GIORNATE EMATOLOGICHE VICENTINE

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Palazzo Bonin Longare - Vicenza

Linfoma mantellare: dalla definizione del rischio al trattamento

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Disclosures of Rita Tavarozzi

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie					x		
BeOne					x		
Lilly			x		x		
Roche							x

LYMPHOID NEOPLASIA | MARCH 1, 2012

Comparative outcome of initial therapy for younger patients with mantle cell lymphoma: an analysis from the NCCN NHL Database

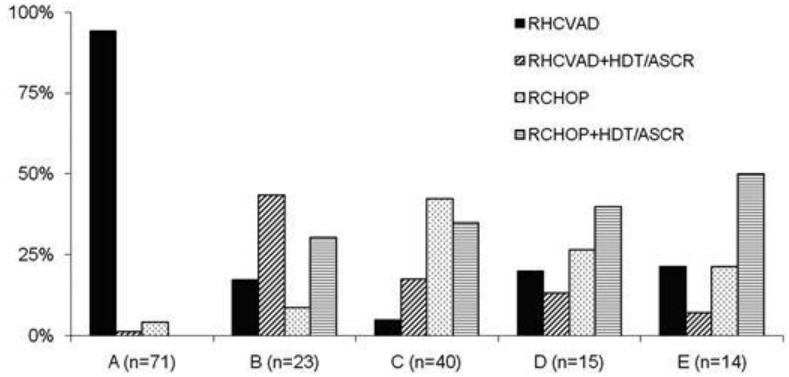
Clinical Trials & Observations

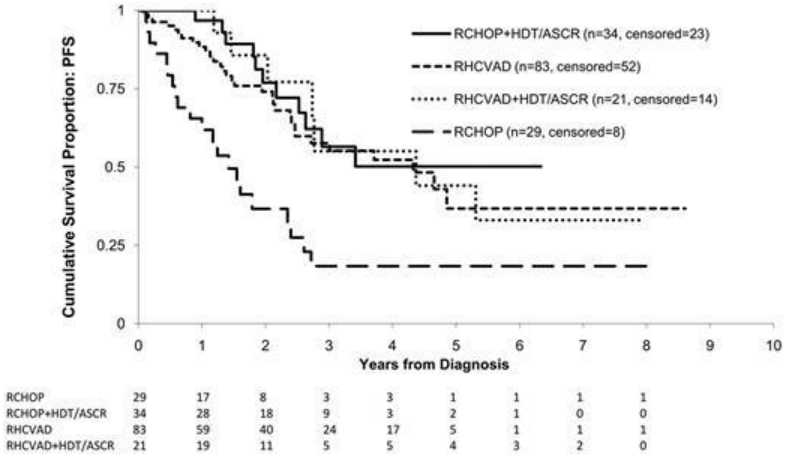
Ann S. LaCasce, Jonathan L. Vandergrift, Maria A. Rodriguez, Gregory A. Abel, Allison L. Crosby, Myron S. Czuczman, Auayporn P. Nademanee, Douglas W. Blayney, Leo I. Gordon, Michael Millenson, Ann Vanderplas, Eva M. Lepisto, Andrew D. Zelenetz, Joyce Niland, Jonathan W. Friedberg

Check for updates

Blood (2012) 119 (9): 2093–2099.

HISTORICAL COHORTS – preBTKi era





- HIGH-RISK MCL PATIENT
- HOW I TREAT MCL PATIENTS (1L)? – WHERE ARE WE NOW?
- HOW I TREAT MCL PATIENTS (R/R)?

➢ HIGH-RISK MCL PATIENT

- ➢ HOW I TREAT MCL PATIENTS (1L)? – WHERE ARE WE NOW?
- ➢ HOW I TREAT MCL PATIENTS (R/R)?

NOW.. CAN I PREDICT HIGH RISK DISEASE?

Clinical scores

POD24

Biological predictors

Minimal Residual Disease (MRD)

CONVENTIONAL SCORES

INNOVATIVE SCORES

TABLE 1. Prognostic Risk Scores of Patients With Treated Frontline Mantle Cell Lymphoma[1–3,84]

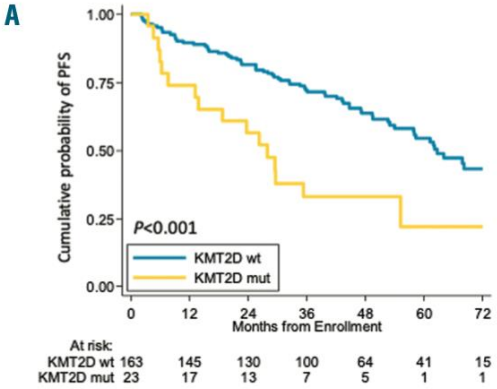
Scoring System	Components	Calculation	Risk Group	Survival
MIPI	Age, ECOG PS, LDH, WCC	0.03535 × age (years) + 0.6978 (if ECOG PS > 1) + 1.367 × $\log_{10}$ (LDH/ULN) + 0.9393 x $\log_{10}$ (WCC per 10^{-6})	LR < 5.70 IR ≥ 5.70 HR ≥ 6.20	Initial data: LR 5-year OS 60% IR median 51 months HR median 29 months Validation: 5-year OS: LR 83%, IR 63%, HR 34% (p < .001) 5-year TTF: LR 59%, IR 37%, HR 22% (p < .001)
MIPI-c	Age, ECOG PS, LDH, WCC, Ki67%	- Initial MIPI calculation as above - Ki67% (< 30% or ≥ 30%)	LR: LR MIPI + Ki67 < 30% LI: either LR MIPI + Ki67 ≥ 30% or IR MIPI + Ki67 < 30% HI: either IR MIPI + Ki67 ≥ 30% or HR MIPI + Ki67 < 30% HR: HR MIPI and Ki67 ≥ 30%	5-year OS: LR 85%, LI 72%, HI 43%, and HR 17% (p < .001)
MIPI-b	Age, ECOG PS, LDH, WCC, Ki67%	CBS: 0.03535 × age (years) + 0.6978 (if ECOG > 1) + 1.367 × $\log_{10}$(LDH/ULN) + 0.9393 x $\log_{10}$(WCC) + 0.02142 × Ki67%.	LR: CBS < 5.7 IR: CBS 5.7–6.5 HR: CBS ≥ 6.5	Median OS: LR not reached IR 58 months HR 37 months
s-MIPI	Age, ECOG PS, LDH, WCC	- Age: 1 point for 50–59, 2 for 60–69, 3 for ≥ 70 years - ECOG: 2 points for ECOG 2–4 - LDH/ULN ratio: 1 point for 0.67–0.99, 2 points for 1.0–1.49, 3 points for ≥ 1.50 - WCC 10^9/L: 1 point 6.7–9.99, 2 points 1.00–14.99, 3 points ≥ 15.0	LR: 0–3 IR: 4–5 HR: 6–11	5-year OS: HR 38%

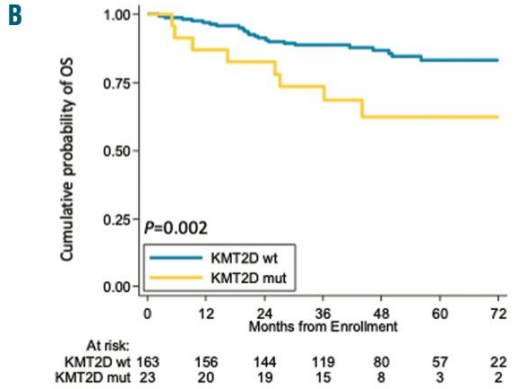
Abbreviations: CBS, combined biologic score; ECOG PS, ECOG Performance Status; HI, high intermediate; HR, high risk; IR, intermediate risk; LDH, lactate dehydrogenase; LI, low intermediate; LR, low risk; MIPI, Mantle Cell Lymphoma International Prognostic Index; MIPI-c, combined MIPI; MIPI-b, biologic MIPI; s-MIPI, simplified MIPI; OS, overall survival; TTF, time-to-treatment failure; ULN, upper limit of normal; WCC, white cell count.

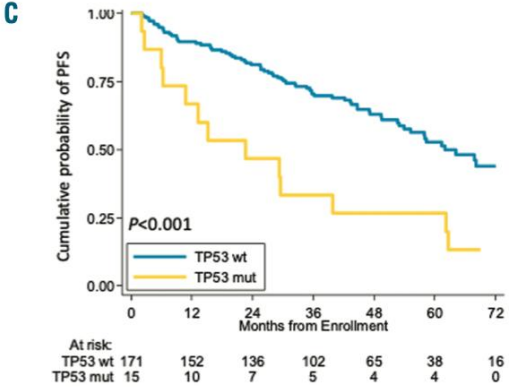
Kumar et al. *American Society of Clinical Oncology Educational Book* 42 (May 13, 2022) 614-628.

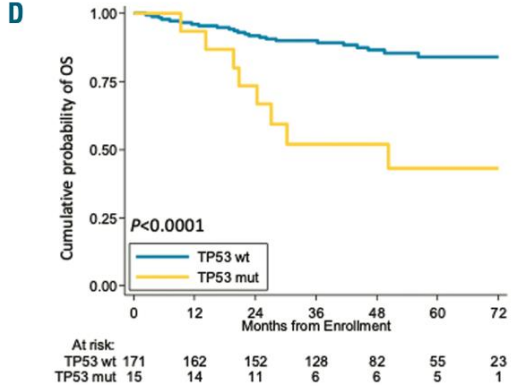
KMT2D mutations and *TP53* disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study

Simone Ferrero,[1,2*] Davide Rossi,[3,4*] Andrea Rinaldi,[4*] Alessio Bruscaggin,[4] Valeria Spina,[4] Christian W. Eskelund,[5,6] Andrea Evangelista,[7] Riccardo Moia Ivo Kwee,[4,9,10] Christina Dahl,[11] Alice Di Rocco,[12] Vittorio Stefoni,[13] Fary Diop, Chiara Favini,[8] Paola Ghione,[1] Abdurraouf Mokhtar Mahmoud,[8] Mattia Schipani,[8] Arne Kolstad,[14] Daniela Barbero,[1] Domenico Novero,[15] Marco Paulli,[16] Alberto Zamò,[17,18] Mats Jerkeman,[19] Maria Gomes da Silva,[20] Armando Santoro,[21] Annalia Molinari,[22] Andres Ferreri,[23] Kirsten Grønbæk,[5] Andrea Piccin,[24] Sergio Cortelazzo,[25] Francesco Bertoni,[4#] Marco Ladetto[26#] and Gianluca Gaidano[8#]









Ferrero S, et al. *KMT2D* mutations and *TP53* disruptions are poor prognostic biomarkers in mantle cell lymphoma receiving high-dose therapy: a FIL study. Haematologica. 2020 Jun;105(6):1604-1612.

