4th edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, March 26-27, 2026

Starhotels Majestic

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

Chemo-free approaches in relapsed/refractory mantle cell lymphoma

Carlo Visco

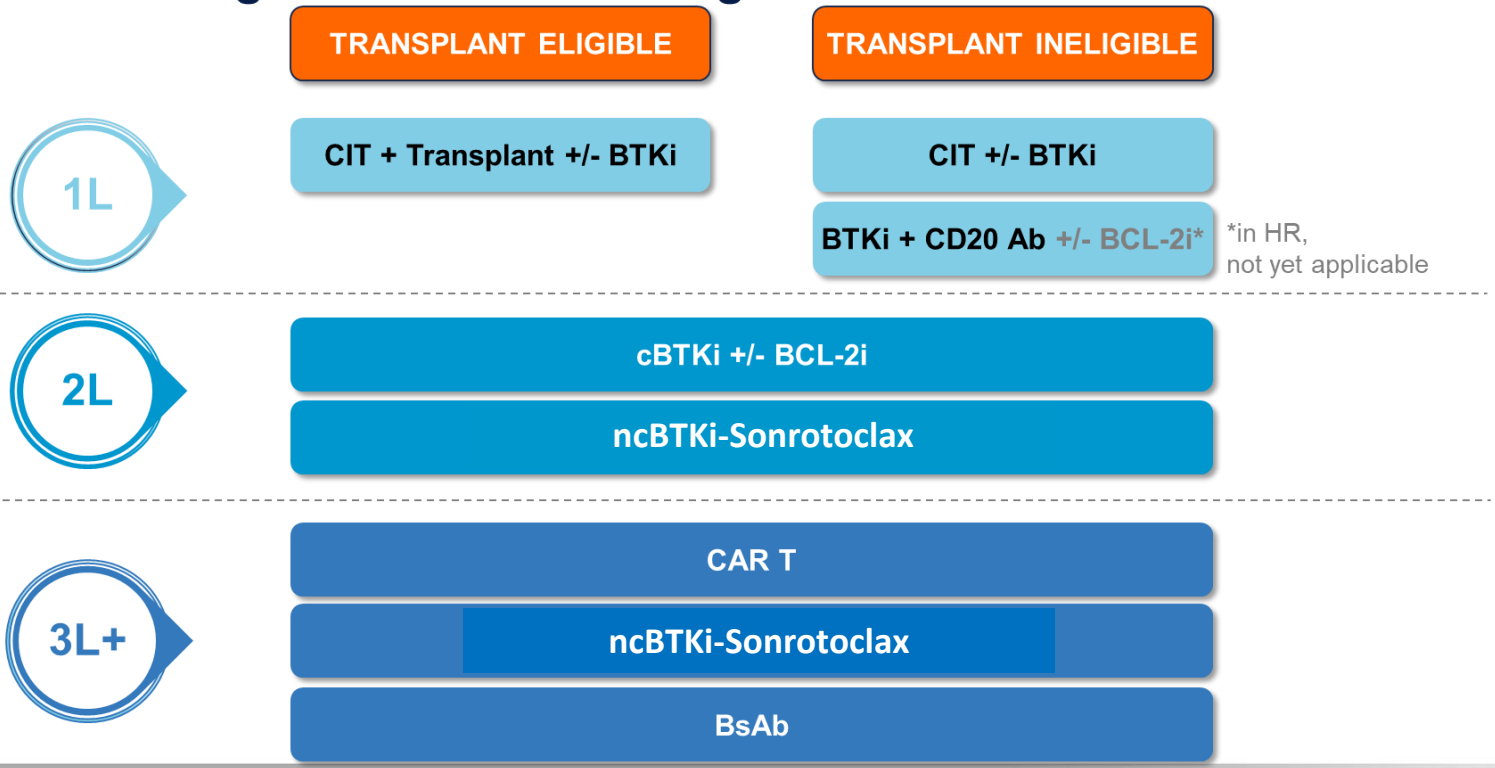
Disclosures of Carlo Visco

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	

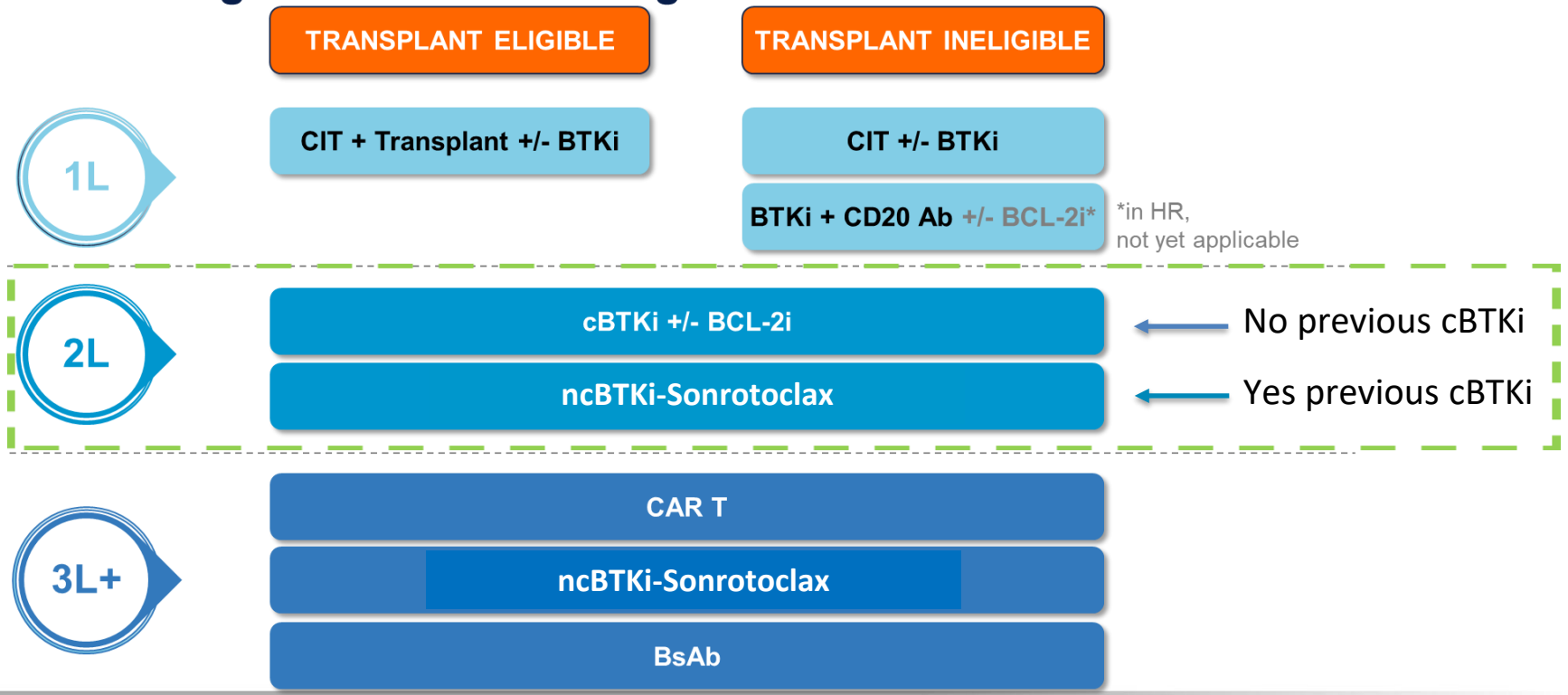
Background and Perspective in R/R MCL

- 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



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

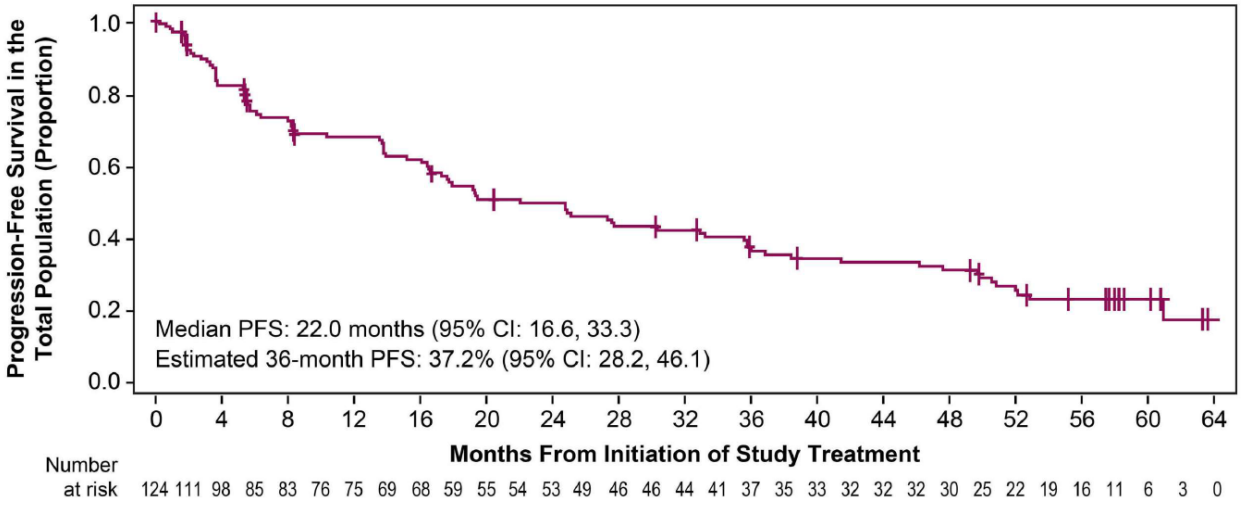
Management at first relapse

- Patients relapsing after first-line immunochemotherapy should be offered a covalent BTKi (1A).
