XX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

ROMA, ERGIFE PALACE HOTEL, 7-8 MAGGIO 2026

COME SI INTEGRANO I NUOVI FARMACI E LE TERAPIE CELLULARI: PRESENTE E FUTURO

MCL

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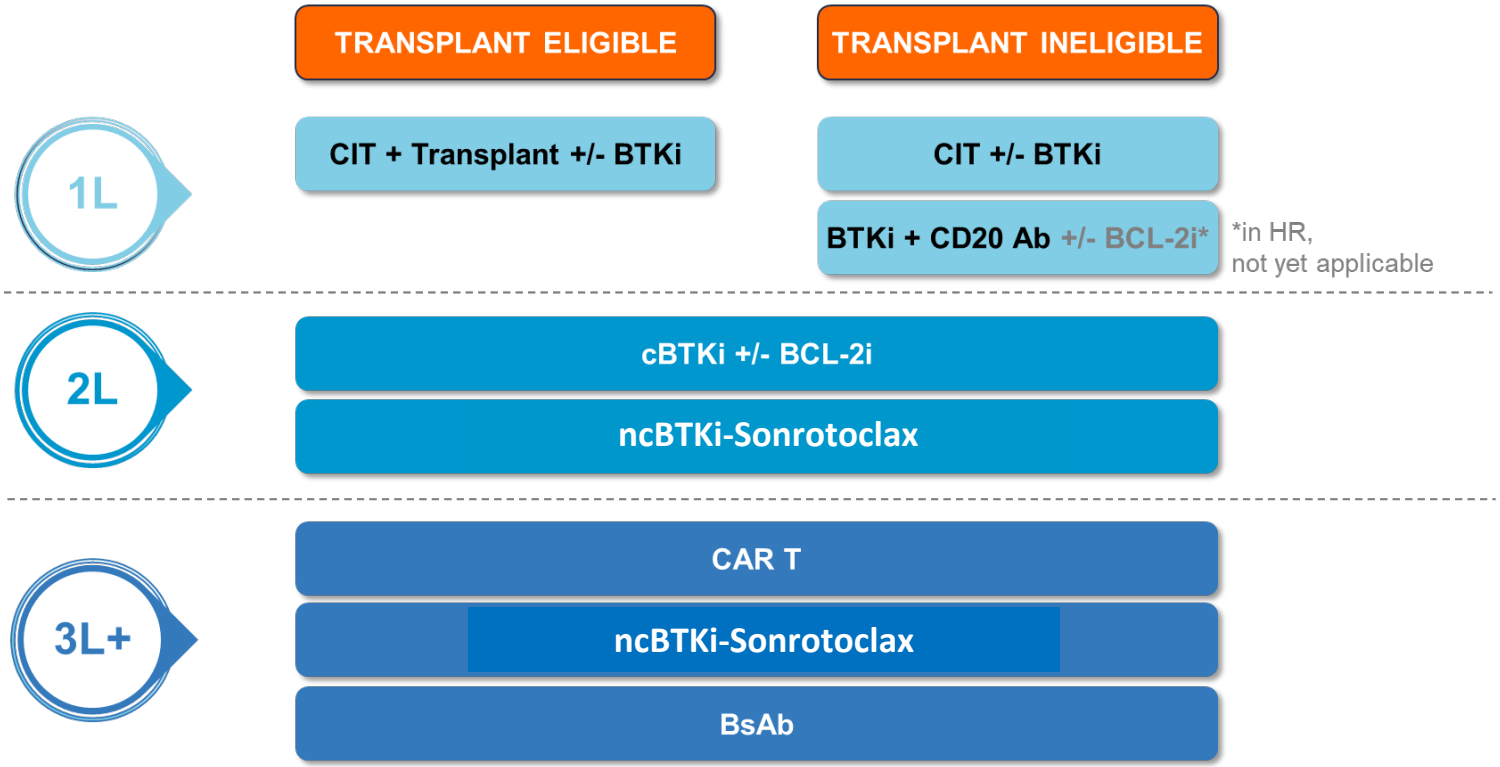
Disclosures of Carlo Visco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X				X	X	
Kite-Gilead					X	X	
Janssen	X		X		X	X	
Gentili					X	X	
Novartis						X	
Pfizer			X		X	X	
Roche					X	X	
Incyte					X	X	
Servier					X		
Astra Zeneca					X		
BMS						X	
Kyowa Kirin					X		
Beigene					X		
Lilly			X		X	X	

