglia[1] · Maria Chiara Tisi[4] ·

Late-POD



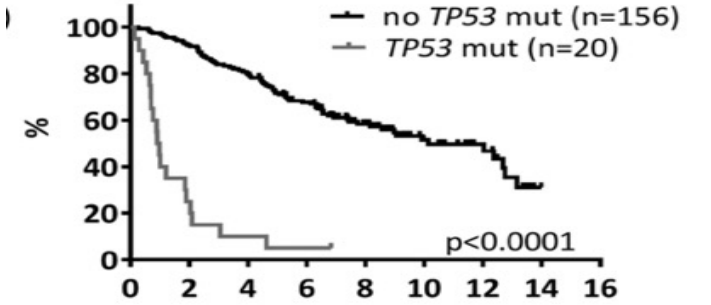
Early-POD

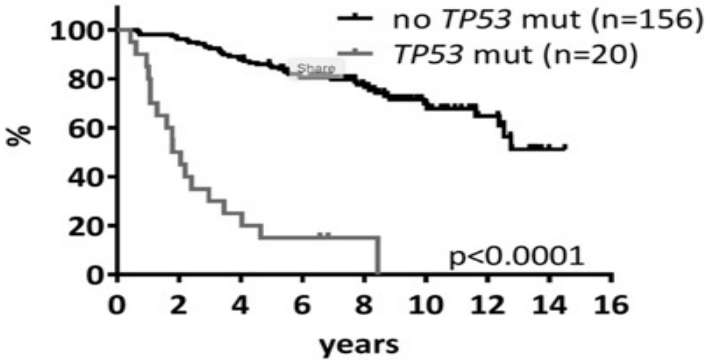


Visco C et al, Leukemia 2021.

Patient selection: High-risk MCL

blood Prepublished online August 17, 2017;
doi:10.1182/blood-2017-04-779736



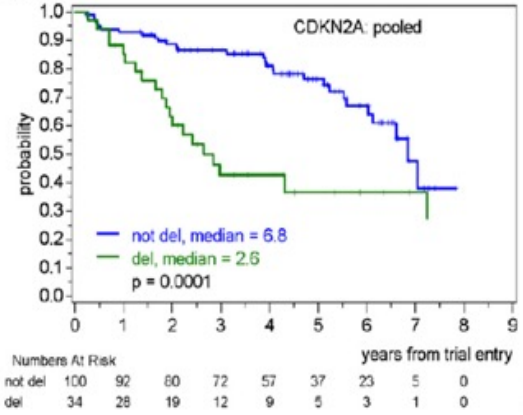


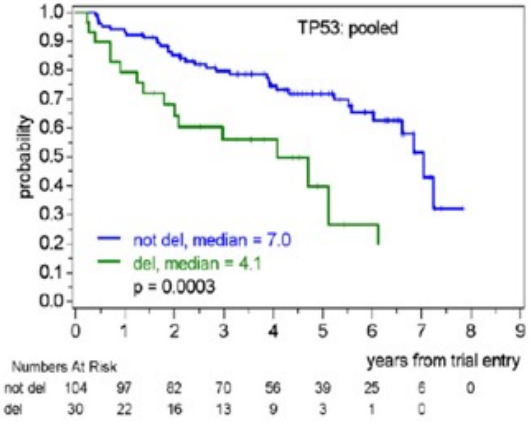
blood 2015 126: 604-611
doi:10.1182/blood-2015-02-628792 originally published online May 28, 2015

High-dose cytarabine does not overcome the adverse prognostic value of *CDKN2A* and *TP53* deletions in mantle cell lymphoma

Marie-Hélène Delfau-Larue, Wolfram Klapper, Françoise Berger, Fabrice Jardin, Josette Briere, Gilles Salles, Olivier Casasnovas, Pierre Feugier, Corinne Haioun, Vincent Ribrag, Catherine Thieblemont, Michael Unterhalt, Martin Dreyling, Elizabeth Macintyre, Christiane Pott, Olivier Hermine and Eva Hoster

A



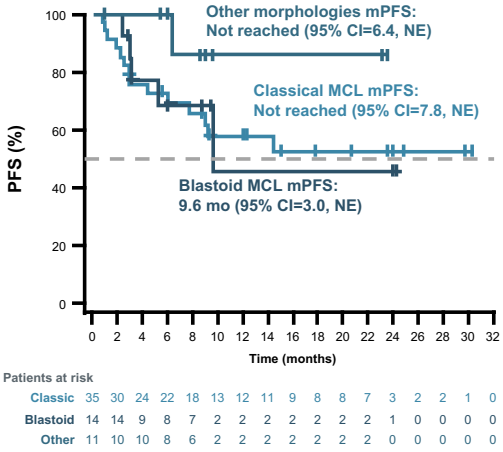


Eskelund CW et al, Blood 2017; Delfau-Larue MH et al, Blood 2015.