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY
British Society for Haematology

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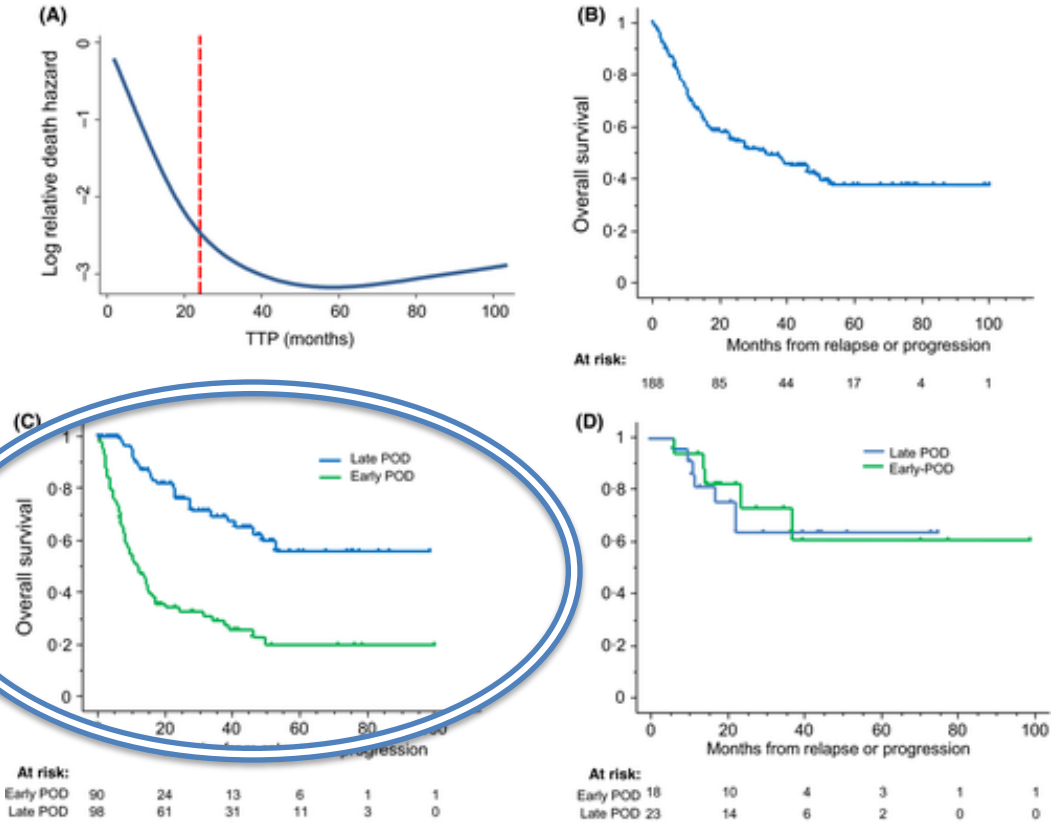
Time to progression of mantle cell lymphoma after high-dose cytarabine-based regimens defines patients risk for death

Carlo Visco, Maria C. Tisi, Andrea Evangelista, Alice Di Rocco ... See all authors

First published: 08 November 2018 | https://doi.org/10.1111/bjh.15643 | Citations: 33

POD24



IS THE PROGNOSTIC VALUE OF MRD DETECTION IN MCL STILL AN ISSUE?

POSITIVE STUDIES

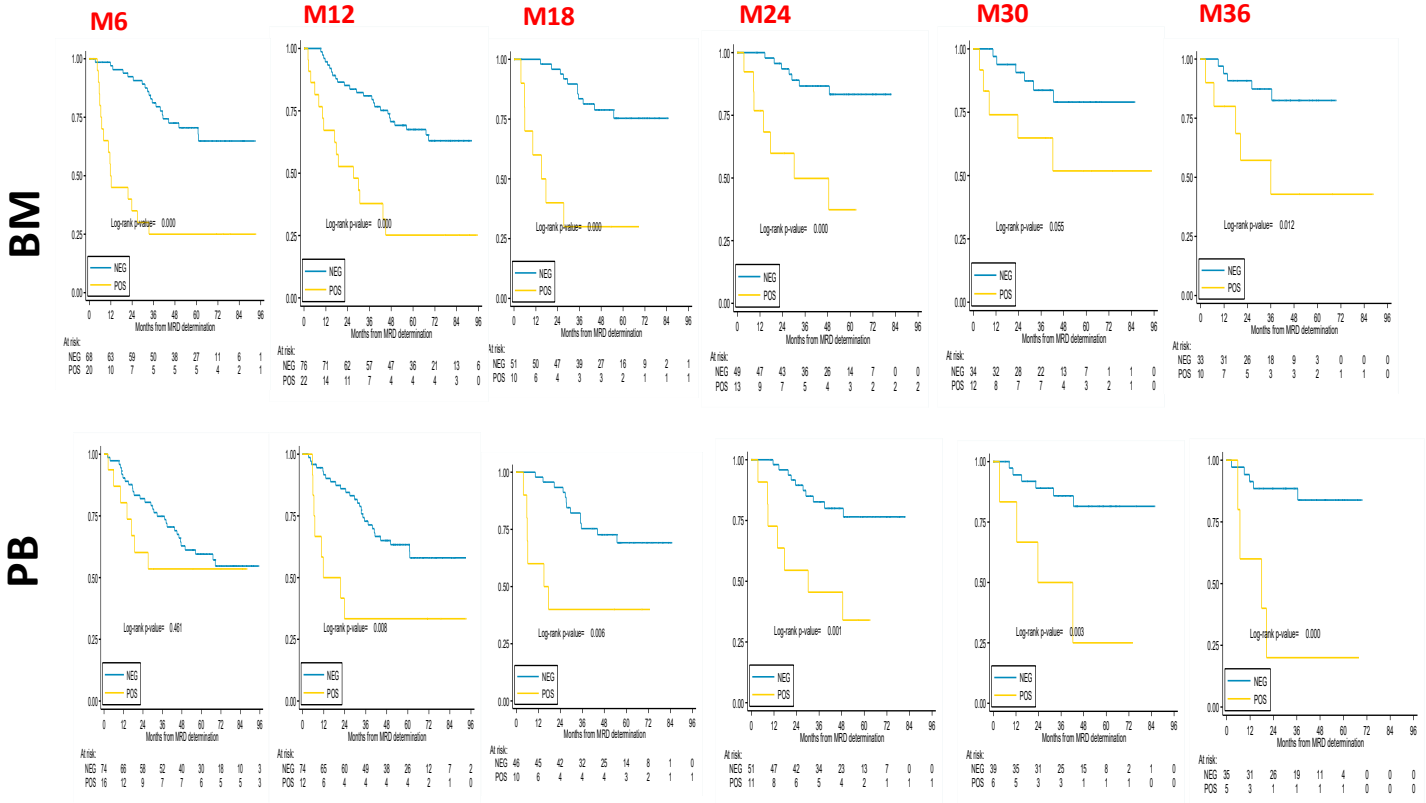
Corradini P et al. Blood 1997
Andersen N et al. Blood 1997
Howard OM et al J Clin Oncol 2002
Corradini P et al. Blood 2002
Corradini P et al. J Clin Oncol 2004
Pott C et al. Blood 2006
Geisler CH et al. Blood 2008
Andersen N et al J Clin Oncol 2009
Pott C et al. Blood 2010
Pott C et al ASH 2014
Callanan M et al ASH 2015
Visco et al ICML 2015
Smith et al ASH 2019
Kaplan et al. AJH 2020
Torka P et al Blood 2019
Cowan AJ et al. Biol BM Transpl 2016
Ferrero et al. Blood 2022

NEGATIVE STUDIES

Howard O et al. J Clin Oncol 2002
Klener P et al. Hematological Oncology 2018

MRD IMPACT ON TTP, MEASURED BY RQ-PCR

FONDAZIONE ITALIANA LINFOMI



TAVARozzi R ET AL, HEMASPHERE, 2025

FONDAZIONE ITALIANA LINFOMI

OS ANALYSIS ACCORDING TO CUMULATIVE NEGATIVITY RESULTS

	BM			PB		
TTP	**HR**	**95%CI**	**p**	**HR**	**95%CI**	**p**
Positive (ref)	1	-	-	1	-	-
1 cumulative negativity	1.13	0.51,2.50	0.766	0.74	0.31,1.76	0.493
2 cumulative negativities	0.47	0.17,1.25	0.129	0.96	0.45,2.02	0.909
3 or more negativities	0.35	0.16,0.73	0.005	0.42	0.19,0.90	**0.025**

BM, PB
RQ-PCR

Tavarozzi R et al, HemaSphere, 2025

- HIGH-RISK MCL PATIENT
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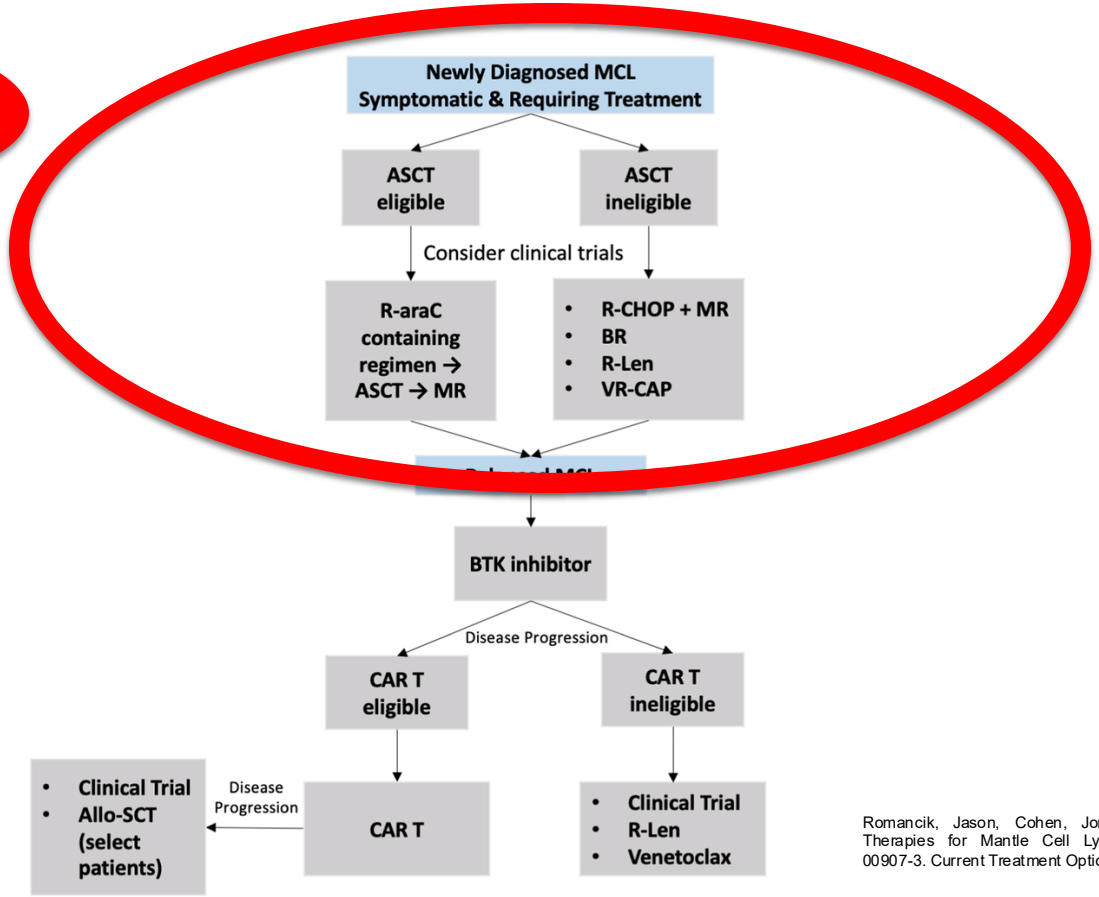
PRE-TRIANGLE ERA



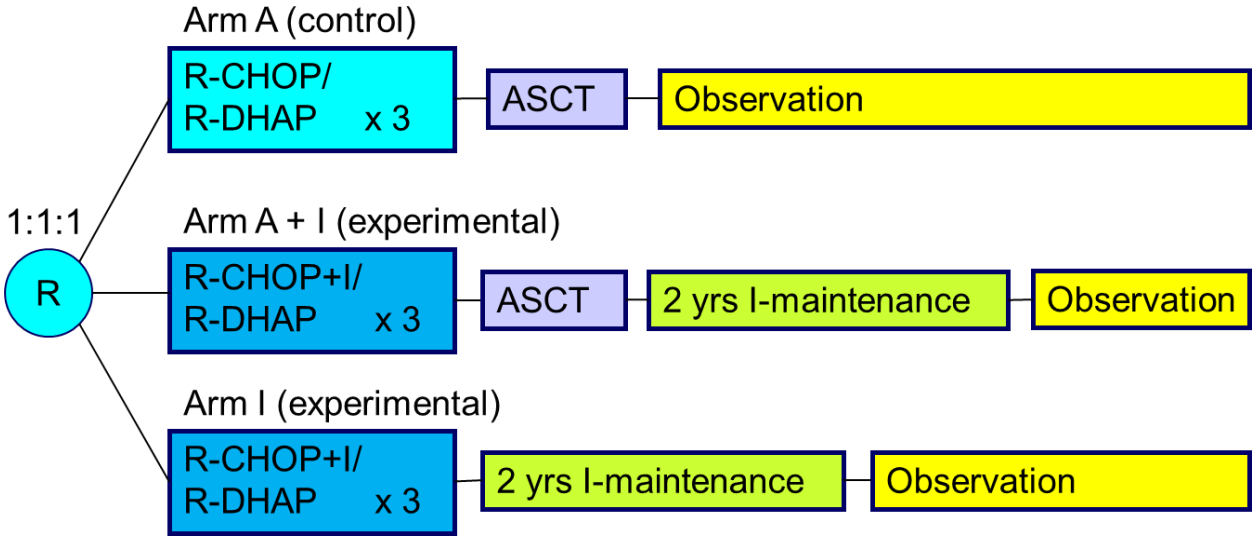
Romancik, Jason, Cohen, Jonathon, Sequencing of Novel Therapies for Mantle Cell Lymphoma- 10.1007/s11864-021-00907-3. Current Treatment Options in Oncology