- Offer ibrutinib monotherapy as an approved and reimbursed standard of care option in the United Kingdom at first relapse (1B).
- Where the choice of ibrutinib, acalabrutinib or zanubrutinib is available, treatment should be individualised based on the specific toxicity profile of each agent (1B).
- Where a covalent BTKi has been used in first line as continuous therapy, consider clinical trials or immunochemotherapy at first relapse (2B).

No previous cBTKi

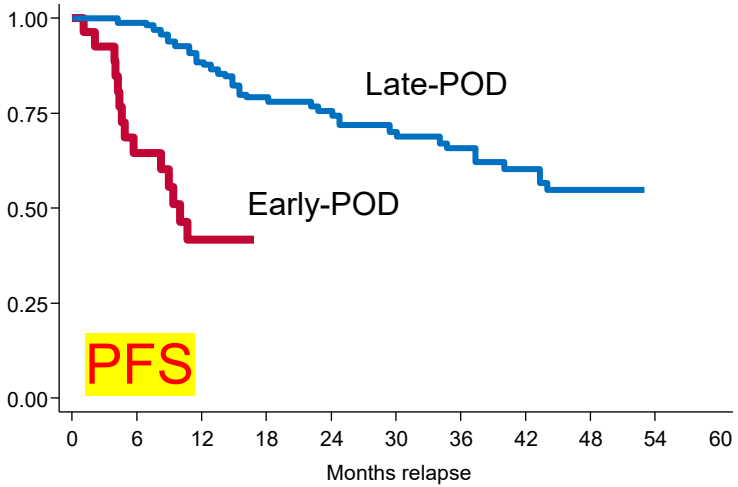
Eyre et al, BJH 2023

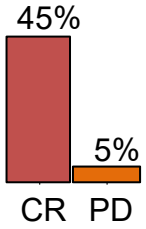
Final results and overall survival data from a phase II study of acalabrutinib monotherapy in patients with relapsed/refractory mantle cell lymphoma, including those with poor prognostic factors