Patient selection: High-risk MCL

ZUMA-2

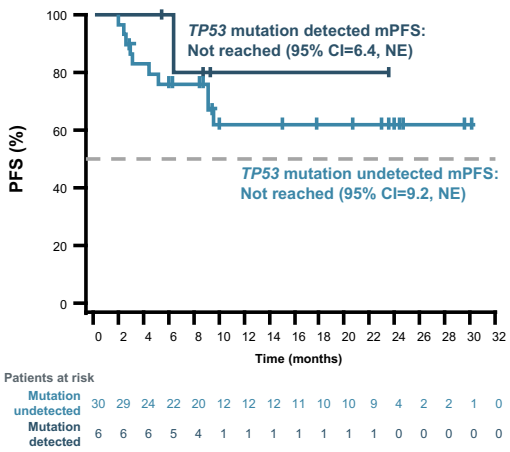
Blastoid morphology



Patients at risk

Classic	35	30	24	22	18	13	12	11	9	8	8	7	3	2	2	1	0
Blastoid	14	14	9	8	7	2	2	2	2	2	2	2	1	0	0	0	0
Other	11	10	10	8	6	2	2	2	2	2	2	2	0	0	0	0	0

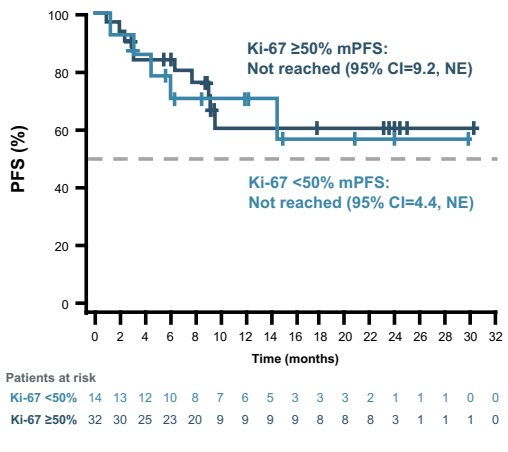
TP53 mutation



Patients at risk

Mutation undetected	30	29	24	22	20	12	12	12	11	10	10	9	4	2	2	1	0
Mutation detected	6	6	6	5	4	1	1	1	1	1	1	1	0	0	0	0	0

Ki-67 ≥50%



Patients at risk

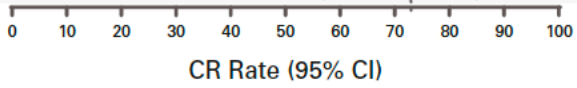
Ki-67 <50%	14	13	12	10	8	7	6	5	3	3	3	2	1	1	1	0	0
Ki-67 ≥50%	32	30	25	23	20	9	9	9	9	8	8	8	3	1	1	1	0

Wang M, et al. N Engl J Med 2020.

Patient selection: High-risk MCL

TRANSCEND NHL-001: In the efficacy set, ORR and CR rates were consistent across prespecified patient subgroups, including those with high-risk disease such as TP53 mutation and blastoid morphology.