TRIANGLE: Trial Design

MCL patients

- **previously untreated**
- **stage II-IV**
- **younger than 66 years**
- **suitable for HD-AraC and ASCT**
- **ECOG 0-2**

- **Primary outcome: FFS**
- **Secondary outcomes:**
  - **Response rates**
  - **PFS, RD**
  - **OS**
  - **Safety**



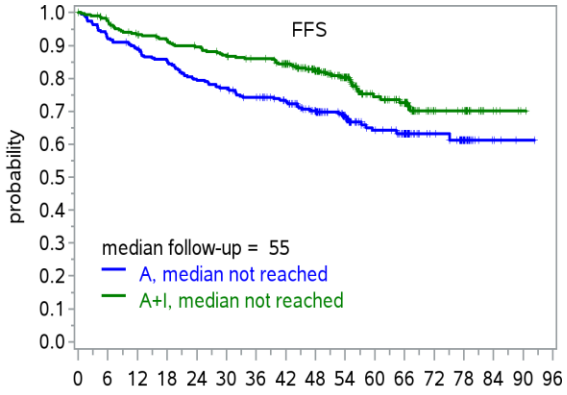
R maintenance was added following national guidelines in all 3 trial arms

Dreyling M, et al. Lancet. 2024 May 25;403(10441):2293-2306.

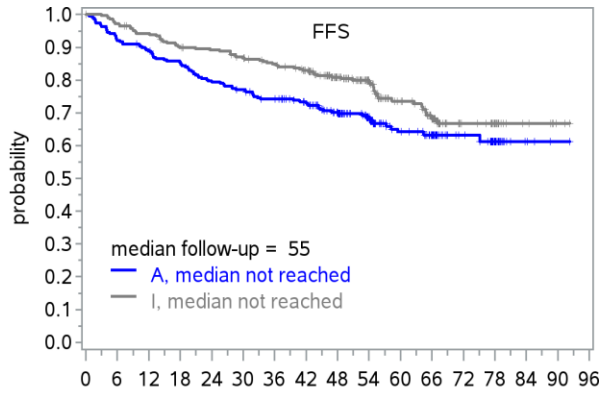
RANDOMIZED POPULATION

FFS FROM RANDOMIZATION (ITT ANALYSIS)

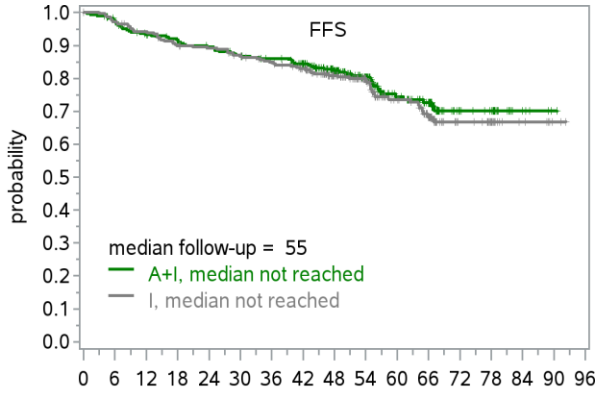
FFS Superiority of A+I vs. A



FFS Superiority of A vs. I



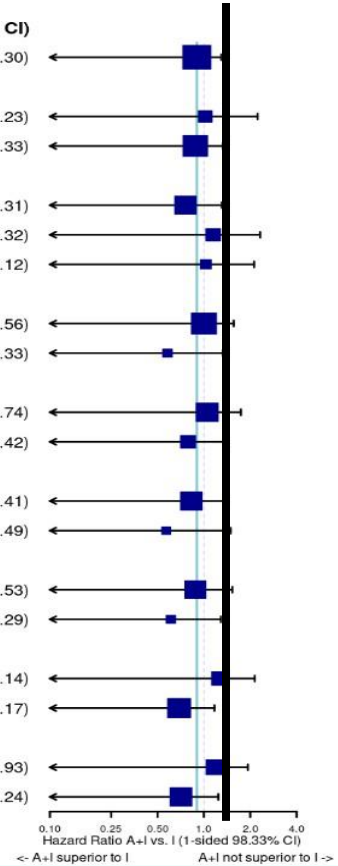
FFS Superiority of A+I vs. I



Dreyling M, et al. ASH 2024

TRIANGLE: No FFS Superiority of A+I vs. I

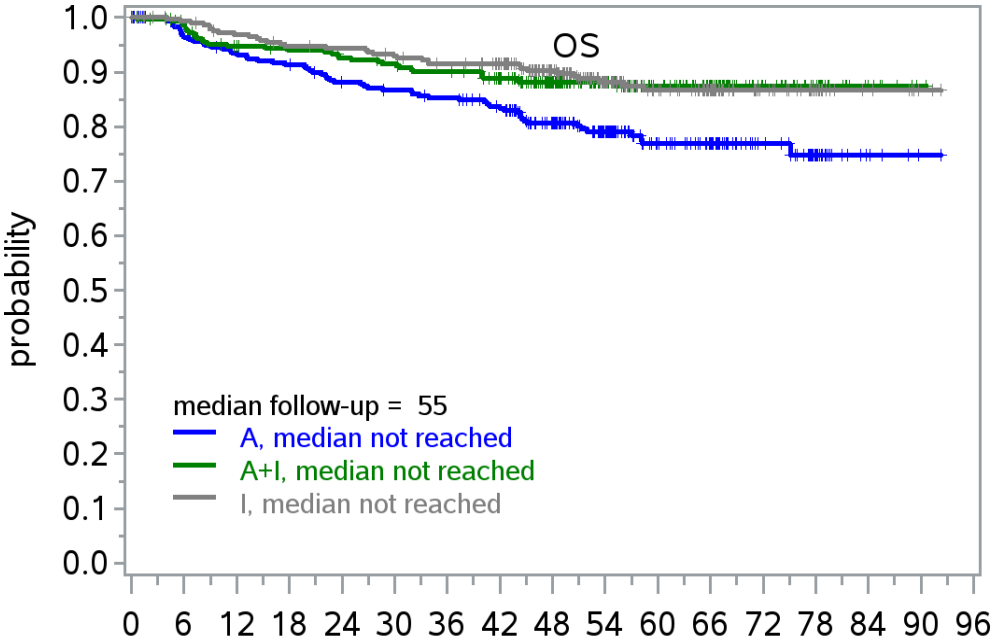
Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	582	134	0.90 (0 - 1.30)
Sex (p=0.71)			
Female	138	30	1.02 (0 - 2.23)
Male	444	104	0.88 (0 - 1.33)
MIPI			
Low	336	62	0.76 (0 - 1.31)
Intermediate (p=0.33)	157	37	1.15 (0 - 2.32)
High (p=0.56)	89	35	1.03 (0 - 2.12)
Cytology (p=0.15)			
Non-blastoid	461	92	1.00 (0 - 1.56)
Blastoid	65	27	0.58 (0 - 1.33)
Ki-67 (p=0.41)			
Low	357	71	1.05 (0 - 1.74)
High	164	54	0.79 (0 - 1.42)
P53 expression (p=0.43)			
Low	342	67	0.83 (0 - 1.41)
High	59	21	0.57 (0 - 1.49)
High risk biology (p=0.33)			
Low	323	60	0.88 (0 - 1.53)
High	64	34	0.61 (0 - 1.29)
R maintenance ITT (p=0.081)			
No	196	66	1.27 (0 - 2.14)
Yes	386	68	0.69 (0 - 1.17)
R maintenance mAT (p=0.14)			
No	228	76	1.18 (0 - 1.93)
Yes	354	58	0.71 (0 - 1.24)



- trend towards superiority of A+I over I in patients in high risk patients:
  - Ki-67 >30%
  - blastoid cytology or
  - high p53 expression

Dreyling M, et al. ASH 2024

TRIANGLE: Overall survival



Numbers At Risk

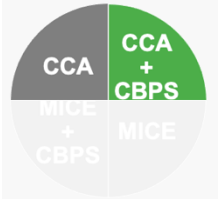
A	288	270	260	255	243	238	233	222	186	145	92	73	41	23	5	1
A+I	292	281	267	262	257	253	248	235	201	160	107	83	39	26	8	2
I	290	282	273	266	264	259	253	243	194	147	101	78	41	21	7	2

- 4-year OS:
  - A: 81%
    (MCL Younger exp.: 80%)
  - A+I: 88%
  - I: 90%

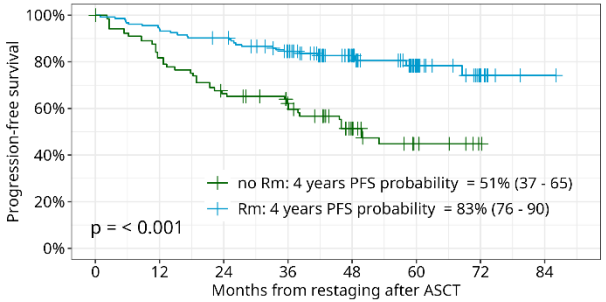
- two-sided test, (□ = 5%):
  - A vs. I: p=0.0019, HR: 0.565
  - A vs. A+I: p=0.0036, HR I: 0.587
  - A+I vs. I: ongoing

Dreyling M, et al. ASH 2024

WHAT DO WE KNOW ABOUT RITUXIMAB MAINTENANCE (Rm) IMPACT ON SURVIVAL?

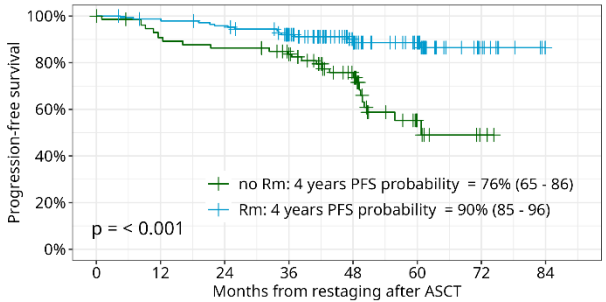


Arm A: PFS



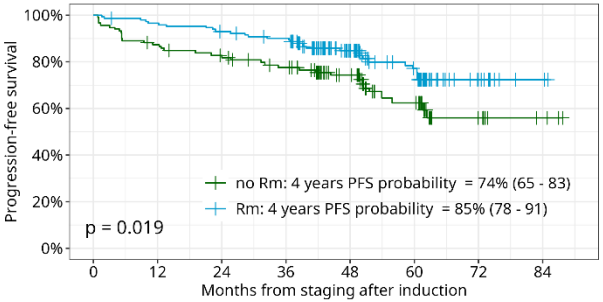
noRm group								
At risk	76.5	66.8	52.2	41	23.8	12.9	2.6	0
Event	0	8.5	21.9	26.2	31.8	33.4	33.4	33.4
Rm group								
At risk	156.8	145.9	140	122.7	86	49.5	16.1	1.7
Event	0	10.9	15.8	24.6	26.9	28.5	30	30

Arm A+I: PFS



noRm group								
At risk	85.3	75.1	71.6	63.8	41	12.9	6	0
Event	0	8.1	11.5	13.5	19.5	28.7	29.7	29.7
Rm group								
At risk	151.8	146.9	142.1	125.8	85.7	63	24.5	0
Event	0	3.1	6.9	12.8	14.6	15.5	16.6	16.6

Arm I: PFS



noRm group								
At risk	116.7	100.7	92.5	82.6	59.8	38.2	19.3	6
Event	0	14.1	20.2	26.2	29.2	35.8	37.7	37.7
Rm group								
At risk	157.2	148.3	141.5	135.3	87.3	57.9	23	3.9
Event	0	7	12.8	16.9	22.8	28.7	30.6	30.6

- Rm does not significantly extend OS

Blood (2024) 144 (Supplement 1): 237.