LeGouille S et al, Haematologica 2024

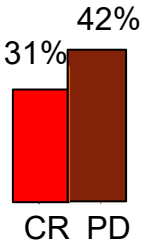
Ibrutinib expected activity at the time of first relapse: survival and tumor response in late- versus early-POD, and management of the referral to CAR-T





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

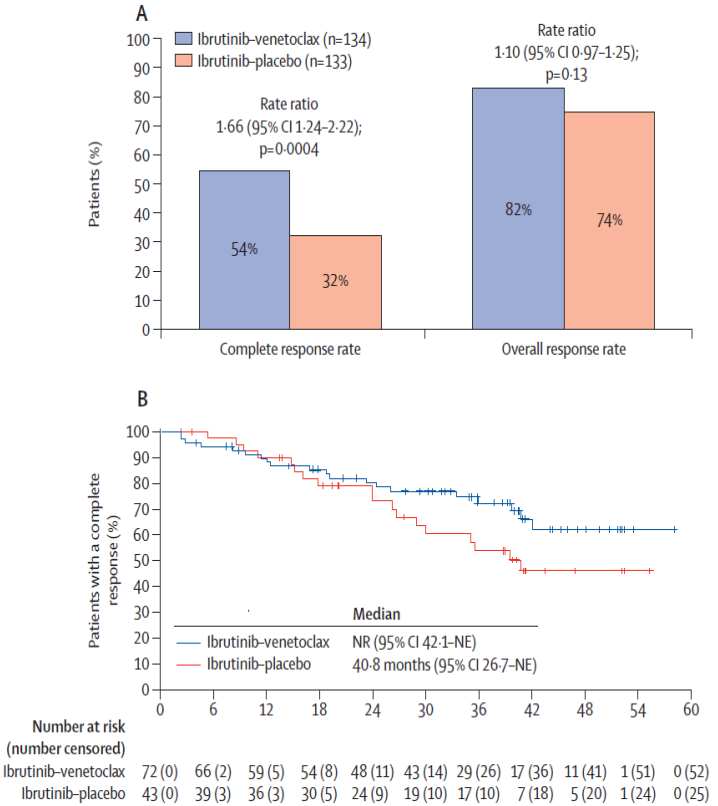
POD: progression of disease; PFS: progression-free survival; CR: complete response; PD: progressive disease