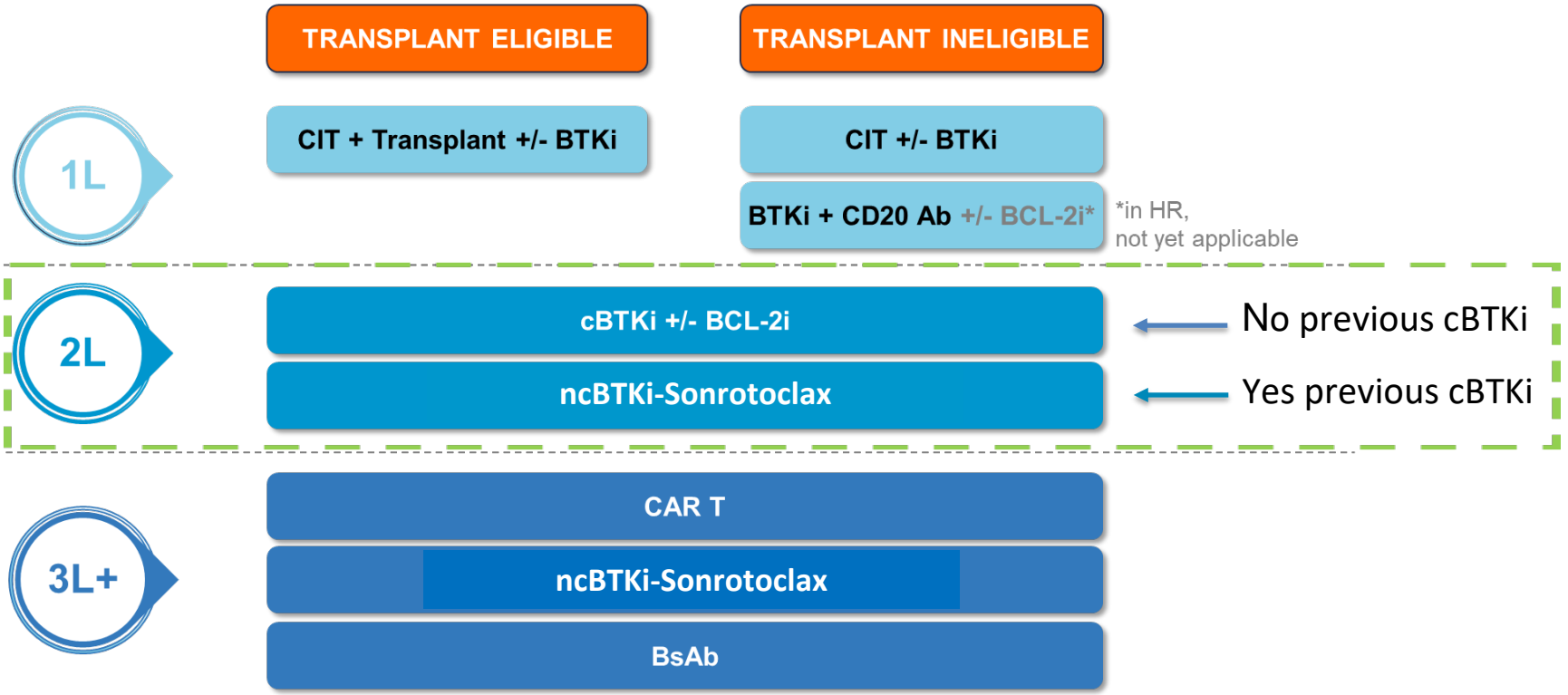
Background and Perspective in R/R MCL

- MCL patients with R/R disease are high-risk patients
- Therapeutic shift ongoing….evolving field
- CarT the mainstay of the R/R algorithm
- Chemo-free options already available, some in development
- CIT (VR-CAP, BR, RBAC) left for debulking purposes

Evolving MCL Treatment Algorithm

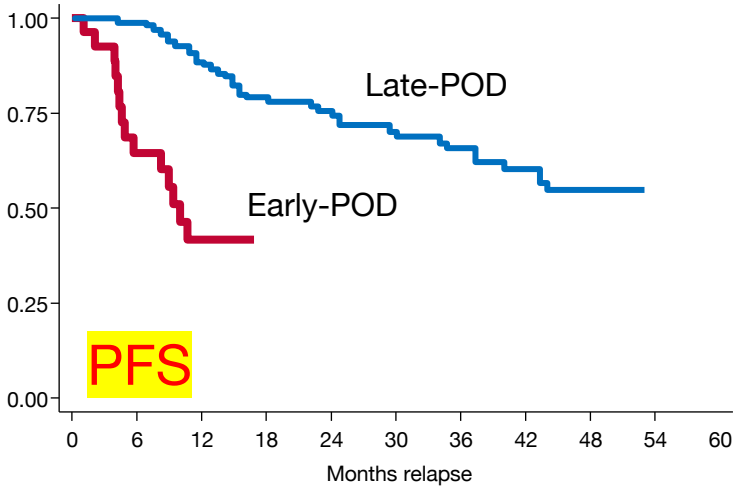


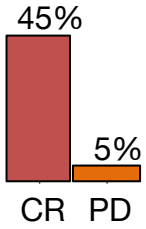
Evolving MCL Treatment Algorithm



No previous cBTKi

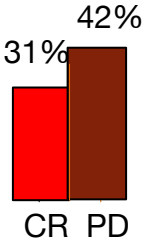
Ibrutinib expected activity at the time of first relapse: survival and tumor response in late- versus early-POD, and management of the referral to CAR-T





Late-POD

Standard approach during BTKi
Refer to CAR-T centre if suboptimal response or high-risk features (i.e. TP53 mutation)



Early-POD

Refer to CAR-T centre at start of therapy
Close clinical monitoring
Restage 8-12 weeks

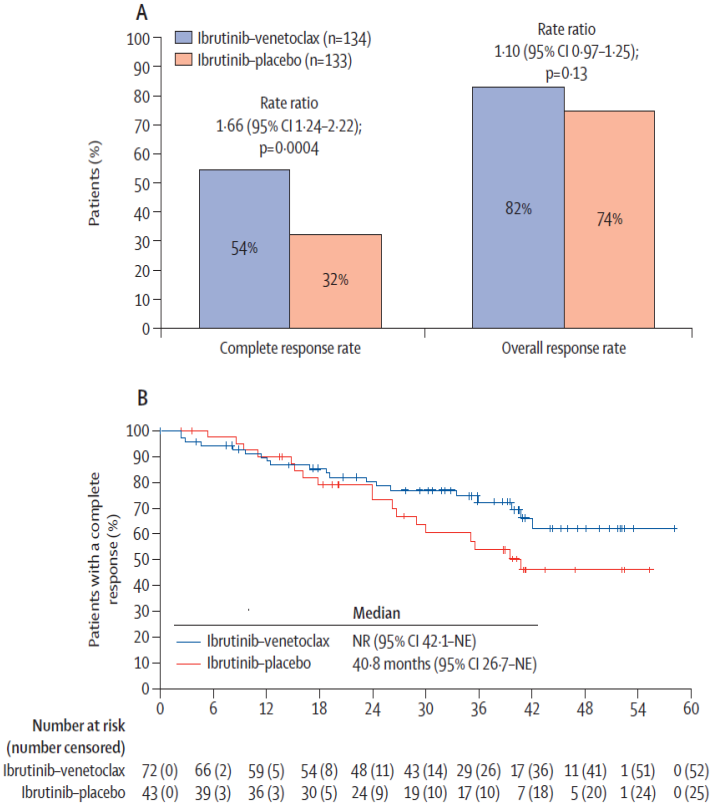
POD: progression of disease; PFS: progression-free survival; CR: complete response; PD: progressive disease