MCL Treatment: The Horizon for MCL

Trials of relevance for an elderly population

- **SHINE trial: BR + ibrutinib until PD**
- **ECHO: BR + acalabrutinib until PD**
- **ENRICH: Ibrutinib-R vs. BR/R-CHOP**
- **VR-BAC: venetoclax consolidation after R-BAC**

PUBLISHED RESULTS

- MANGROVE: Zanubrutinib-R vs. BR

PENDING RESULTS

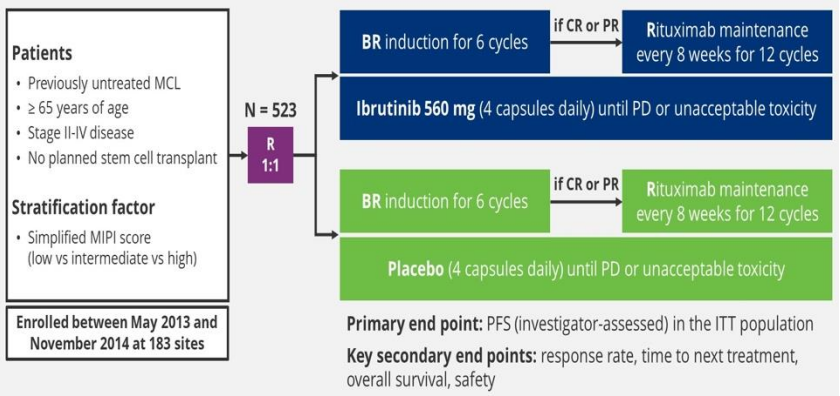
- VIRAL: VR+ibrutinib vs V+R-benda+ibrutinib

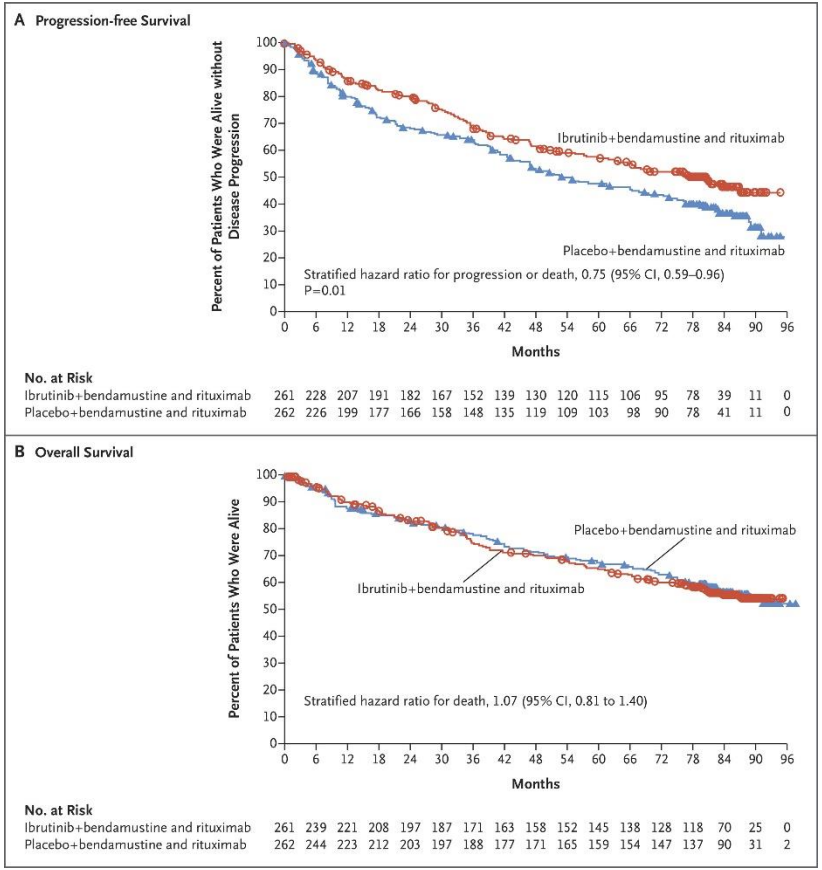
ONGOING TRIAL

ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

Michael L. Wang, M.D., Wojciech Jurczak, M.D., Ph.D., Mats Jerkeman, M.D., Ph.D., Judith Trotman, F.R.A.C.P., Pier L. Zinzani, M.D., Ph.D., David Belada, M.D., Ph.D., Carola Boccomini, M.D., Ian W. Flinn, M.D., Ph.D., Pratyush Giri, F.R.A.C.P., Andre Goy, M.D., Paul A. Hamlin, M.D., Olivier Hermine, M.D., Ph.D., et al., for the SHINE Investigators*



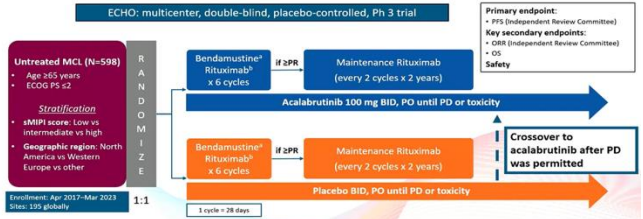


Acalabrutinib Plus Bendamustine-Rituximab in Untreated Mantle Cell Lymphoma

Authors: Michael Wang, MD, David Salek, MD, David Belada, MD, Yuqin Song, MD, Wojciech Jurczak, MD, PhD, Brad S. Kahl, MD, Jonas Paludo, MD, ... SHOW ALL ... for the ECHO investigators | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Just Accepted • https://doi.org/10.1200/JCO-25-00690

Study Design



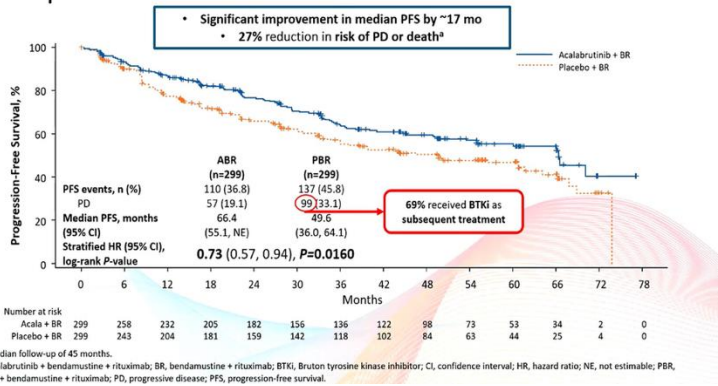
[a]Bendamustine 90 mg/m² on days 1 and 2. [b]Rituximab 375 mg/m² on day 1.
BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; MCL, mantle cell lymphoma; sMIPI, simplified Mantle Cell Lymphoma International Prognostic Index; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, orally; PR, partial response.

Demographics and Baseline Characteristics

	Acalabrutinib + BR (n=299)	Placebo + BR (n=299)
Age, median (range), y	71 (65–85)	71 (65–86)
≥75 y, n (%)	84 (28.1)	77 (25.8)
Male, n (%)	214 (71.6)	209 (69.9)
ECOG PS, n (%)		
1	129 (43.1)	132 (44.1)
2	12 (4.0)	23 (7.7)
Tumor bulk ≥5 cm, n (%)	112 (37.5)	113 (37.8)
Blastoid/pleomorphic histology, n (%)	41 (13.7)	38 (12.7)
Simplified MIPI score, n (%)		
Low risk	99 (33.1)	101 (33.8)
Intermediate risk	128 (42.8)	125 (41.8)
High risk	72 (24.1)	73 (24.4)
Extranodal disease, n (%)	264 (88.3)	277 (92.6)
TP53 status, n (%)[a]		
Mutated	22 (7.4)	29 (9.7)
Unmutated	97 (32.4)	83 (27.8)
Ki-67, n (%)		
<30%	133 (44.5)	126 (42.1)
≥30%	139 (46.5)	147 (49.2)

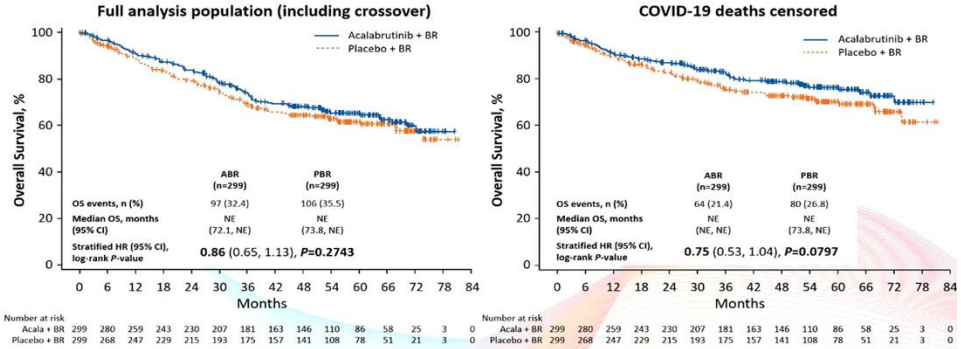
[a]All other patients in the acalabrutinib (n=180) and placebo (n=187) groups had unknown *TP53* mutation status.
BR, bendamustine + rituximab; ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, Mantle Cell Lymphoma International Prognostic Index.

PFS (primary endpoint) Was Significantly Improved With Acalabrutinib + BR



[a]At a median follow-up of 45 months.
ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; NE, not estimable; PBR, placebo + bendamustine + rituximab; PD, progressive disease; PFS, progression-free survival.

OS With and Without COVID-19 Deaths: Prespecified Sensitivity Analysis

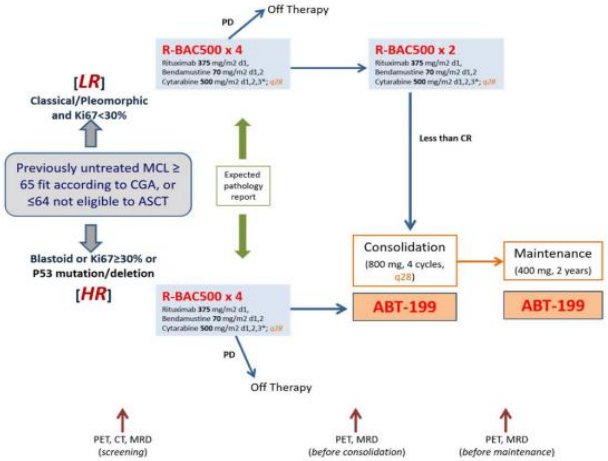


ABR, acalabrutinib + bendamustine + rituximab; CI, confidence interval; COVID-19, coronavirus disease 2019; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo + bendamustine + rituximab.