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

No previous cBTKi

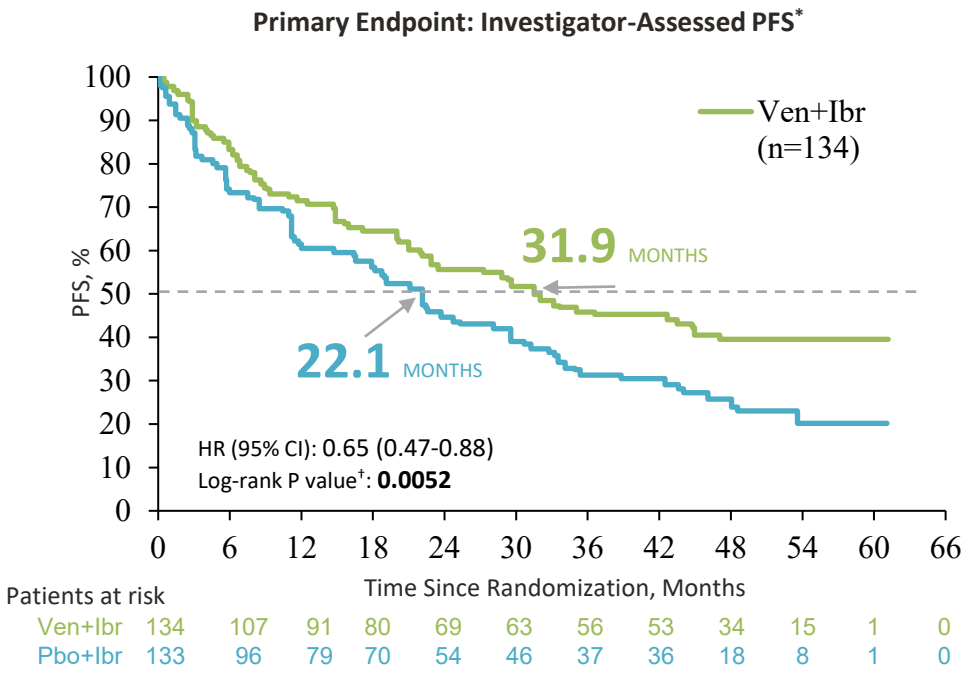
Venetoclax + Ibrutinib: SYMPATICO

	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

Venetoclax + Ibrutinib: SYMPATICO



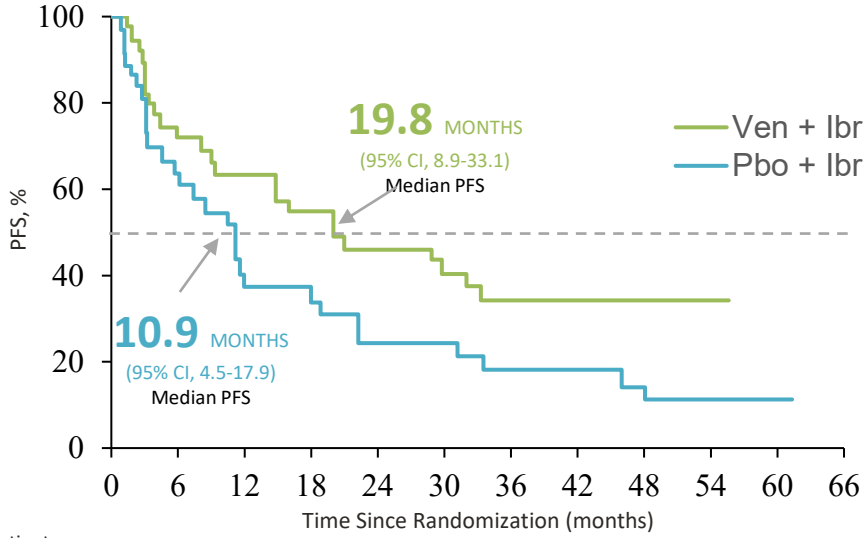
Most Frequent Adverse Events

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

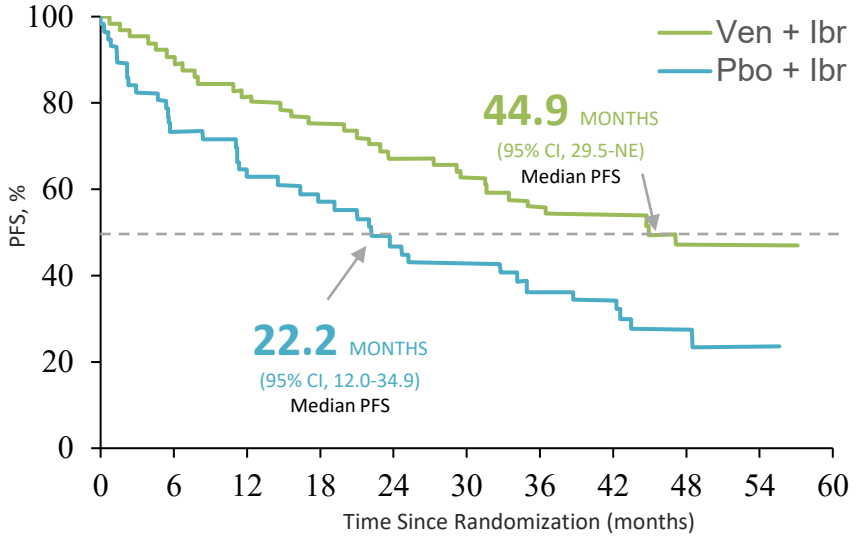
Venetoclax + Ibrutinib: SYMPATICO

Progression-Free Survival: Patients With *TP53* Mutations



Patients at risk												
Ven+Ibr	40	27	23	19	15	13	11	11	7	2	0	
Pbo+Ibr	37	21	12	11	7	7	5	5	3	2	1	0

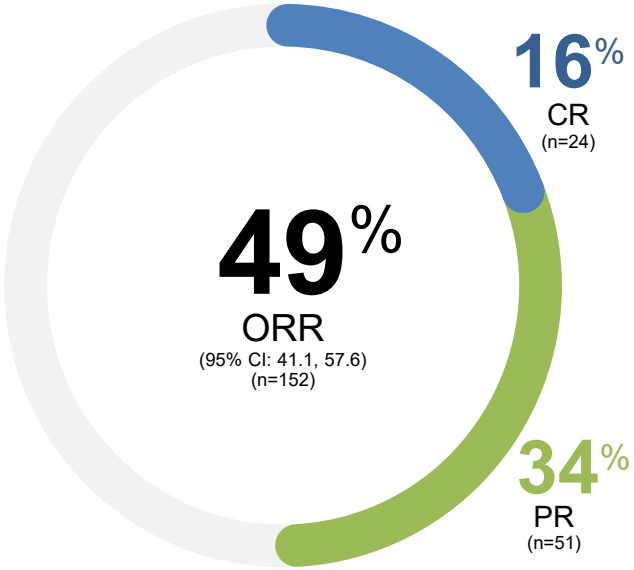
Progression-Free Survival: Patients Without *TP53* Mutations

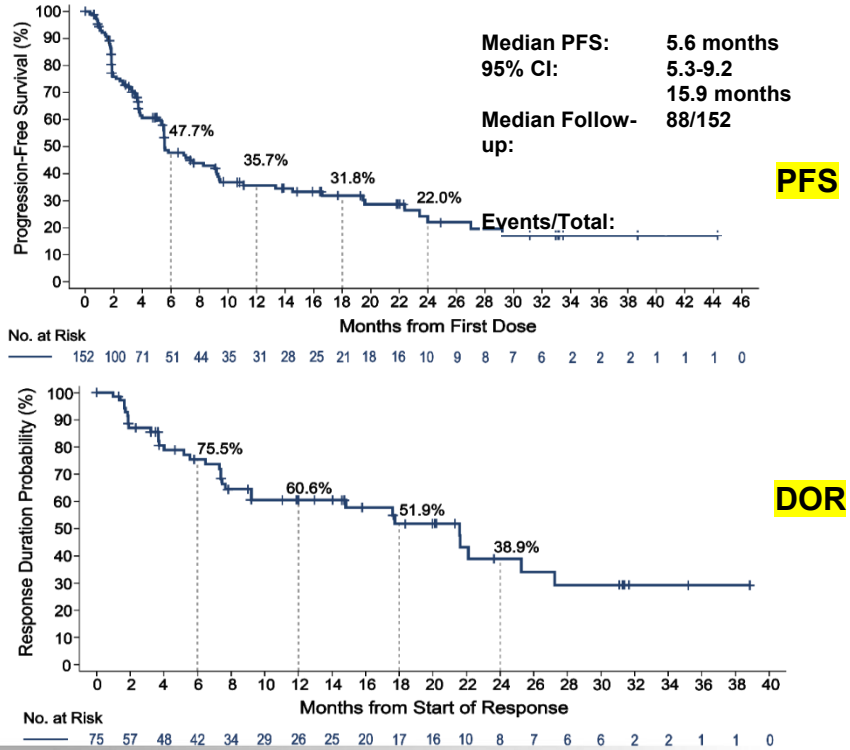


Patients at risk											
Ven+I	66	58	52	47	42	38	34	32	20	9	0
Pbo+I	57	41	36	30	23	20	17	16	7	3	0