Visco C, modified from Leukemia 2020, and ICML-2023, Abstr 348 [https://doi.org/10.1002/hon.3164_348]

No previous cBTKi

Venetoclax + Ibrutinib: SYMPATICO

	Ibrutinib–venetoclax (n=134)	Ibrutinib–placebo (n=133)
Age, years	69 (62–74)	67 (60–73)
<65	41 (31%)	47 (35%)
≥65	93 (69%)	86 (65%)
Sex		
Female	31 (23%)	25 (19%)
Male	103 (77%)	108 (81%)
Race		
White	116 (87%)	115 (86%)
Asian	2 (1%)	3 (2%)
Black	1 (1%)	1 (1%)
Not reported	15 (11%)	14 (11%)
Ethnicity		
Hispanic, Latino, Latina, or Latinx	8 (6%)	7 (5%)
Other	112 (84%)	110 (83%)
Not reported	14 (10%)	16 (12%)
ECOG performance status		
0	74 (55%)	74 (56%)
1 or 2	60 (45%)	59 (44%)
Previous lines of therapy	1 (1–2)	1 (1–2)
1	80 (60%)	79 (59%)
2	32 (24%)	31 (23%)
≥3	22 (16%)	23 (17%)
Previous SCT	39 (29%)	50 (38%)



Wang M et al, Lancet Oncol 2025

No previous cBTKi

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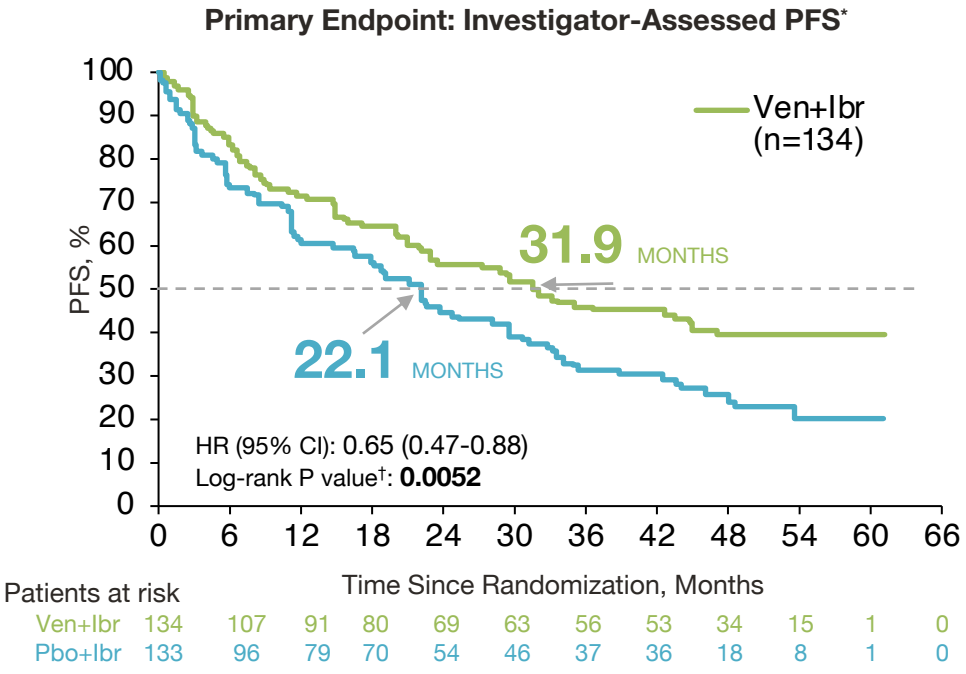