Characteristic	Evaluable Patients (n)	Patients With CR (n)	CR Rate (95% CI)
Previous BTKi exposure			
Refractory to BTKi	45	29	64.4 (48.8 to 78.1)
Not refractory to BTKi	35	28	80.0 (63.1 to 91.6)
Ki-67 proliferation index			
<30%	14	8	57.1 (28.9 to 82.3)
≥30%	62	47	75.8 (63.3 to 85.8)
Unknown	7	5	71.4 (29.0 to 96.3)
TP53 mutation status			
Yes	19	11	57.9 (33.5 to 79.7)
No	32	27	84.4 (67.2 to 94.7)
Not tested	29	20	69.0 (49.2 to 84.7)
Indeterminate	3	2	66.7 (9.4 to 99.2)
Blastoid morphology			
Yes	27	17	63.0 (42.4 to 80.6)
No	45	37	82.2 (67.9 to 92.0)
Not tested	11	6	54.5 (23.4 to 83.3)
sMIPI risk category			
Low risk	34	28	82.4 (65.5 to 93.2)
Intermediate/high risk	49	32	65.3 (50.4 to 78.3)
LDH			
≥ULN, U/L	39	28	71.8 (55.1 to 85.0)
<ULN, U/L	44	32	72.7 (57.2 to 85.0)

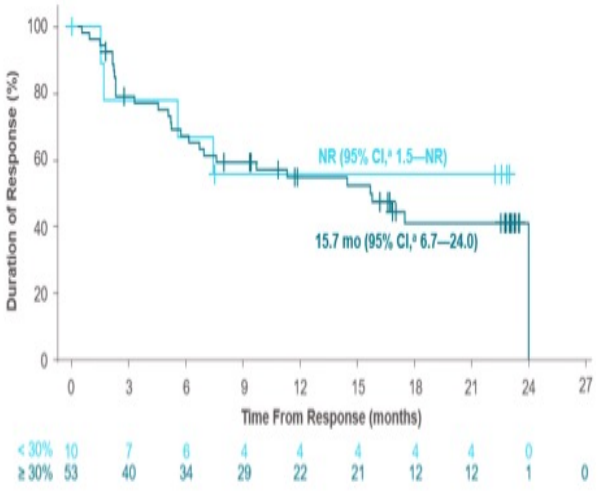


Wang M, et al. J Clin Oncol 2024.

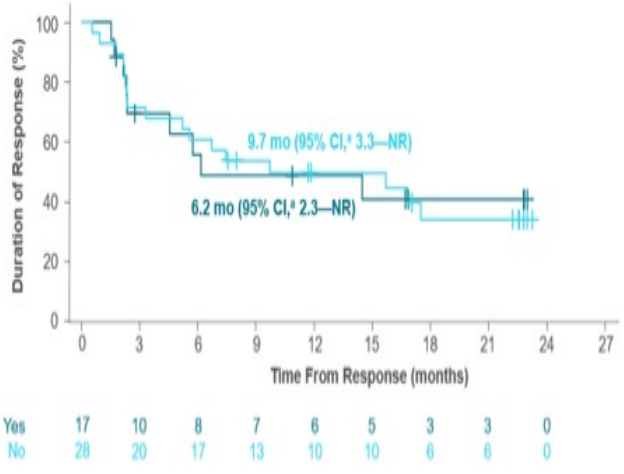
Patient selection: High-risk MCL

TRANSCEND NHL-001: Duration Of Response.

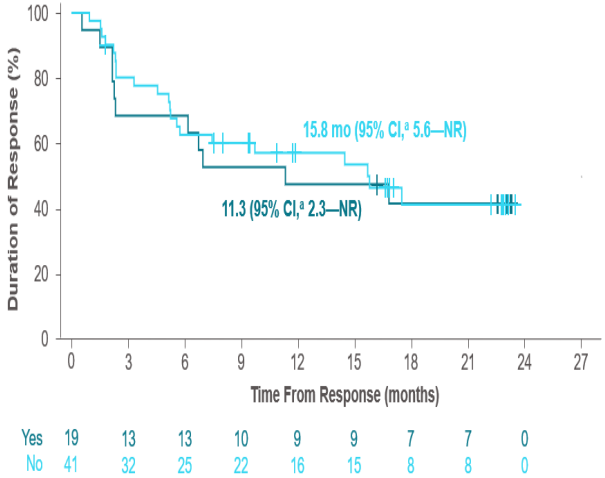
Ki-67



TP53 mutation



Blastoid morphology



Wang M, et al. J Clin Oncol 2024.