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

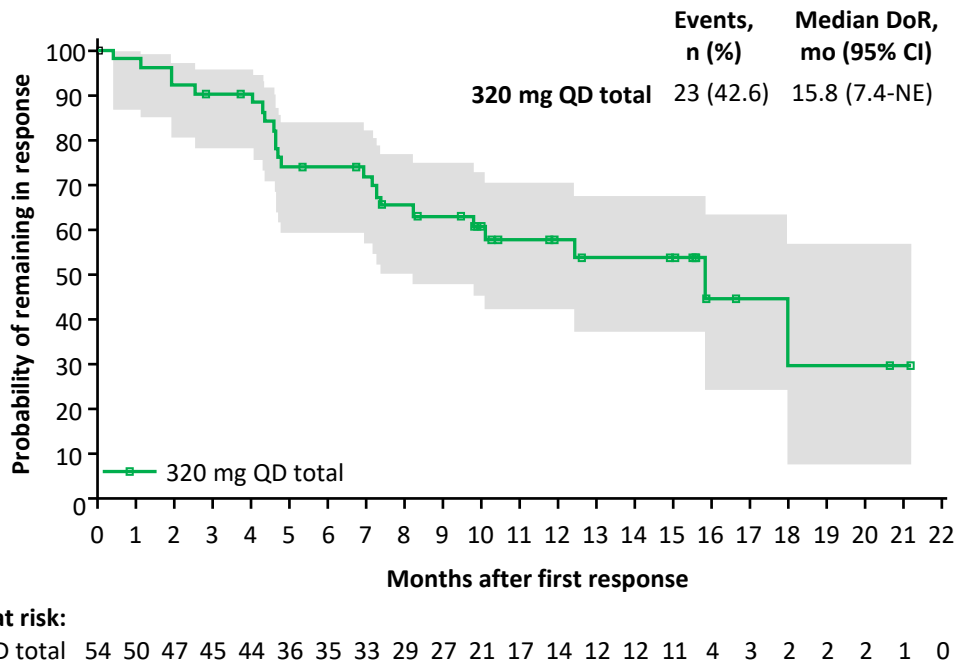
	Sonrotoclax	Venetoclax	Differences in Design
Potency (IC_{50})	0.014 nM[1]	0.20 nM[1]	14-fold more potent, which may potentially lead to deeper target inhibition
Selectivity (vs BCL-xL)	2000×[1]	325×[1]	Improved (6-fold) selectivity
Half-life in humans	≈5 hours[2]	26 hours[3]	Short half-life and no accumulation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

Wang M et al, ASH 2025

Yes previous cBTKi

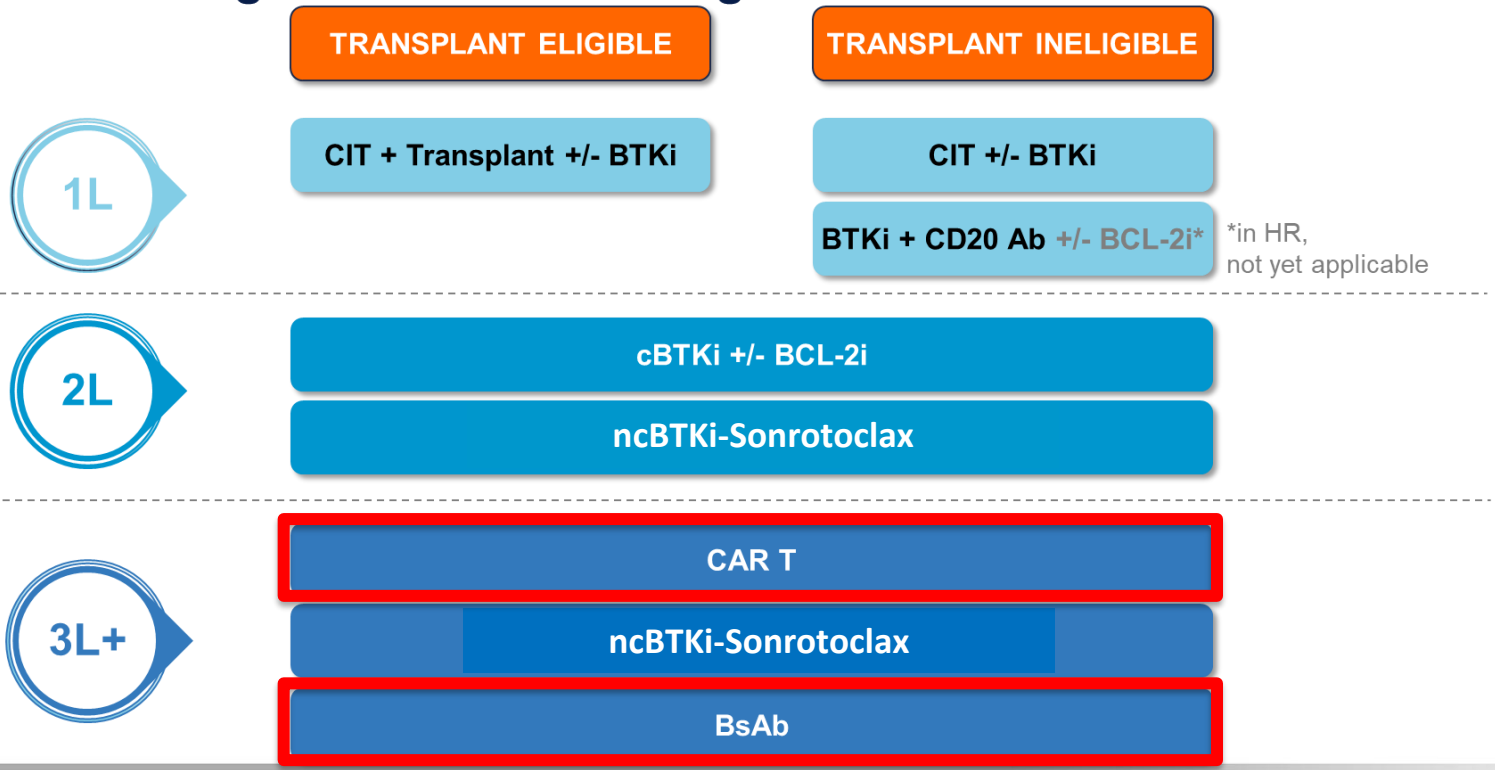
Efficacy for Sonrotoclax at RP2D 320 mg QD