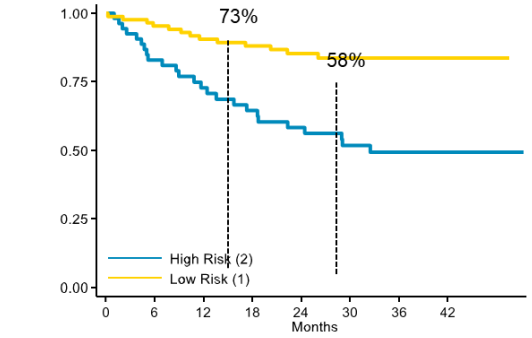
HIGH-RISK PERSPECTIVES

PRESENTE.PASSATO,FUTURO
di Ruxi Dalmazio

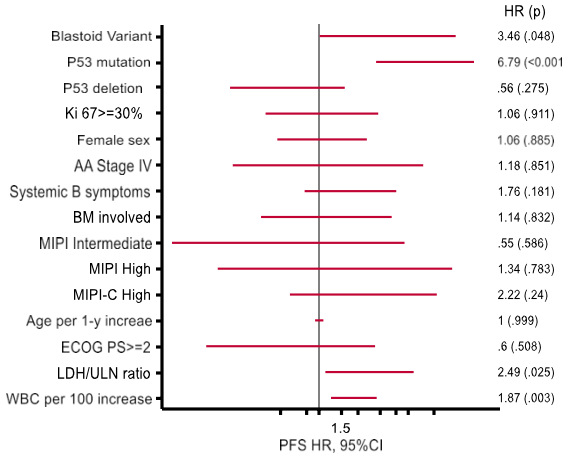
V-RBAC



		Low Risk	High Risk	p-value
N		**86 (61%)**	**54 (39%)**	
Sex	Male	67 (78%)	40 (74%)	0.60
Age, median (IQR)		72 (69, 74)	73 (69, 76)	0.12
Systemic B symptoms	Present	16 (19%)	10 (19%)	0.98
Ann Arbor Stage	III-IV	82 (96%)	50 (94%)	0.53
ECOG Performance Status	0-1	83 (98%)	50 (92%)	0.35
	2	3 (3%)	4 (8%)	
Bone marrow involvement	Positive	60 (71%)	40 (74%)	0.51
LDH abnormal	Yes	18 (22%)	24 (46%)	0.003
MIPI score	Low (0-3)	9 (10.8%)	1 (1.9%)	0.017
	Intemediate (4-5)	43 (51.8%)	20 (38.5%)	
	High (6-11)	31 (37.3%)	31 (59.6%)	
SUV max of lesion	Median (IQR)	8.8 (6.9, 12.2)	10.9 (8.8, 15.6)	0.051



Time	Survivor Function	Std. Error	[95% Conf.	Int.]
Low Risk (1)				
12	0.9046	0.0321	0.8182	0.9511
24	0.8519	0.0396	0.7534	0.9133
High Risk (2)				
12	0.7274	0.0624	0.5830	0.8288
24	0.5819	0.0701	0.4329	0.7046



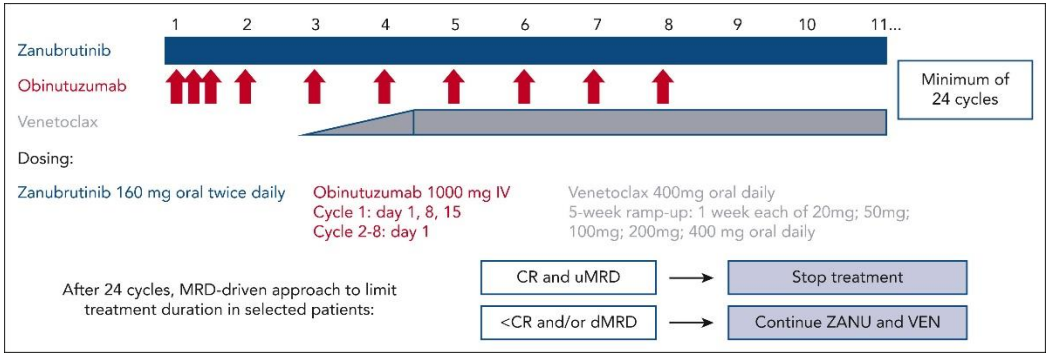
Carlo Visco, et al. Rituximab, Bendamustine and Cytarabine Followed By Venetodax (V-RBAC) in High-Risk Older Patients with Mantle Cell Lymphoma: A Phase 2 Study By the Fondazione Italiana Linfomi (FIL). *Blood (2023) 142 (Supplement 1): 737.*

CLINICAL TRIALS AND OBSERVATIONS | JANUARY 30, 2025

Zanubrutinib, obinutuzumab, and venetoclax for first-line treatment of mantle cell lymphoma with a *TP53* mutation

Clinical Trials & Observations

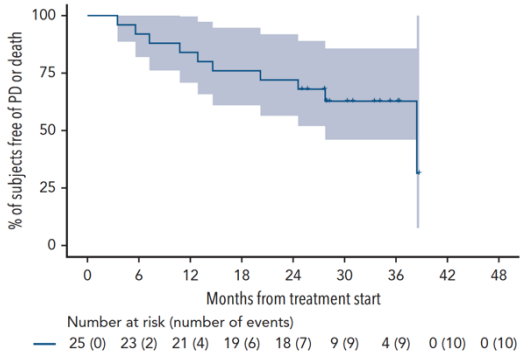
Anita Kumar, Jacob Soumerai, Jeremy S. Abramson, Jeffrey A. Barnes, Philip Caron, Shalini Chhabra, Maria Chabowska, Ahmet Dogan, Lorenzo Falchi, Clare Grieve, J. Erika Haydu, Patrick Connor Johnson, Ashlee Joseph, Hailey E. Kelly, Alyssa Labarre, Jennifer Kimberly Lue, Rosalba Martignetti, Joanna Mi, Alison Moskowitz, Colette Owens, Sean Plummer, Madeline Puccio, Gilles Salles, Venkatraman Seshan, Elizabeth Simkins, Natalie Slupe, Honglei Zhang, Andrew D. Zelenetz

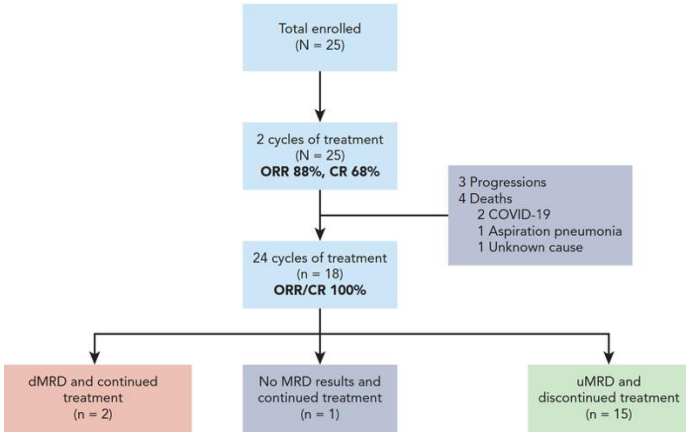


- Median age was 68 (29-82) years
- 2-year progression-free 72%
- 2-year overall survival 76%

- Common Aes low grade and included diarrhea (64%), neutropenia (32%), and infusion-related reactions (24%).

Median follow-up of 28.2 months





Clinical Protocol
CARMAN

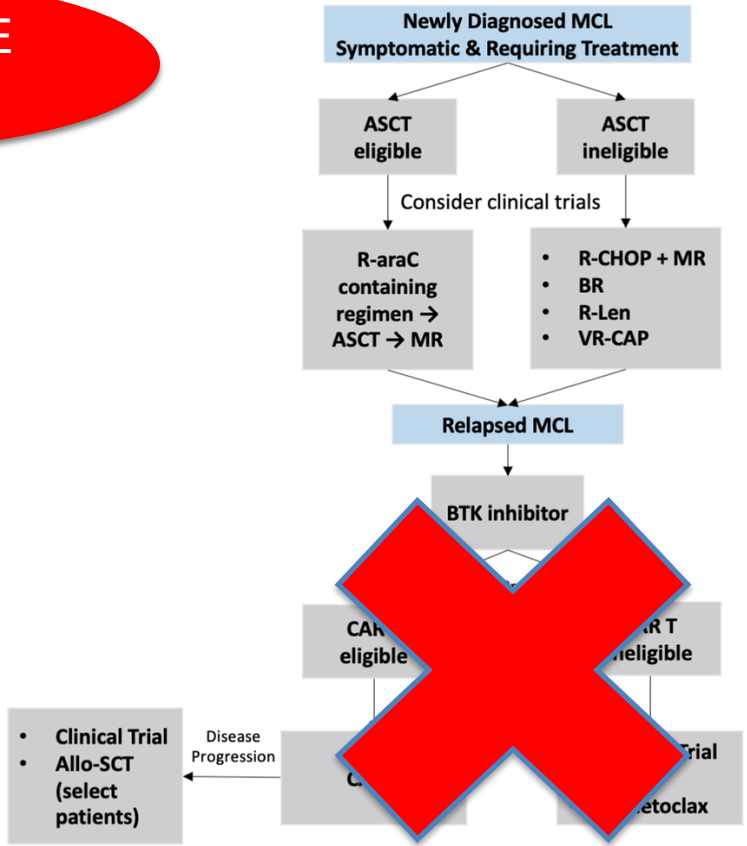
Early treatment intensification in patients with high-risk Mantle Cell Lymphoma using CAR-T-cell treatment after an abbreviated induction therapy with Rituximab and Ibrutinib and 6 months Ibrutinib maintenance (Arm A) as compared to standard of care induction and maintenance (Arm B)

Trial Short Title:	**CAR**-T-cell treatment for untreated high risk **MAN**tle Cell Lymphoma
Sponsor Code:	**CARMAN**
EudraCT No.:	2021-004426-30
Protocol Version and Date:	Version 2.0_Mar2022
Protocol Amendment:	
Sponsor:	LMU Klinikum München, Germany

- HIGH-RISK MCL PATIENT
- HOW I TREAT MCL PATIENTS (1L)? – WHERE ARE WE NOW?

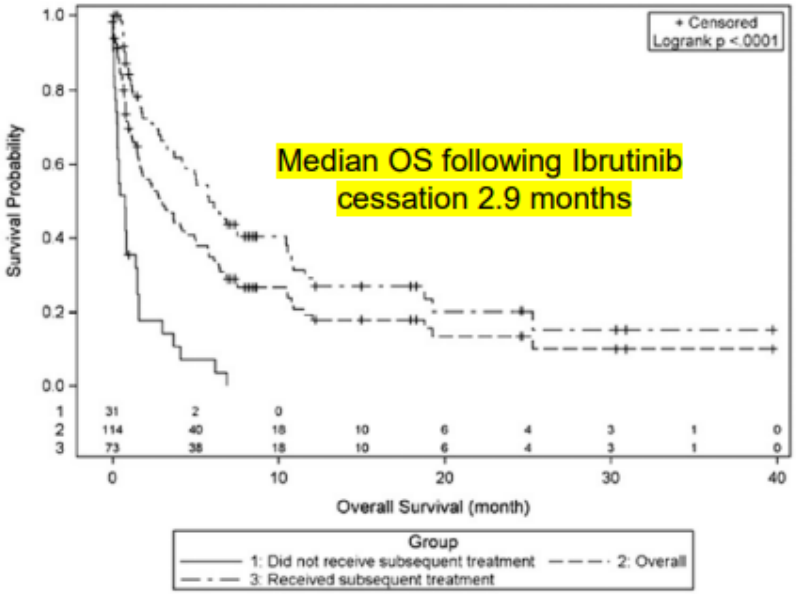
➢ HOW I TREAT MCL PATIENTS (R/R)?

PRE-TRIANGLE ERA



Romancik, Jason, Cohen, Jonathon, Sequencing of Novel Therapies for Mantle Cell Lymphoma- 10.1007/s11864-021-00907-3. Current Treatment Options in Oncology

Poor outcome after BTKi failure



Characteristics	Number	Range, %, or 95% CI
All	114	
Median Age	68 y	46-85
Median prior systemic therapies	3	0-10

Response rates 29-32%

Few patients surviving beyond one year

Comment on Martin et al, page 1559

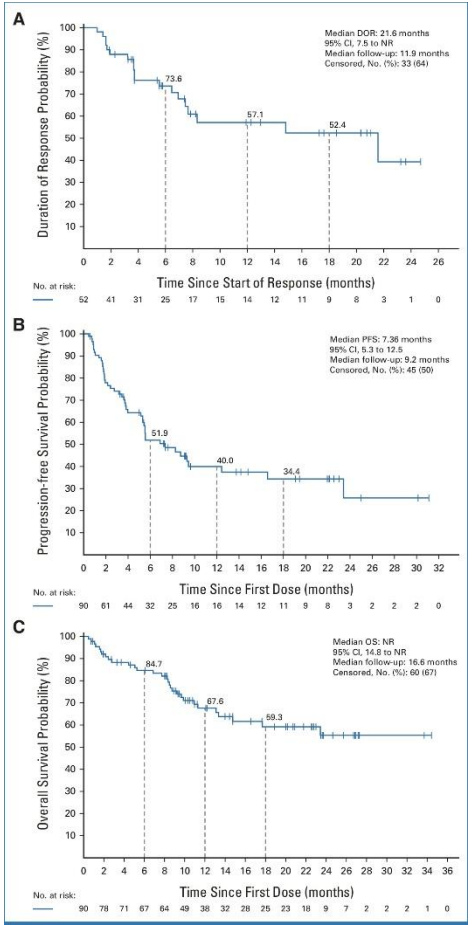
Ibrutinib: a force with a dark side?