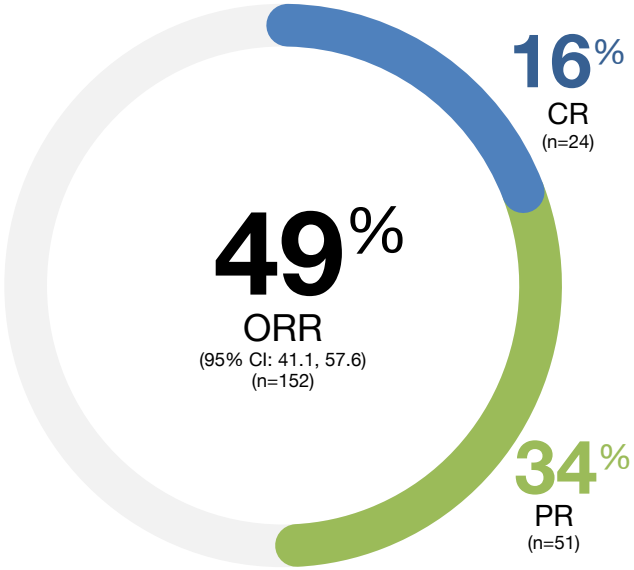
Most Frequent Adverse Events

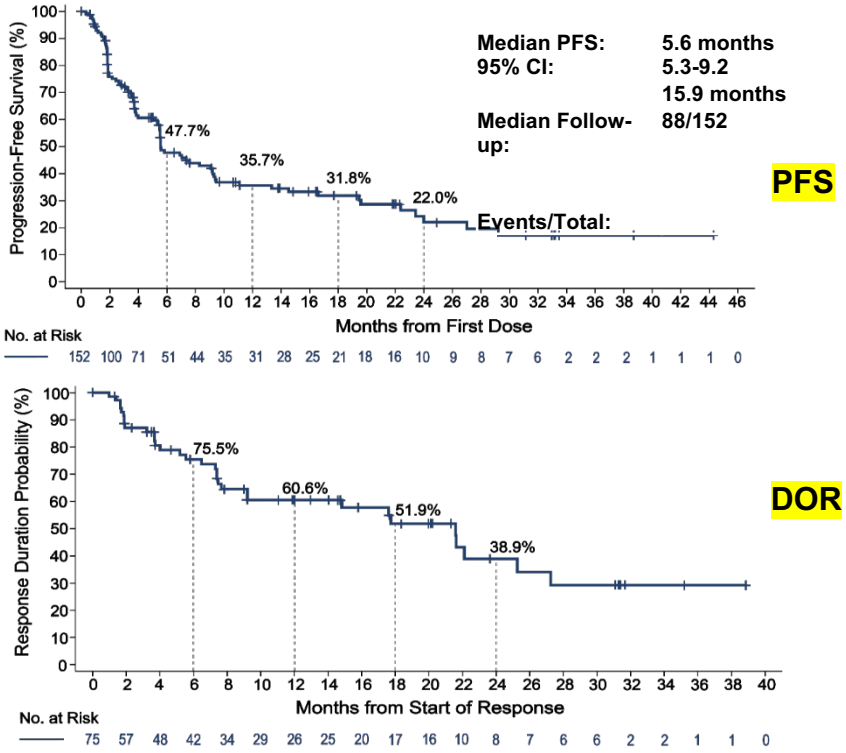
AE, n (%)	Ven+Ibr (n=134)	Pbo+Ibr (n=132)
Most frequent any-grade AEs‡		
Diarrhea	87 (65)	45 (34)
Neutropenia	46 (34)	19 (14)
Nausea	42 (31)	22 (17)
Fatigue	39 (29)	36 (27)
Anemia	30 (22)	16 (12)
Pyrexia	28 (21)	26 (20)
Cough	27 (20)	36 (28)
Asthenia	26 (20)	18 (14)
Thrombocytopenia	26 (20)	21 (15)
Most frequent grade ≥3 AEs§		
Neutropenia	42 (31)	14 (10)
Pneumonia	17 (13)	14 (11)
Thrombocytopenia	17 (13)	10 (7)
Anemia	13 (9)	4 (3)
Diarrhea	11 (8)	3 (2)
Leukopenia	10 (7)	0
MCL¶	9 (7)	16 (13)
Atrial fibrillation	7 (5)	7 (5)
Hypertension	6 (4)	12 (9)

Wang M et al, Lancet Oncol 2025

Yes previous cBTKi

Pirtobrutinib in MCL previously treated with a cBTKi (n=152)





Cohen et al.; ASH 2023

Yes previous cBTKi

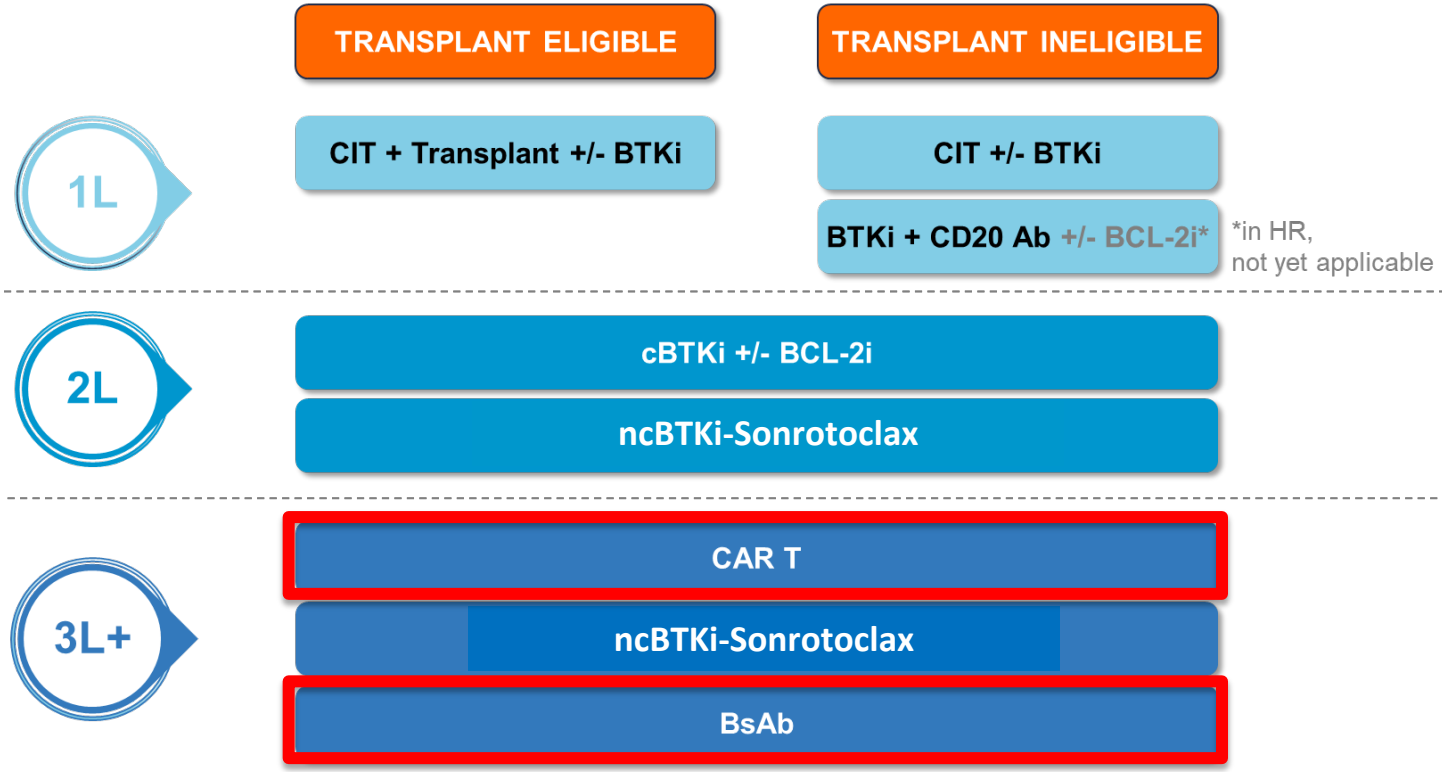
Sonrotoclax in R/R MCL previously treated with a cBTKi