	Part 2: Sonrotoclax 320 mg (n=103)
ORR, n (%)	54 (52.4)
95% CI, %	42.4-62.4
CR rate, n (%)	16 (15.5)
95% CI, %	9.1-24.0
TTR, median (range), months	1.9 (1.6-6.2)



Wang M et al, ASH 2025

Evolving MCL Treatment Algorithm



CAR T in R/R MCL: Data Summary

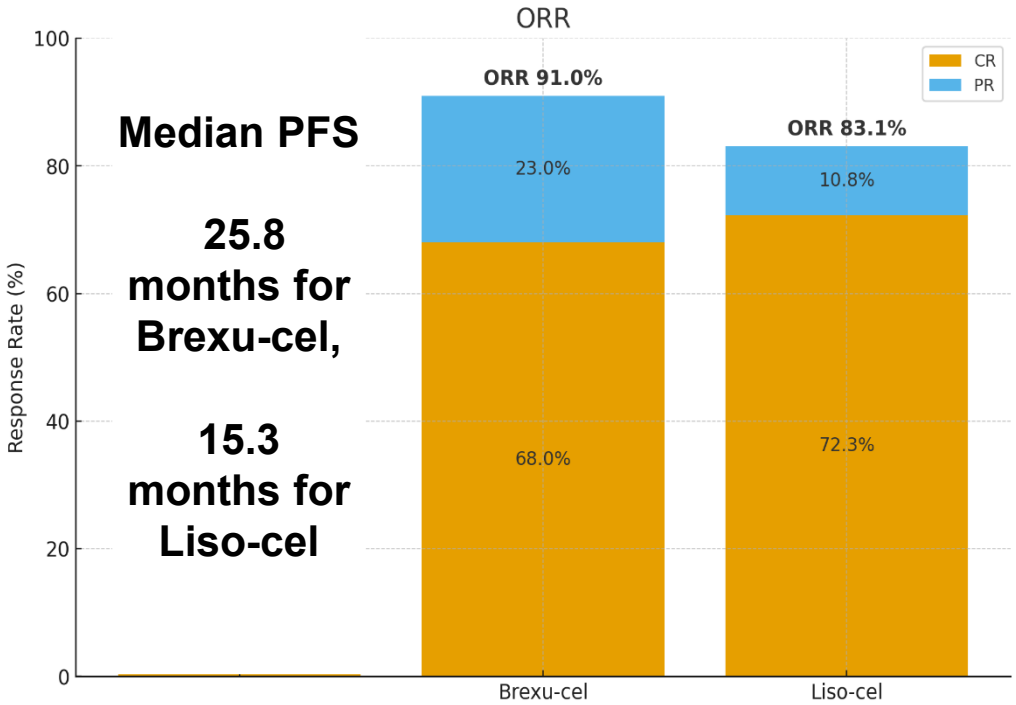
quite

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.

CAR T in R/R MCL: Efficacy with the two compounds



Wang M et al. Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study. JCO 41, 555-567(2023).
Wang M et al. Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Study. J Clin Oncol. 2024 Apr 1;42(10):1146-1157.