Martin P et al, Blood 2016
Smith MR, Blood 2016
Wang M et al, ASH 2017

TABLE 2. Efficacy of Pirtobrutinib in Patients With cBTKi Pre-treat and cBTKi-Naïve MCL

Response	cBTKi Pretreated MCL (n = 90)	cBTKi-Naïve MCL (n = 14)
Overall response rate, % (95% CI)	57.8 (46.9 to 68.1)	85.7 (57.2 to 98
Best overall response, No. (%)		
Complete response	18 (20.0)	5 (35.7)
Partial response	34 (37.8)	7 (50)
Stable disease	14 (15.6)	0
Progressive disease	15 (16.7)	1 (7.1)
Not evaluable[a]	9 (10.0)	1 (7.1)
DOR		
Patients with a response, No.	52	12
Patients with censored data, No. (%)	33 (63.5)	12 (100)
DOR, months, median (95% CI)	21.6 (7.5 to NR)	NR (NR to NR)
Median follow-up, months	11.9	7.1
PFS		
Patients with censored data, No. (%)	45 (50.0)	13 (92.9)
PFS, months, median (95% CI)	7.4 (5.3 to 12.5)	NR (NR to NR)
Median follow-up, months	9.2	8.6
OS		
Patients with censored data, No. (%)	60 (66.7)	13 (92.9)
OS, months, median (95% CI)	NR (14.8 to NR)	NR (NR to NR)
Median follow-up, months	16.6	9.4

NOTE. Overall response and best response were determined accord to the 2014 Lugano criteria[20] and on the basis of independent revi committee assessment.
Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; DC duration of response; MCL, mantle-cell lymphoma; NR, not reached; overall survival; PFS, progression-free survival.
[a]Patients without postbaseline disease assessment were not



OPEN ACCESS | RAPID COMMUNICATIONS | May 16, 2023

Pirtobrutinib in Covalent Bruton Tyrosine Kinase Inhibitor Pretreated Mantle-Cell Lymphoma

Authors: Michael L. Wang, MD, Wojciech Jurczak, MD, PhD, Pier Luigi Zinzani, MD, PhD, Toby A. Eyre, MD, MBChB, DipMedEd, MRCP, FRCPath, Chan Y. Cheah, MD, Chaitra S. Ujjani, MD, Youngil Koh, MD, ... SHOW ALL ... , and Nirav N. Shah, MD | AUTHORS INFO & AFFILIATIONS

Publication: Journal of Clinical Oncology • Volume 41, Number 24 • https://doi.org/10.1200/JCO.23.00562

TABLE 3. Adverse Events in At Least 10% of All Patients With MCL

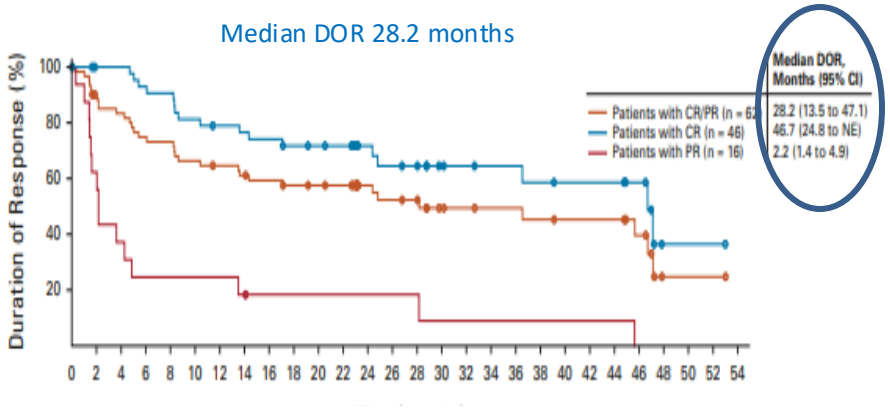
	MCL Safety Population (n = 164)			
	TEAE, (≥10%), No. (%)		TRAE, No. (%)	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade
Fatigue	49 (29.9)	4 (2.4)	34 (20.7)	4 (2.4
Diarrhea	35 (21.3)	0	20 (12.2)	0
Dyspnea	27 (16.5)	3 (1.8)	15 (9.1)	1 (0.6
Contusion	24 (14.6)	0	16 (9.8)	0
Anemia	21 (12.8)	8 (4.9)	10 (6.1)	4 (2.4
Back pain	21 (12.8)	2 (1.2)	2 (1.2)	0
Cough	20 (12.2)	0	10 (6.1)	0
Pyrexia	19 (11.6)	0	6 (3.7)	0
Constipation	18 (11.0)	0	3 (1.8)	0
Nausea	18 (11.0)	0	7 (4.3)	0
Pneumonia	17 (10.4)	14 (8.5)	5 (3.0)	4 (2.4
Myalgia	17 (10.4)	0	14 (8.5)	0
Adverse event of special interest[a]				
Infections	59 (36.0)	28 (17.1)	24 (14.0)	5 (3.0
Bleeding	45 (27.4)	6 (3.7)	26 (15.9)	1 (0.6
Thrombocytopenia	24 (14.6)	11 (6.7)	2 (1.2)	0
Neutropenia[b]	23 (14.0)	22 (13.4)	15 (9.1)	14 (8.5
Bruising[c]	27 (16.5)	0	19 (11.6)	0 (0.0
Hemorrhage	25 (15.2)	6 (3.7)	11 (6.7)	1 (0.6
Atrial fibrillation/atrial flutter[d]	6 (3.7)	2 (1.2)	1 (0.6)	0 (0.0

NOTE. There were 11 grade 5 adverse events, none of which were considered treatment-related (two respiratory failure and one each of pneumo COVID-19 pneumonia, multiple organ dysfunction syndrome, cardiac arrest, hemorrhage, malignant pleural effusion, mucormycosis, streptococ infection, and sudden death).
Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma; TEAE, treatment-emergent adverse event; TRA treatment-related adverse event.
[a]Adverse events of special interest are those that were previously associated with cBTKi and are all composite terms.
[b]Combines neutrophil count decreased, neutropenia, febrile neutropenia, and neutropenic sepsis.
[c]Bruising includes contusion, petechia, ecchymosis, and increased tendency to bruise.

CAR-T cells therapy: KTE-X19 – ZUMA 2 trial

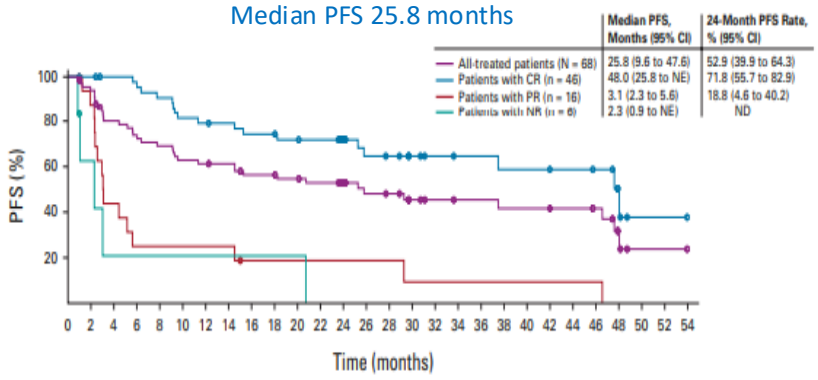
A

Median DOR 28.2 months



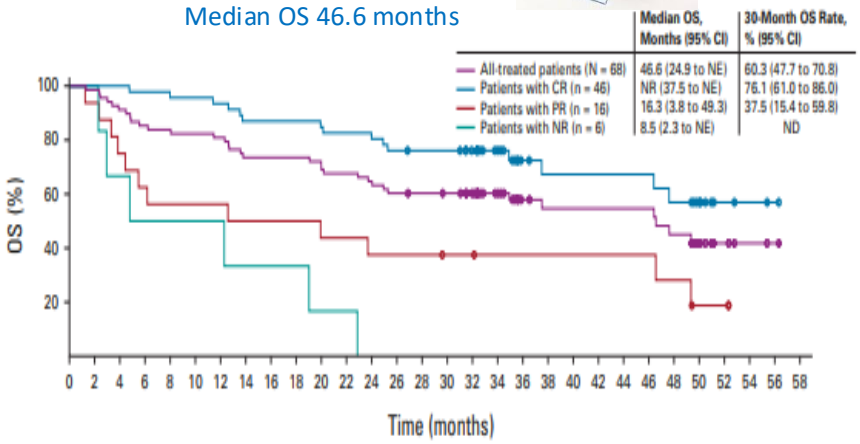
B

Median PFS 25.8 months



C

Median OS 46.6 months



Associations with long-term benefits of KTE-X19:

- ✓ high-peak CAR T-cell expansion in responders
- ✓ predictive value of minimal residual disease for relapse

Wang et al. JCO,2022 Jun 4;JCO2102370.

Table 5. Brexucel real-world studies in r/r MCL.

	UK [82]	DESCAR-T [87]	SIE [83]	DRST/GLA/ SAKK [98]	US CART consortium [26]
Study type	Registry retrospective	Registry retrospective	Registry retrospective	Registry retrospective	Registry retrospective
Eligibility	≥2L incl. BTKi; PS 0-1; no CNS disease	EMA label	≥2L; r/r to BTKi; ZUMA-2 eligible	EMA label	FDA label
N					
# intended	119	178	n.a.	n.a.	n.a.
# apheresed (%)	104 (87%)	n.a.	n.a.	n.a.	189
# infused (%)	83 (70%)	152 (85%)	106	111	168 (89%)
Period	2021–2023	2019–2023	2019–2024	2021–2023	2020–2021
Age (years; median (range))	68 (41–80)	68 (39–83)	63 (42–79)	68 (50–84)	67 (34–89)
PS > 1 (ECOG)	0	12%	0	7%	14%
High-risk features					
Ki-67 ≥ 30%	78%	79%	54%	79%	78%
Blastoid/pleomorph.	42%	31%	30%	33%	40%
TP53abn	53%	30%	29%	27%	48%
POD24	57%	n.a.	42%	n.a.	51%
Prior lines/median (range)	2 (2–7)	3 (1–9)	3 (2–5)	3 (1–8)	3 (1–10)
Prior autoHCT	34%	40%	58%	55%	28%
Prior alloHCT	13%	6%	-	8%	3%
BTKi refractory	30%	n.a.	35%	58%	76%
Holding/Bridging	90%	83%	79%	74%	68%
CIT	50%	n.a.	31%	35%	34%
BTKi ± CD20.	17%	n.a.	45%	28%	24%
Venetoclax ± x	10%	n.a.	13%	20%	27%
Response to Bridging	41% (37/91)	41% (51/125)	18% (15/83)	65% (42/65)	33% (32/95)
Toxicity					
Neurotox ≥ G3 (any)	22% (55%)	15% (55%)	18% (48%)	28% (54%)	32% (61%)
Late ICAHT ≥ G2	59%	9% (≥G3)	4.4% (≥G3)	n.a.	>18%
Severe infection	>30%	>25%	n.a.	31%	>21%
ICU admission	27%	34%	18%	22%	20%
T cell recovery 6mo	na	na	na	23%	na
Non-relapse mortality (12mo)	18%[d]	18%[a]	7.3%	10%[a]	7.1% 10.7%[d]
Best ORR/CR	87%/81%	85%/72%	88%/75%	88%/64%	90%/82%
PFS from infusion (12mo)	62%	46%	62%	69%	69%
OS from infusion (12mo)	74%	70%[c]	82%	74%	82%
Median follow-up (months)	13	12	12	12	14

CAR-T cells therapy: Real World data

Dreger, P., Ahmed, S., Bazarbachi, A. et al. How we treat mantle cell lymphoma with cellular therapy in 2025: the European and American perspectives. Bone Marrow Transplant 60, 759–768 (2025).