Early results from a Phase 1-2 study

	Sonrotoclax	Venetoclax	Differences in Design
Potency (IC_{50})	0.014 nM[1]	0.20 nM[1]	14-fold more potent, which may potentially lead to deeper target inhibition
Selectivity (vs BCL-xL)	2000×[1]	325×[1]	Improved (6-fold) selectivity
Half-life in humans	≈5 hours[2]	26 hours[3]	Short half-life and no accumulation may potentially result in simplified TLS monitoring during sonrotoclax ramp-up

Wang M et al, ASH 2025

Evolving MCL Treatment Algorithm



CAR T in R/R MCL: Data Summary

quite

CAR T provides high response rates but short duration of response in MCL.

Trial/ Treatment	Source	N Receiving Leukapheresis/ Infusion	Follow-Up from Infusion (months)	No. Lines, (median [range])	Patients Post-BTKi (%)	CR/ORR (%)	DOR	PFS	OS
Clinical Trials									
ZUMA-2/ Brexu-cel	Wang 2020[1]	74/68	47.5	3 (1-5)	52%	68/91	28.2 m	25.8 m	46.4 m
ZUMA-18/ Brexu-cel	Goy 2023[2]	27/23	33.5	4 (1-10)	-	57/87	-	-	2-y: 54%
TRANSCEND/ Liso-cel	Wang 2023[3]	104/88	16.1	3 (1-11)	53%	72/83	15.7 m	15.3 m	18.2 m
Real World Evidence									
Brexu-cel	Wang 2023[4]	189/168	14.3	3 (1-10)	86%	82/90	17.2 m	16.4 m	-
Brexu-cel	Iacoboni 2022[5]	39/33	10.1	2 (1-8)	100%	79/91	-	12-m: 50.8%	12-m: 61.4%
Brexu-cel	Herbaux 2024[6]	178/152	12.2	3 (1-9)	97%	72.2/85.7	12 m	9.5 m	12-m: 70%
Brexu-cel	Kambhampati 2023[7]	500	12.2	4 (1-12)	87%	80/91	12-m: 65%	12-m: 62%	12-m: 75%

Brexu-cel=Brexucabtagene Autoleucel. BTKi=BTK Inhibitor. CAR T=Chimeric Antigen Receptor T-cell Therapy. CR=Complete Response. DOR=Duration of Response. Liso-cel=Lisocabtagene Maraleucel. m=Months. MCL=Mantle Cell Lymphoma. No.=Number. ORR=Overall Response Rate. OS=Overall Survival. PFS=Progression-Free Survival. R/R=Relapsed/Refractory. y=Years. 1. Wang M et al. N Engl J Med. 2020 Apr 2;382(14):1331-42. 2. Goy A, et al. Oral #106. 65th ASH Annual Meeting . Dec 9-12, 2023. San Diego, CA. 3. Wang M, et al. J Clin Oncol. 2024 Apr 1;42(10):1146-57. 4. Wang Y et al. J Clin Oncol. 2023 May 10;41(14):2594-606. 5. Iacoboni G, et al. Blood Adv. 2022 Jun 28;6(12):3606-10. 6. Herbaux C, et al. Haematologica. 2024 Jun 20;109(11):3745. 7. Kambhampati S et al. Blood. 2023 Nov 2;142:107.

Brexu-cel for R/R MCL in Standard-of-Care Practice

E

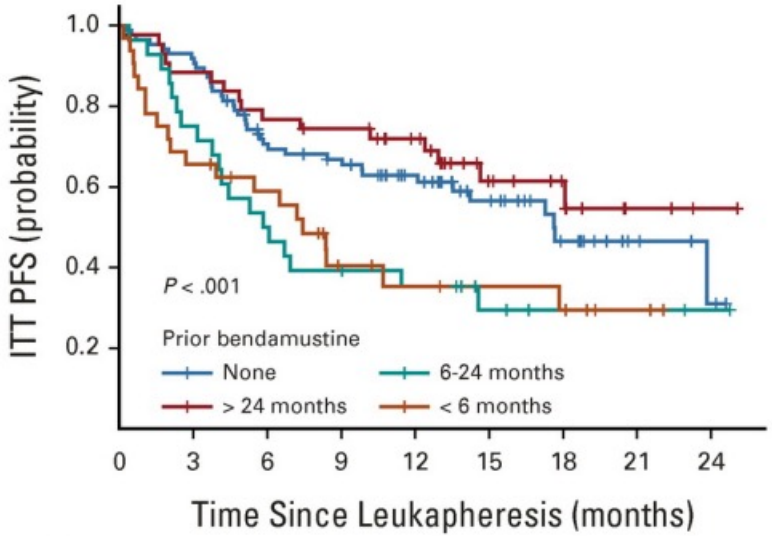
Subgroup	ORR (95% CI)
No prior bendamustine (n = 86)	91 (82 to 96)
Prior bendamustine (n = 103)	71 (61 to 79)
Bendamustine within 6 months (n = 32)	53 (35 to 71)
Bendamustine within 6-24 months (n = 28)	75 (55 to 89)
Bendamustine > 24 months before (n = 43)	81 (67 to 92)

0 10 20 30 40 50 60 70 80 90 100

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)

0 10 20 30 40 50 60 70 80 90 100

F



No. at risk:

None	86	79	57	51	39	23	13	5	2
> 24 months	43	38	33	31	25	13	9	3	1
6-24 months	28	21	14	11	9	5	3	2	1
< 6 months	32	21	17	9	7	6	5	2	0

Wang Y et al, JCO 2023

Ibrutinib and CAR-T cell fitness

Associated with robust CAR-T expansion and less exhausted baseline T-cell phenotype (minor senescence)