Glofitamab Monotherapy in R/R MCL

A Phase 1/2, open-label study of **glofitamab** in R/R MCL

3.3% were treated with prior CAR T therapy

Arm	N	Primary Endpoint
Glofitamab	60	ORR= 85% CR=78%

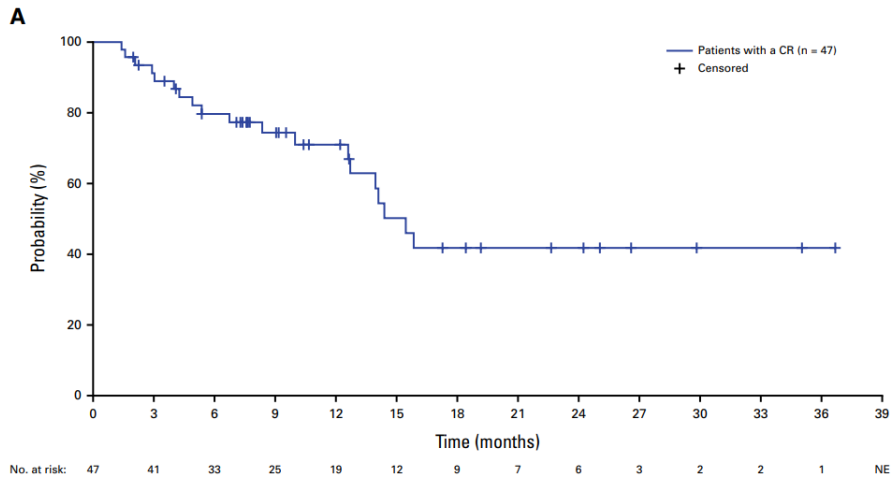
Adverse Events

Adverse Events (AE)	All patients (n = 60) n (%)
Any AE	60 (100.0)
Grade 3/4 AE	39 (65.0)
SAE	47 (78.3)
AE leading to glofitamab withdrawal	4 (6.7)
AE leading to glofitamab dose interruption	36 (60.0)
Grade 5 AE	9 (15.0)
Grade 5 AE related to glofitamab	0

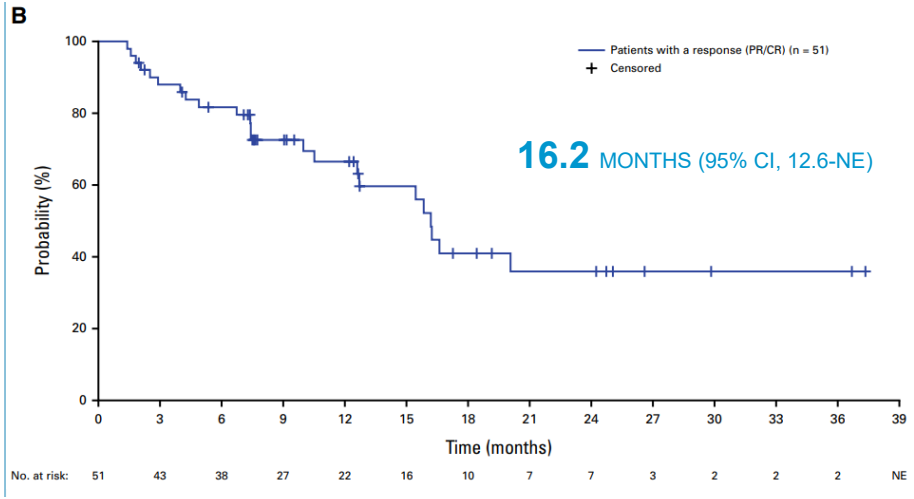
AE=Adverse Event. BTKi=BTK inhibitor. CAR T=Chimeric Antigen Receptor T-cell Therapy. CI=Confidence Intervals. DOCR=Duration of Complete Response. DOR=Duration of Response. INV=Investigator.
MCL=Mantle Cell Lymphoma. NE=Not Estimable. No.=Number. PFS=Progression-Free Suvival. R/R=Relapsed/Refractory. SAE=Serious AE.