FUTURE PERSPECTIVES

PRESENTE.PASSATO,FUTURO
di Ruxi Dalmazio

Ibrutinib plus venetoclax in relapsed or refractory mantle cell lymphoma (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

Michael Wang, Wojciech Jurczak, Marek Trneny, David Belada, Tomasz Wrobel, Nilanjan Ghosh, Mary-Margaret Keating, Tom van Meerten, Ruben Fernandez Alvarez, Gottfried von Keudell, Catherine Thieblemont, Frederic Peyrade, Marc Andre, Marc Hoffmann, Edith Szafer-Glusman, Jennifer Lin, James P Dean, Jutta K Neuenburg, Constantine S Tam

SYMPATICO Study Design

- SYMPATICO (NCT03112174) is multinational, randomized, double-blind, placebo-controlled, phase 3 study

SYMPATICO (N=267)
- Age ≥18 years
- R/R MCL
- 1–5 prior therapies for MCL
- ≥1 prior rituximab/ anti-CD20-containing regimen
- ECOG PS 0–2

Randomized 1:1

Ibrutinib + venetoclax (n=134)
Ibrutinib 560 mg once daily + venetoclax 5-week ramp-up to 400 mg once daily for 24 months

Ibrutinib + placebo (n=133)
Ibrutinib 560 mg once daily + placebo once daily for 24 months

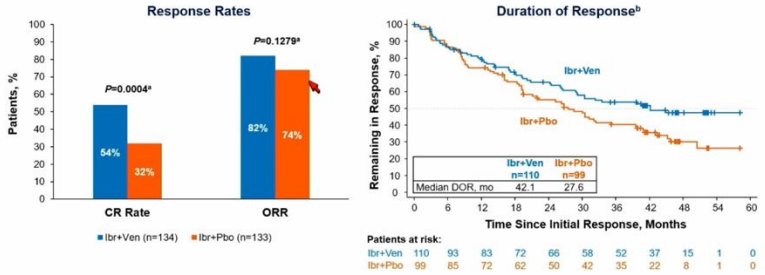
Single-agent ibrutinib 560 mg once daily until PD or unacceptable toxicity

Stratification: ECOG PS, prior lines of therapy, TLS risk[a]

- **Primary endpoint:**
  - PFS by investigator assessment using Lugano criteria
- **Secondary endpoints (tested hierarchically in the following order):**
  - CR rate by investigator assessment
  - TTNT[b]
  - OS (interim analysis)
  - ORR by investigator assessment

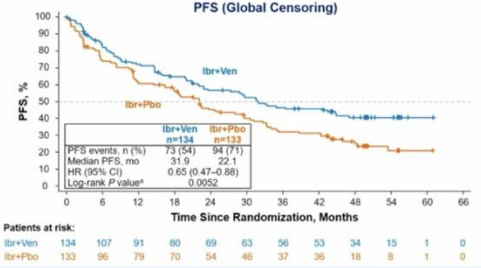
CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; PFS, progression-free survival; ORR, overall response rate; OS, overall survival; TLS, tumor lysis syndrome; TTNT, time to next treatment.
[a]Increased TLS risk was defined as at least 1 lesion >10 cm, or at least 1 lesion >5 cm with circulating lymphocytes >25,000 cells/mm³, and/or creatinine clearance <60 mL/min. [b]For hierarchical testing per US FDA censoring, TTNT was tested after OS.

CR Rate Was Significantly Improved With Ibrutinib + Venetoclax



DOR, duration of response.
[a]*P* values were determined by stratified Cochran-Mantel-Haenszel test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Global censoring (censoring at last non-PD assessment for patients without PD or death).

Primary Endpoint: Investigator-Assessed PFS Was Significantly Improved With Ibrutinib + Venetoclax Versus Ibrutinib + Placebo



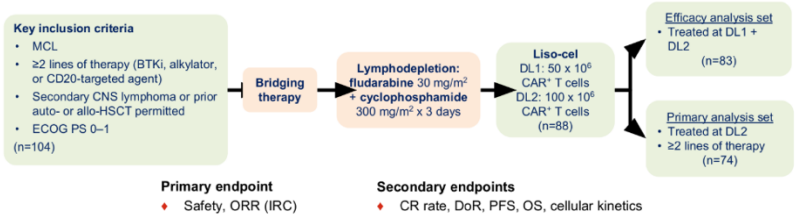
Median PFS, mo	Global Censoring[b]				US FDA Censoring[c]			
	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]	Ibr+Ven n=134	Ibr+Pbo n=133	HR (95% CI)	Log-rank *P* value[a]
Investigator assessment	31.9	22.1	0.65 (0.47–0.88)	0.0052	42.6	22.1	0.60 (0.44–0.83)	0.0021
IRC assessment	31.8	20.9	0.67 (0.49–0.91)	0.0108	43.5	22.1	0.63 (0.45–0.87)	0.0057

HR, hazard ratio; Ibr, ibrutinib; Pbo, placebo; Ven, venetoclax.
[a]*P* values were determined by stratified log-rank test (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]). [b]Censoring at last non-PD assessment for patients without PD or death. [c]Patients were censored at last non-PD assessment before start of subsequent anticancer therapy or missing ≥2 consecutive visits prior to a PFS event, whichever occurred first.

Novel BTK Inhibitor Platforms: Is Rechallenge a Viable Option?

Lisocabtagene maraleucel in R/R MCL: primary results from the MCL cohort of the TRANSCEND NHL 001 study

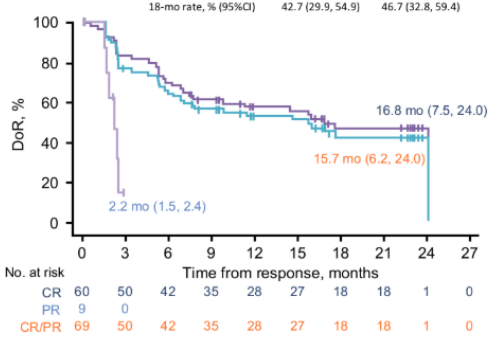
- To evaluate the safety and efficacy of lisocabtagene maraleucel (liso-cel, a CD19-directed CAR T cell therapy) in patients with R/R MCL in the TRANSCEND NHL 001 study



This oral presentation was presented at 17-ICML (13–17 June 2023 - www.icml.ch)
Wang M, et al. *Hematol Oncol* 2023;41(suppl 42):Abstract LBA3

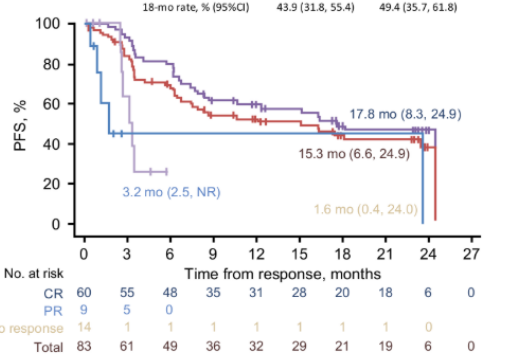
Duration of response

	Responders (n=69)	Patients with CR (n=60)
12-mo rate, % (95%CI)	52.9 (40.1, 64.2)	57.8 (44.2, 69.2)
18-mo rate, % (95%CI)	42.7 (29.9, 54.9)	46.7 (32.8, 59.4)



Progression-free survival

	Total (n=83)	Patients with CR (n=60)
12-mo rate, % (95%CI)	52.8 (40.6, 63.6)	59.8 (46.3, 71.0)
18-mo rate, % (95%CI)	43.9 (31.8, 55.4)	49.4 (35.7, 61.8)



This oral presentation was presented at 17-ICML (13–17 June 2023 - www.icml.ch)
Wang M, et al. *Hematol Oncol* 2023;41(suppl 42):Abstract LBA3

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Glofitamab in Relapsed/Refractory Mantle Cell Lymphoma: Results From a Phase I/II Study

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TABLE 1. Baseline Characteristics in the Overall Populations and in Patients With and Without Previous BTKi Treatment

Characteristic	Previous BTKi (n = 31)	No Previous BTKi (n = 29)	All Patients (N = 60)
Age, years, median (range)	70.0 (41-84)	72.0 (52-86)	72.0 (41-86)
Male sex, No. (%)	23 (74.2)	21 (72.4)	44 (73.3)
ECOG PS, No. (%)			
0	14 (45.2)	14 (48.3)	28 (46.7)
1	17 (54.8)	15 (51.7)	32 (53.3)
Ann Arbor stage at study entry, No. (%)			
I	1 (3.2)	2 (6.9)	3 (5.0)
II	2 (6.5)	3 (10.3)	5 (8.3)
III	5 (16.1)	6 (20.7)	11 (18.3)
IV	23 (74.2)	18 (62.1)	41 (68.3)
MCL IPI score ≥6, No. (%)	7 (22.6)	8 (27.6)	15 (25.0)
Extranodal disease present, No. (%)	20 (64.5)	19 (65.5)	39 (65.0)
Bulky disease, cm, No. (%)			
>6	7 (22.6)	6 (20.7)	13 (21.7)
>10	2 (6.5)	3 (10.3)	5 (8.3)
Time since last previous therapy to first study treatment, months, median (range)	1.3 (0.1-53.2)	7.4 (1.1-132.5)	2.4 (0.1-132.5)
Time since last anti-CD20 therapy to first study treatment, months, median (range)	15.1 (0.7-159.0)	25.1 (1.4-132.5)	16.3 (0.7-159.0)
No. of previous lines of therapy, median (range)	3.0 (1-5)	2.0 (1-4)	2.0 (1-5)
Previous therapy for lymphoma, No. (%)			
CAR T-cell therapy	1 (3.2)	1 (3.4)	2 (3.3)
ASCT	7 (22.6)	9 (31.0)	16 (26.7)
Refractory status, No. (%)			
Any previous therapy	30 (96.8)	20 (69.0)	50 (83.3)
First-line therapy	17 (54.8)	14 (48.3)	31 (51.7)
Last previous therapy	27 (87.1)	17 (58.6)	44 (73.3)
Progress or relapse ≤24 months after first-line treatment start, No. (%)	17 (54.8)	14 (48.3)	31 (51.7)

TABLE 2. Efficacy in the Overall Population (efficacy-evaluable population), and in Patients With and Without Previous BTKi Treatment

Efficacy (INV-assessed)	Glofitamab SUD		All Patients		
	1,000 mg Gpt Cohort (n = 16)	2,000 mg Gpt Cohort (n = 44)	Previous BTKi (n = 31)	No Previous BTKi (n = 29)	All Patients (N = 60)
Complete response rate					
No. (%)	11 (68.8)	36 (81.8)	22 (71.0)	25 (86.2)	47 (78.3)
95% CI	41.3 to 89.0	67.3 to 91.8	52.0 to 85.8	68.3 to 96.1	65.8 to 87.9
Partial response rate					
No. (%)	1 (6.3)	3 (6.8)	1 (3.2)	3 (10.3)	4 (6.7)
95% CI	0.2 to 30.2	1.4 to 18.7	0.1 to 16.7	2.2 to 27.4	1.9 to 16.2
Overall response rate					
No. (%)	12 (75.0)	39 (88.6)	23 (74.2)	28 (96.6)	51 (85.0)
95% CI	47.6 to 92.7	75.4 to 96.2	55.4 to 88.1	82.2 to 99.9	73.4 to 92.9

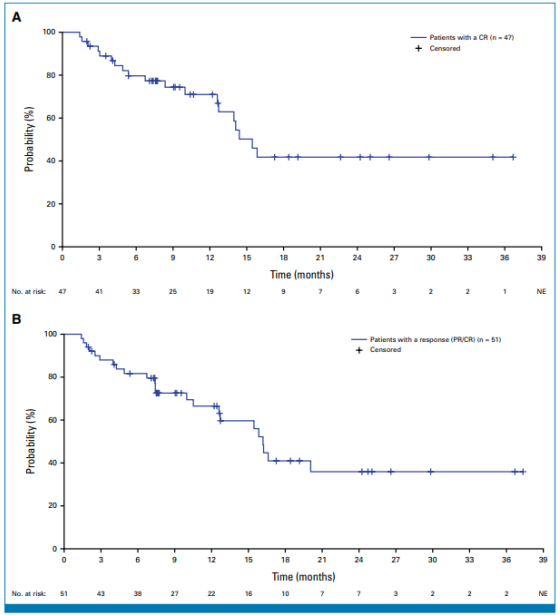
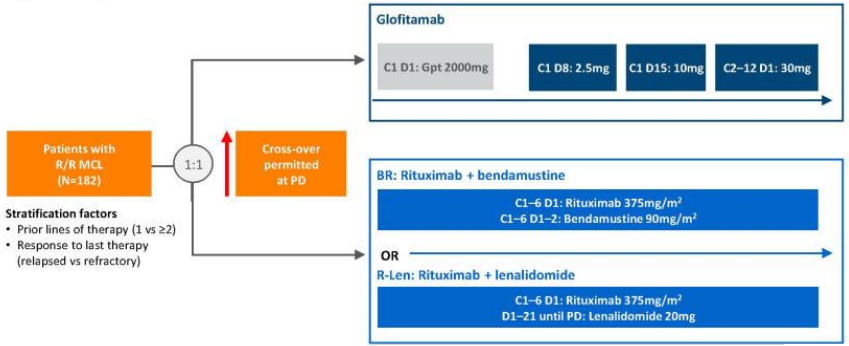


FIG 2. (A) Duration of CR, (B) duration of response, and (C) time on treatment. CR, complete response; CT, computed tomography; NE, not estimable; PD, progressive disease; PR, partial response. (continued on following page)

GLOBRYTE: A Phase III, Open-Label, Multicenter, Randomized Trial Evaluating Glofitamab Monotherapy in Patients with Relapsed or Refractory Mantle Cell Lymphoma

Figure. Study schema



B, bendamustine; C, cycle; D, day; Gpt, obinutuzumab pretreatment; Len, lenalidomide; MCL, mantle cell lymphoma; PD, progressive disease; R/R, relapsed/refractory; R, rituximab. Relapsed disease is defined as disease progression after the last regimen; refractory disease is defined as fai to achieve a partial response or complete response to the last regimen.