Patient selection: High-risk MCL

Frontline Treatment

TP53-aberrant (*TP53* mutations, deletion 17p, p53 overexpression)	Other High-risk (Blastoid/pleomorphic, Ki-67 ≥30-50%, High-risk MIPI)
- Clinical trial - BTKi + BCL2i + CD20Ab - CIT + BTKi + RM	- Clinical trial - CIT ± BTKi + RM
• Worse outcomes in *TP53*-mutated MCL; no benefit from intensive CIT and ASCT. • Unclear prognostic impact for *TP53* aberrations in leukemic non-nodal MCL. • Avoid bendamustine-based CIT. • Early consideration for CAR T-cell (preferred) or alloSCT, if feasible.	• Unclear benefit from adding BTKi to CIT in older patients.

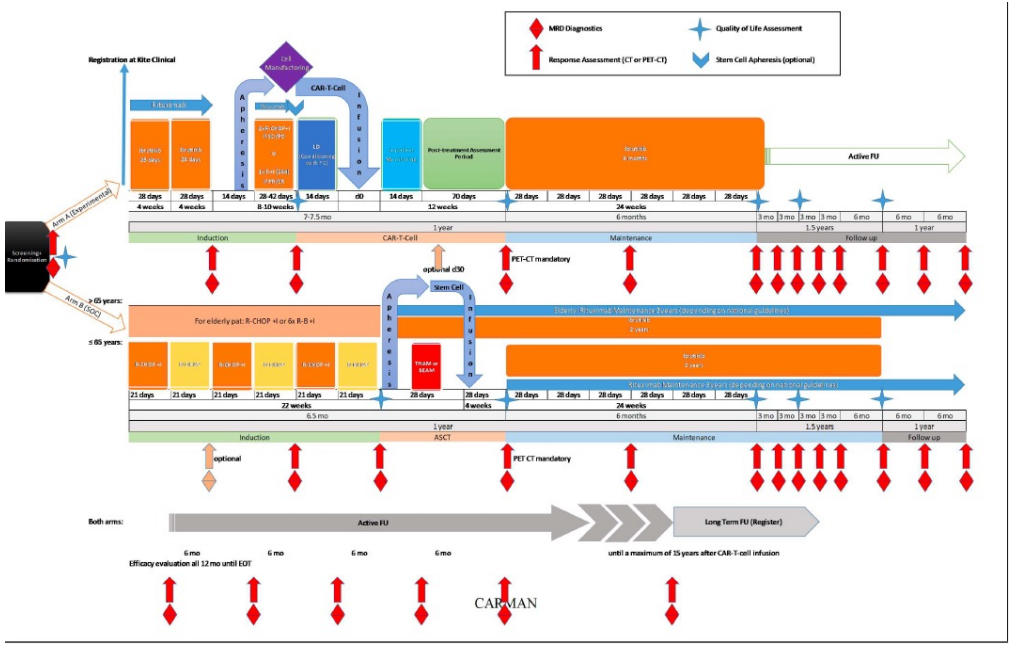
Relapsed/Refractory

- BTKi-based therapy if not used frontline; BTKi + BCL2i ± CD20Ab favored in *TP53*-aberrant MCL
- CAR-T cell (if feasible)
- Clinical trial

Sawalha Y and Maddocks K. Hematology 2024.

Phase II randomized trial CARMAN. CAR-T cell treatment for untreated high-risk mantle cell lymphoma

EUROPEAN MCL NETWORK



Inclusion criteria:

Age 18-75 years

Confirmed diagnosis of MCL

At least one High-risk MCL feature as defined as:

- MIPI-c HI/H risk
- or MIPI-c I risk and Ki-67 ≥ 30%

and/or

- TP53 mutation and/or TP53 overexpression by IHC (> 50%)

Endpoint: FFS

Conclusions

- Brexu-cel and Liso-cel provides high rates of durable responses in R/R MCL with prior iBTK failure
- The selection of the patients eligible to CAR-T is a crucial time-point
- Refractoriness to iBTK represents a challenge, and new strategies are needed
- Risk-adapted study designs and clinical trials focused on high-risk patients are needed
- Consider treatment with CART early and refer the patient as soon as possible

Acknowledgements

Dept. of Hematology
Paolo Corradini
Angelica Barone
Annalisa Chiappella
Anna Dodero
Anna Guidetti
Martina Pennisi
Federico Stella

Research Support and Statistics
Anisa Bermema
Silva Ljevar
Rosalba Miceli

Lab
Cristiana Carniti
Martina Magni
Giada Zanirato
Sadhana Jonnalagadda

All the Italian qualified centers, referral centers, patients, families, nurses and study coordinators.