Enhances in vivo CAR T-cell phenotype (++central memory cells and CD8/CD4 ratio) that correlates with improved disease response

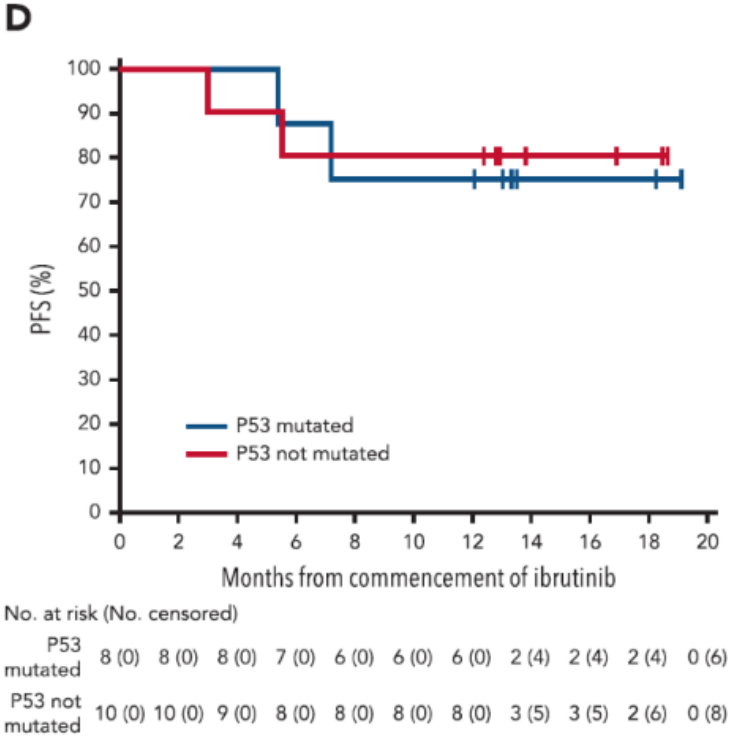
Linked to a more proliferative CAR T-cell compartment, poised to differentiate into effector cells after infusion

NJ Haradhvala et al. Nat Med 2022; JA Dubovsky et al, Blood 2013; J Gauthier et al, Blood 2020; JA Fraietta et al, Blood 2015

CAR T cells and time-limited ibrutinib as treatment for R/R MCL: the phase 2 TARMAC study

KEY POINTS

- **CD19-directed CAR T and time-limited ibrutinib are a deliverable and effective combination in relapsed/refractory MCL.**
- **Novel combination therapy may overcome negative clinical and molecular features, including BTKi refractoriness and TP53 mutation.**

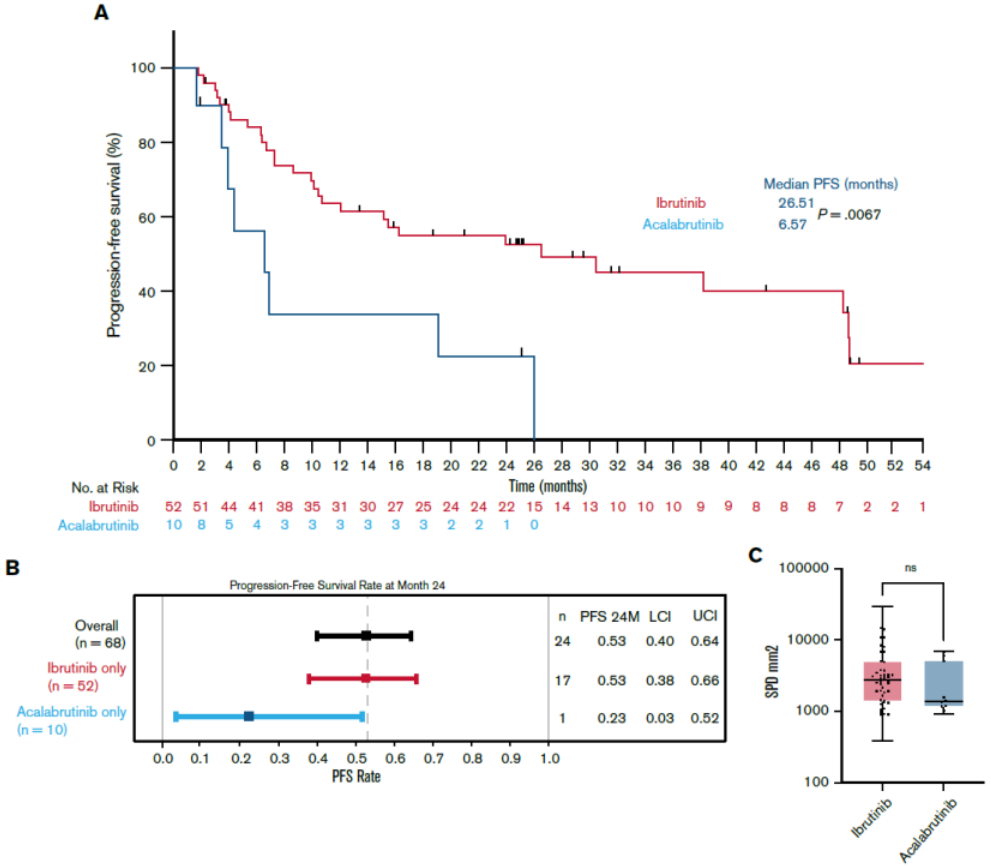


Minson A et al, Blood 2024

Ibrutinib exposure correlates with improved efficacy of CAR T cells in MCL

Key Points

- Patients with MCL previously treated with ibrutinib had longer progression-free survival after brexu-cel in ZUMA-2.
- Patients with previous exposure to ibrutinib had greater CAR T-cell expansion, CAR-toxicity, and effector-polarized CAR T cells.