Phillips TJ, et al. J Clin Oncol. 2025

Glofitamab Monotherapy in R/R MCL



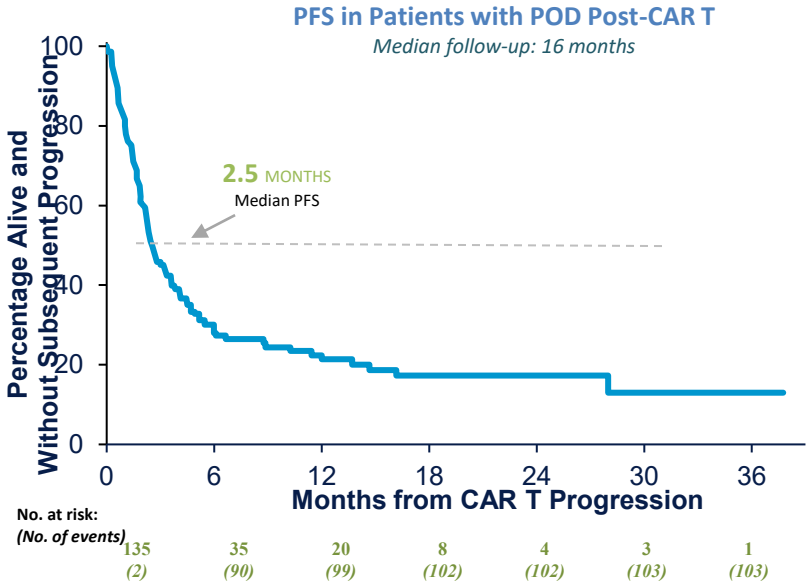
DoCR

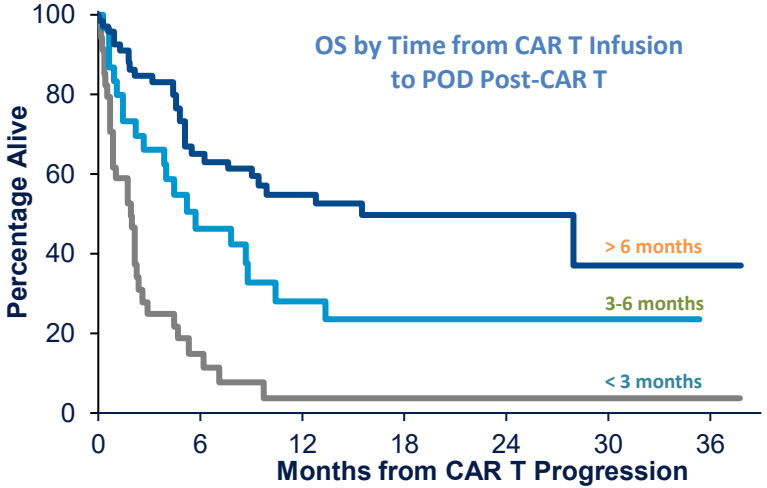


DoR

Phillips TJ et al, JCO 2025

Outcomes Post-CAR T Failure

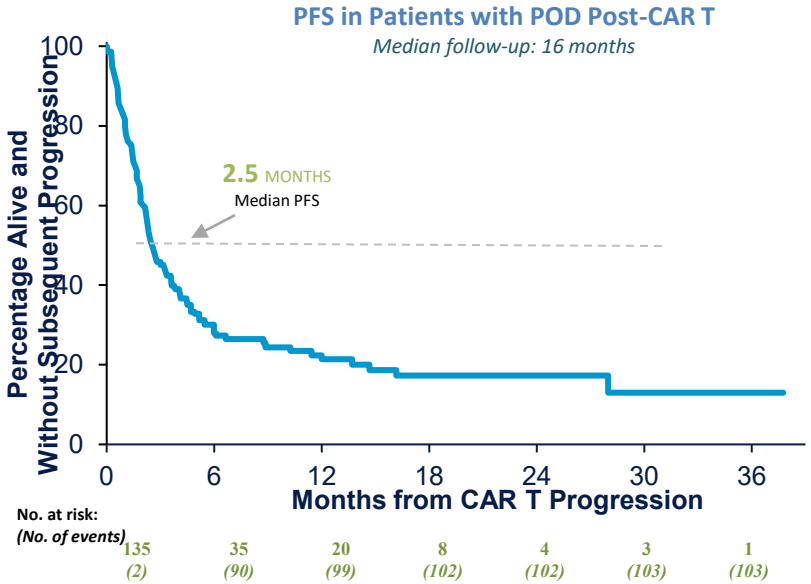


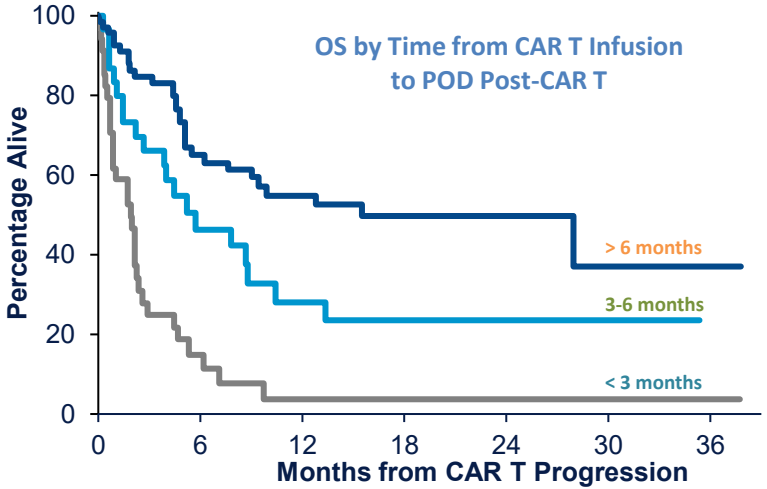


Epstein-Peterson ZD, et al. Blood Adv 2025

Outcomes Post-CAR T Failure

Clinical trials
Newer drugs/CarT





Epstein-Peterson ZD, et al. Blood Adv 2025

GOLD by FIL

FONDAZIONE ITALIANA LINFOMI

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

CaDAnCe-104, an ongoing, open-label, phase 1b/2 master protocol study of **BTK degrader** BGB-16673 in combination with other agents in patients with R/R B-cell malignancies: *Trial in Progress*

Cheah CY, et al. Poster Presentation at ASH 2025 (n 1839)

First-in-class **dual BTK-MALT1** fusion inhibitors for treating resistant Mantle Cell Lymphoma

Vivian J, et al. Oral Presentation at ASH 2025 (n 802)

Efficacy and tolerability of **mesutoclax** monotherapy in R/R MCL: High remission rates even in prior BTKi-refractory patients

Keshu Z, et al. Oral Presentation at ASH 2025 (n 887)

- Novel selective BCL2 inhibitor
- Single arm, multicenter, phase 2, across 27 centers from China
- 43 MCL enrolled, 74% refractory to previous cBTKi; ORR 87%, CRR 47%

Efficacy and safety of **rocbrutinib**, the fourth generation BTKi, in patients with BTK inhibitor pre-treated relapsed or refractory MCL: Results from a Phase II rock-1 trial

Yuqin S, et al. Oral Presentation at ASH 2025 (n 886)

- Highly selective, covalent and non-covalent inhibitor
- Single arm, multicenter, phase 2, across 27 centers from China
- Median number of prior cBTKi=1 (1-4); ORR 64%, CRR 23%;

Decentralized, 7-day vein-to-vein, fresh-to-fresh, fit cells

Potential for rapid, automated and scalable CAR-T treatment

GLP-5101

FRESH CELLS → T-CELL SELECTION & ACTIVATION → TRANSDUCTION → CULTURE → SAMPLING → HARVEST & FORMULATION → FRESH PRODUCT DIRECTLY REINFUSED

CONTINUOUS PRODUCTION & QC REVIEW → BATCH RELEASE

MANUFACTURING AT DMU

DAY -X | DAY -7 | DAY -6 TO DAY -4 PATIENT CONDITIONING | DAY 0 | DAY 28 | EVERY 3 MONTHS

Screening | Leukapheresis | CAR-T single fresh infusion | Follow-up visits

Conclusions on chemo-free approaches in R/R MCL

- 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*]
- After CarT, outcome still unsatisfactory *[++ bispecifics or clinical trials*]
- Several new drugs and combinations in development

Thanks for your attention

FONDAZIONE ITALIANA LINFOMI

UNIVERSITÀ di VERONA