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FONDAZIONE ITALIANA LINFOMI

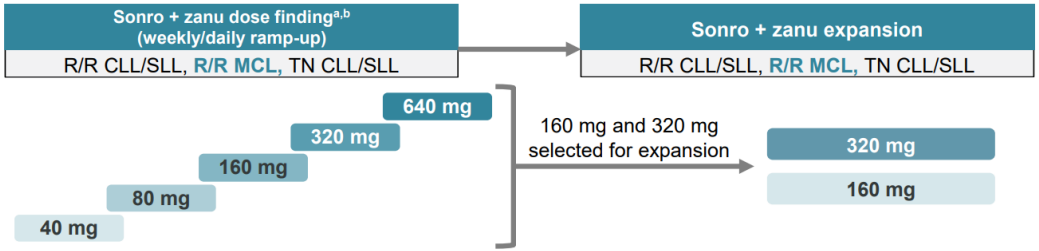
Clinical Protocol

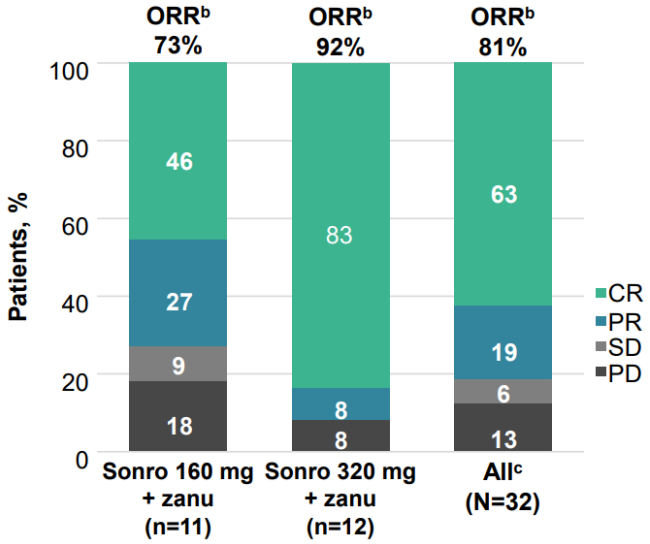
Title

A phase II, multicenter study of GlOfitamab in patients with mantle cell Lymphoma and inaDequate response or relapse following CAR T-cell therapy (GOLD)

Sonrotoclax (BGB-11417) and Zanubrutinib

Ongoing Phase 3





Patients, n (%)	Sonro 80 mg + zanu (n=6)	Sonro 160 mg + zanu (n=13)	Sonro 320 mg + zanu (n=16)	Sonro 640 mg + zanu (n=5)	All (N=40)
Any TEAE	4 (67)	13 (100)	15 (94)	5 (100)	37 (93)
Grade ≥3	4 (67)	6 (46)	7 (44)	1 (20)	18 (45)
Serious TEAEs	3 (50)	4 (31)	2 (13)	0	9 (23)
Leading to death	1 (17)	1 (8)	1 (6)	0	3 (8)[a]
Leading to zanu discontinuation	1 (17)	3 (23)	2 (13)	0	6 (15)[b]
Leading to zanu dose reduction	1 (17)	1 (8)	0	0	2 (5)[c]
Treated with sonro, n (%)	6 (100)	11 (85)	13 (81)	5 (100)	35 (88)
Leading to sonro discontinuation	0	3 (23)	2 (13)	0	5 (13)[d]
Leading to sonro dose reduction	0	0	0	0	0
Leading to death	0	1 (8)	0	0	1 (3)[e]

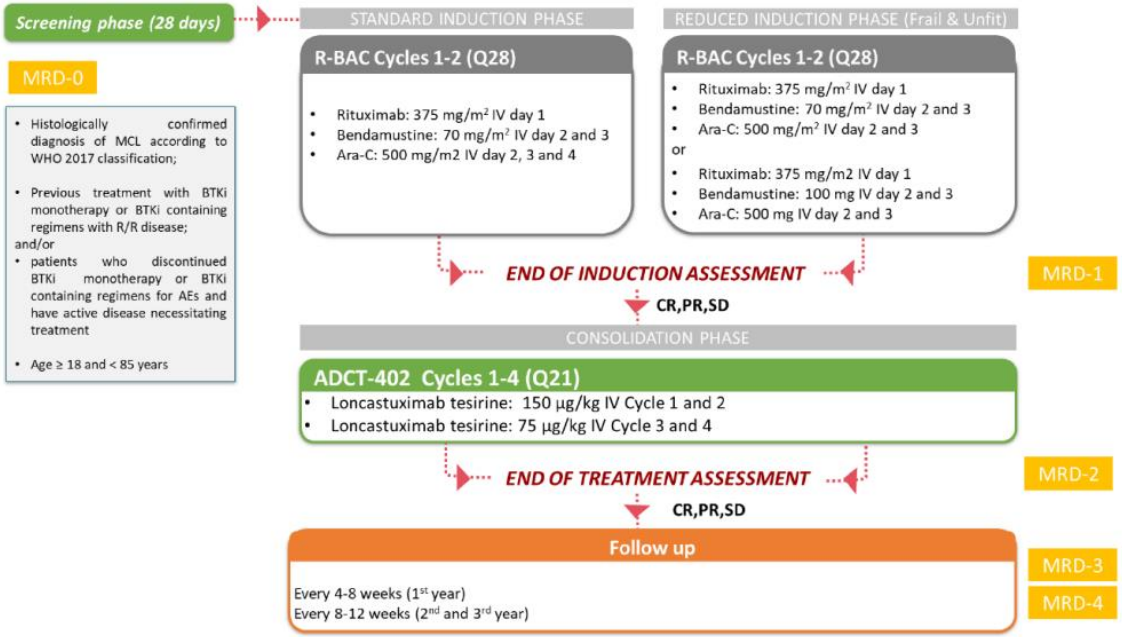
Tam, et al. EHA 2024

FONDAZIONE ITALIANA LINFOMI

Clinical Protocol

Consolidation with ADCT-402 (loncastuximab tesirine) after a short course of immunochemotherapy: a phase II study in BTKi-treated (or BTKi intolerant) Relapsed/Refractory (R/R) Mantle Cell Lymphoma (MCL) patients

ID Study: FIL_COLUMN
EudraCT number: 2021-000715-23

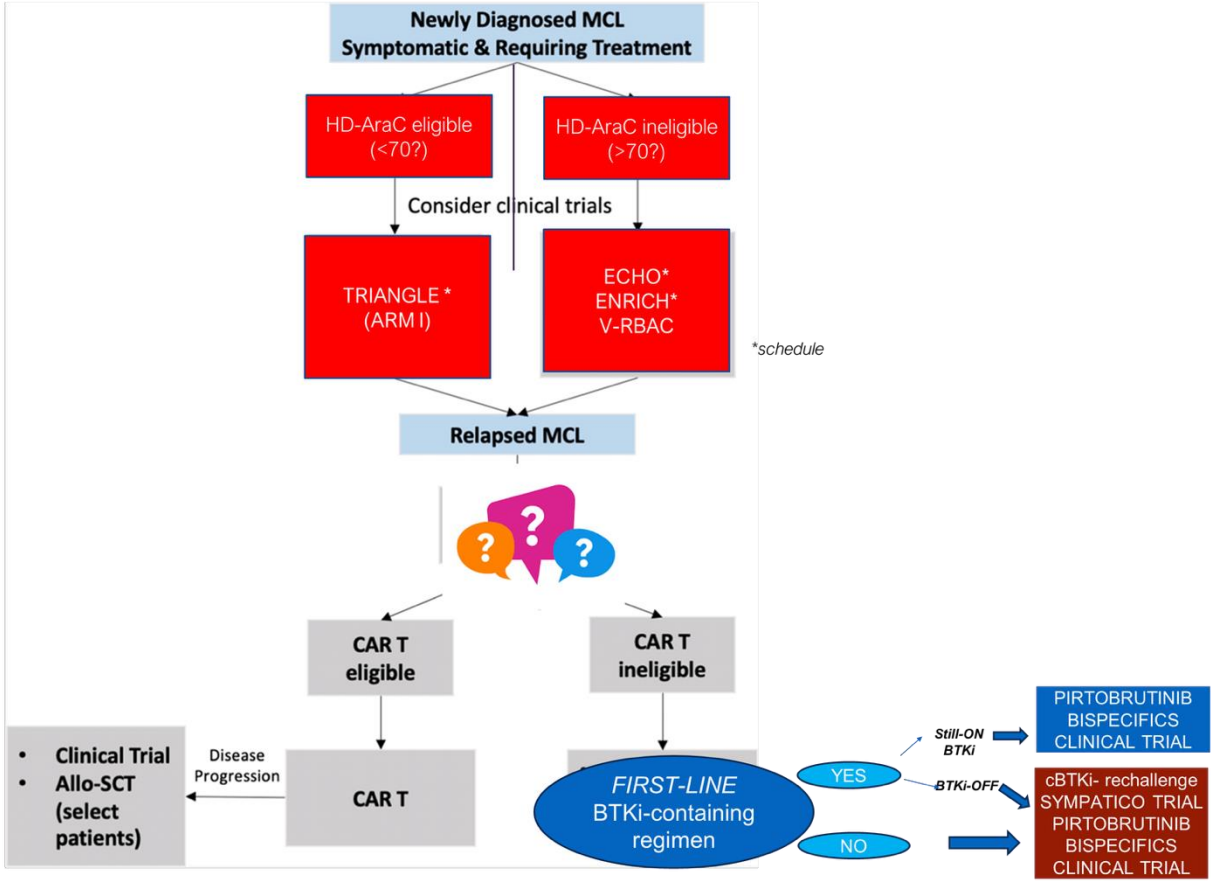


ACTIVE RECRUITING

COORDINATORS Marco Ladetto
Carlo Visco

BTKi ERA

Personal Opinion



CONCLUSION

- MCL is a B-cell lymphomas harboring unique pathological characteristics.
- From optimizing traditional therapies to the advent of novel approaches, including the advance of CAR-T cell therapy, the field of MCL therapy has expanded into a wide variety of novel therapeutics.
- Relapse/Refractory (R/R) MCL is still an unmet clinical need, particularly if already exposed to BTK inhibitors.
- As BTKi are moving to first line, R/R patient's management will be a critical issue.
- CAR-T cells are the most effective approach, after BTKi failure.
- These new therapies show promising efficacy, even among high-risk patients, and will likely translate to improvements in survival outcomes.


Ευχαριστώ
謝謝
Gracias
Merci
Cnacubo
감사합니다
Thank you
Danke
شكرا
Merci
谢谢
Danke
謝謝
Dziękuję
Gracias
Obrigado