Darnell EP et al, Blood Adv 2026

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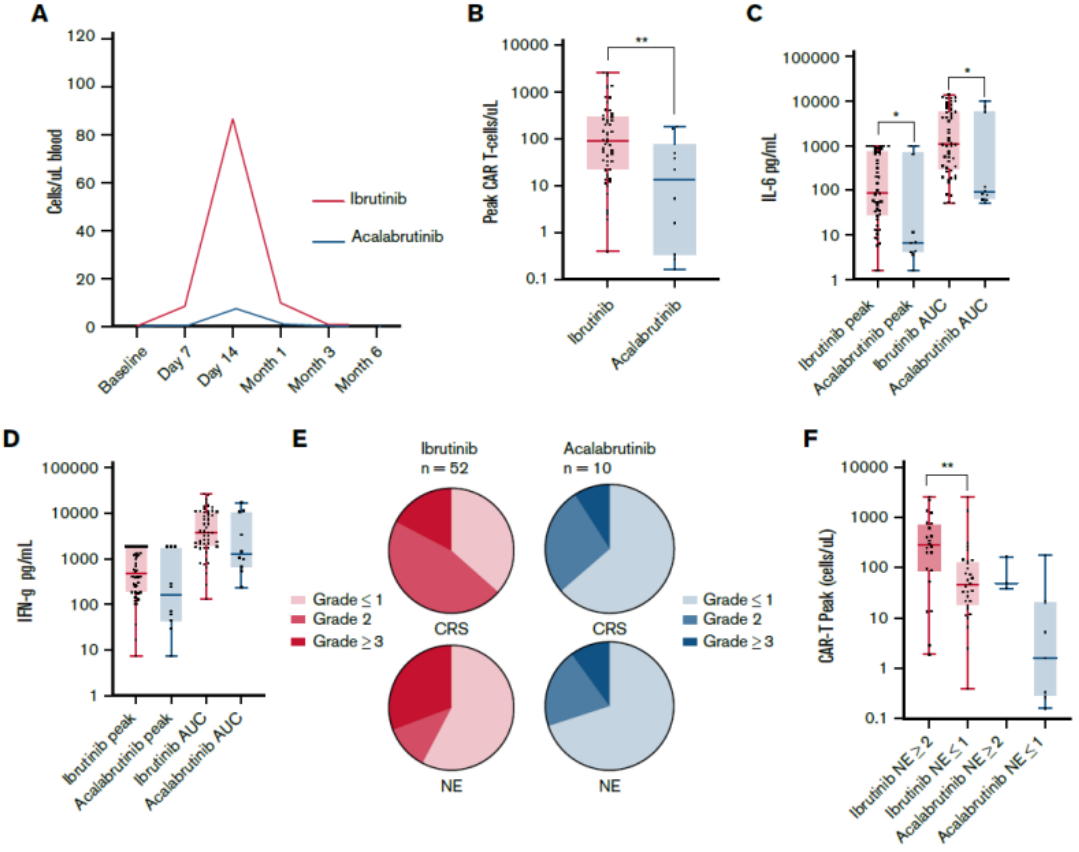


Darnell EP et al, Blood Adv 2026

News in the Car-T cell field (from ASH 2025)

GLPG5101

- Fresh, early memory-enriched phenotype CD19 CarT product with robust expansion and long-term persistence
- 7-day vein-to-vein time, 4% drop-out rate, no need for bridging (!)

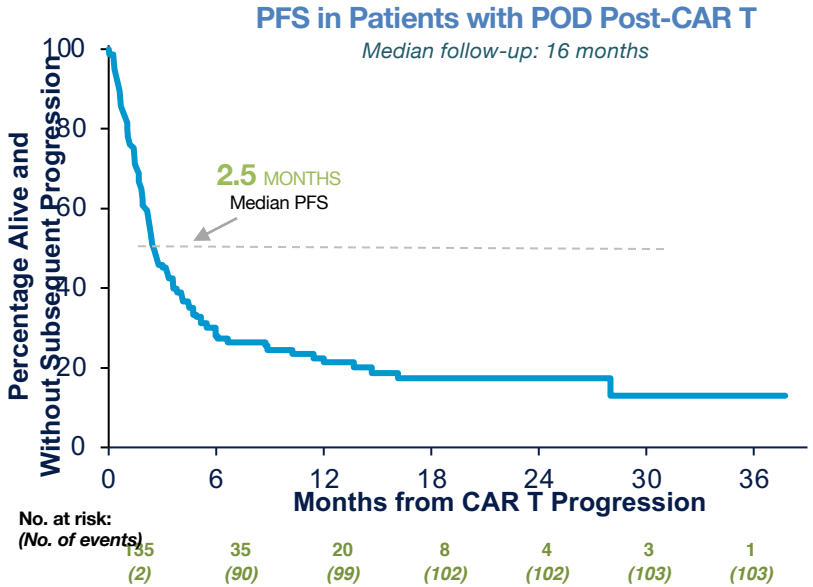
Kersten MJ et al, ASH 2025

ZAMTO-CEL (LV20.19)

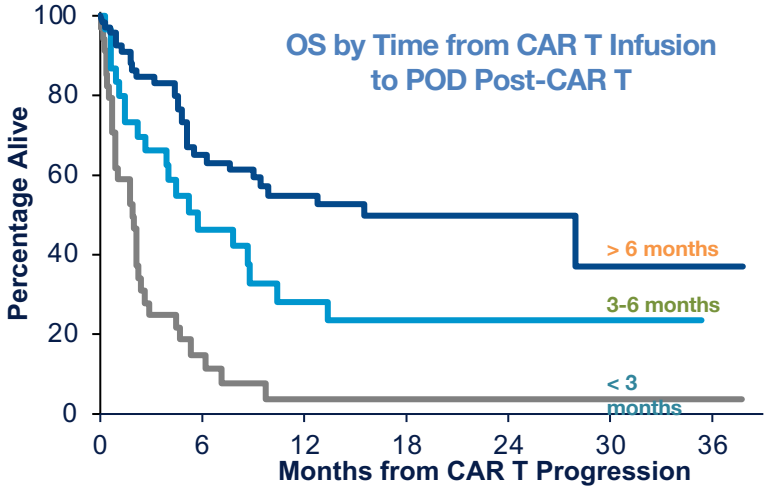
- Lentiviral Anti-CD20/Anti-CD19 CarT product with robust expansion and long-term persistence
- 8-12 days vein-to-vein time, enriched for higher percentages of T-$_{SCM}$/T-naïve cells

Shah *J et al, JCO 2025*

Outcomes post-CAR T failure



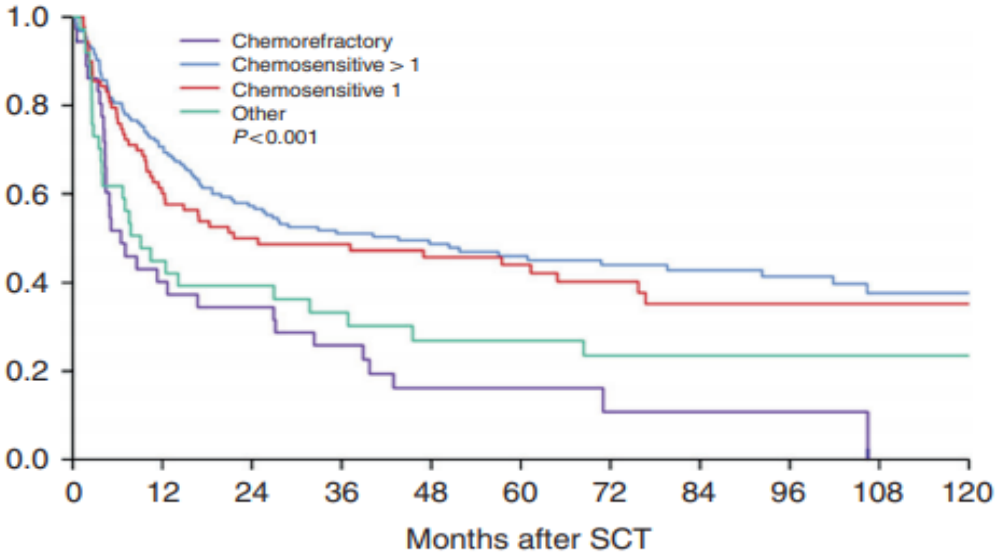
Clinical trials
Allo-transplant in selected HR



Bone Marrow Transplantation
https://doi.org/10.1038/s41409-017-0067-3

ARTICLE

Long-term outcome analysis of reduced-intensity allogeneic stem cell transplantation in patients with mantle cell lymphoma: a retrospective study from the EBMT Lymphoma Working Party

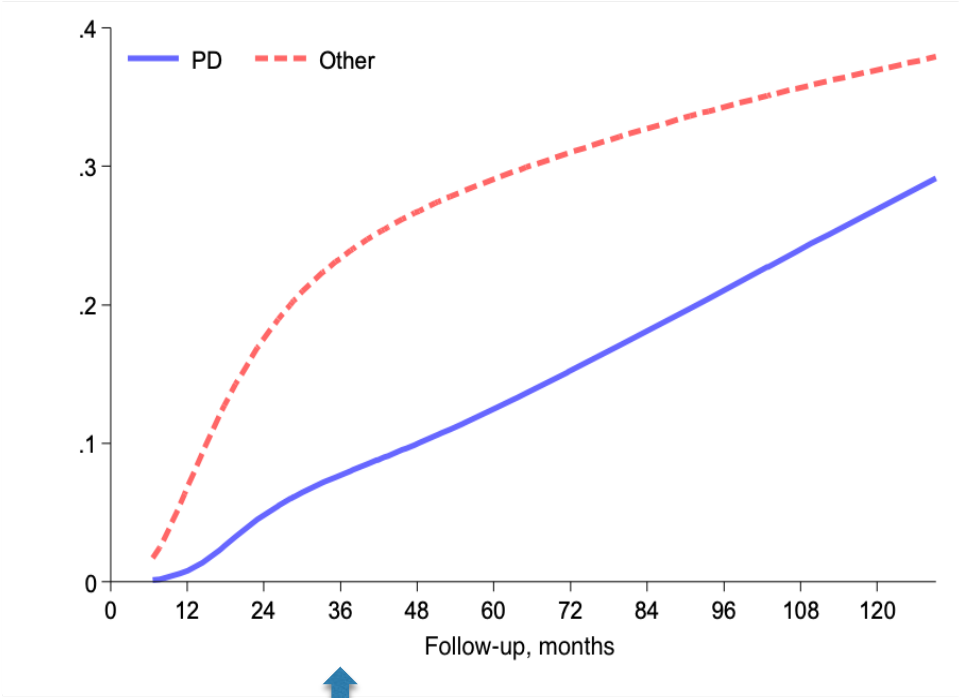


	PFS	OS
1-YR	51%	62%
4-5 YR	**31%**	**40%**

NRM 100 days 10%
NRM 1 year 24%

Robinson SP et al, BMT 2018

Cumulative incidence of death for PD or other causes



8% vs 23%

NRM 7% at 1 year, worse if aGVHD, >2 prior lines, Age>60

GOLD by FIL

FONDAZIONE ITALIANA LINFOMI

A phase II, multicenter trial investigating Glofitamab treatment in pOst CAR-T failure Mantle Cell Lymphoma (MCL) Disease

Conclusions

- Patients not previously treated with cBTKi still in clinical practice [*cBTKi, Sympatico*]
- Patients previously treated with cBTKi undergoing a therapeutic shift in second line [n*cBTKi, CarT, Sonrotoclax*]
- Ibrutinib beneficial when before/after CarT
- After CarT, outcome still unsatisfactory *[++ bispecifics or clinical trials*]
- Allo-SCT still an option for selected HR patients after CarT

Thanks for your attention

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