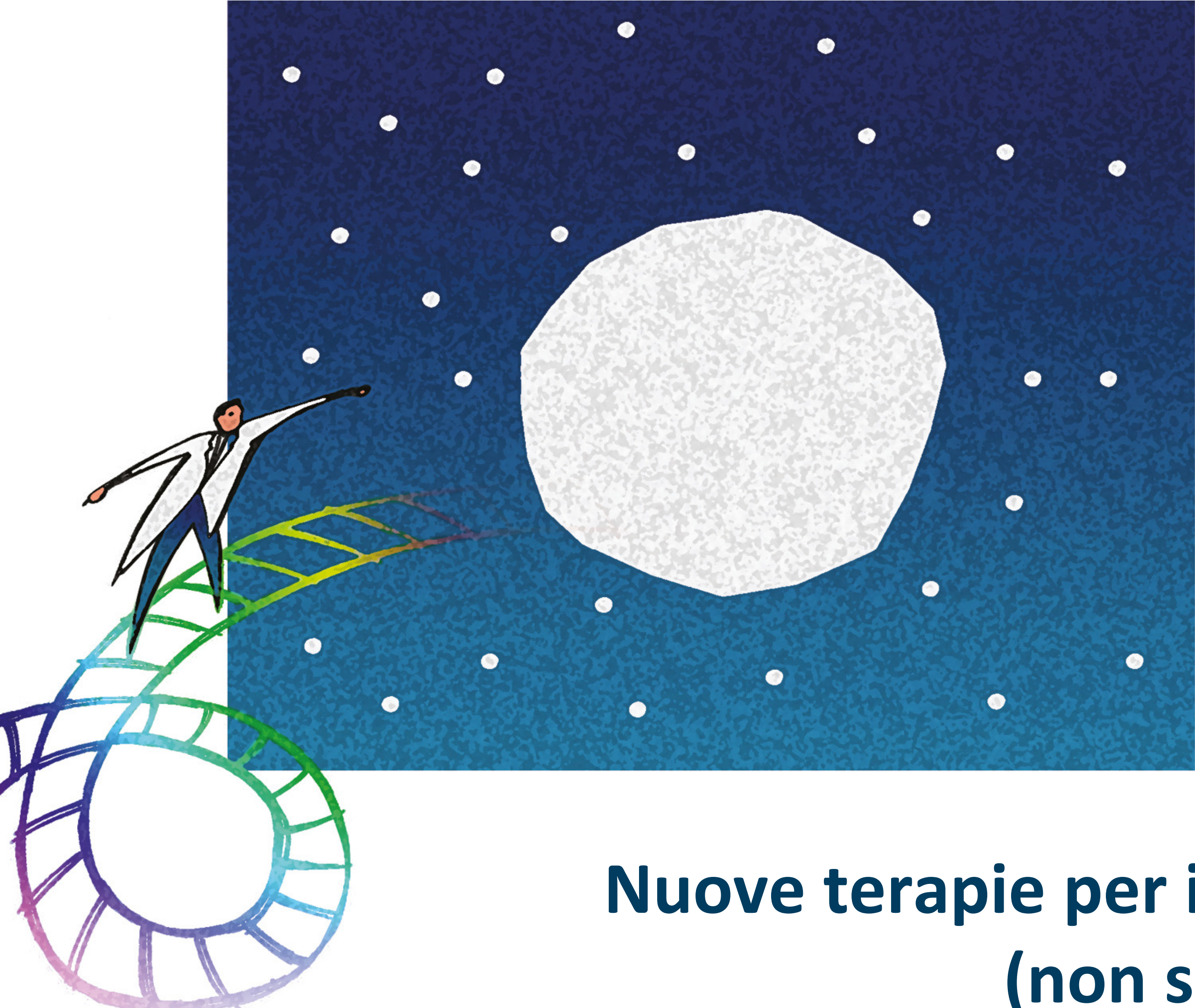




The young side of **LYMPHOMA**

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
26-27 settembre 2025

Nuove terapie per il paziente con MCL R/R (non solo CAR-T)

Rita Tavarozzi

*AOU SS Antonio e Biagio e Cesare Arrigo,
Alessandria
Università degli Studi del Piemonte Orientale*



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

Mantle Cell Lymphoma – *Case Presentation*

Nov 2020

- Patient:** 58-year-old male
- History:** Hypertension, hyperlipidemia

- Symptoms:**

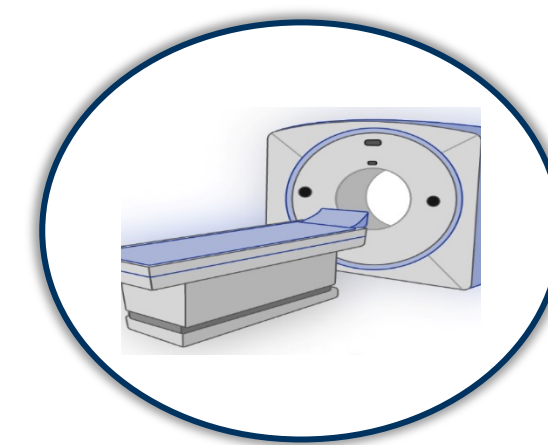
- Fatigue
- Weight loss (8 kg / 6 months)
- Night sweats
- Painless lymphadenopathy

- Exam:**

- Cervical, axillary, inguinal lymphadenopathy
- Splenomegaly

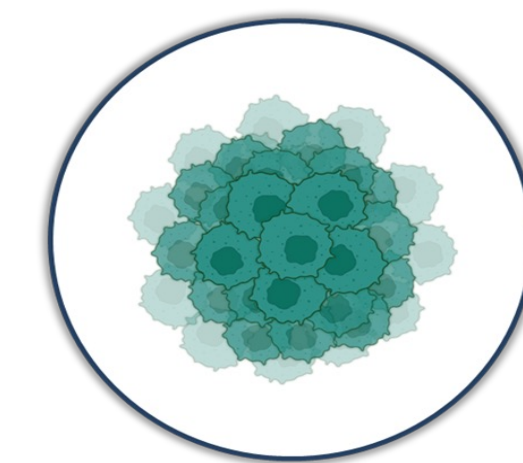
- Labs:**

- Mild anemia (Hb 11.2 g/dL)
- Elevated LDH
- Normal renal/liver function



- Imaging:**

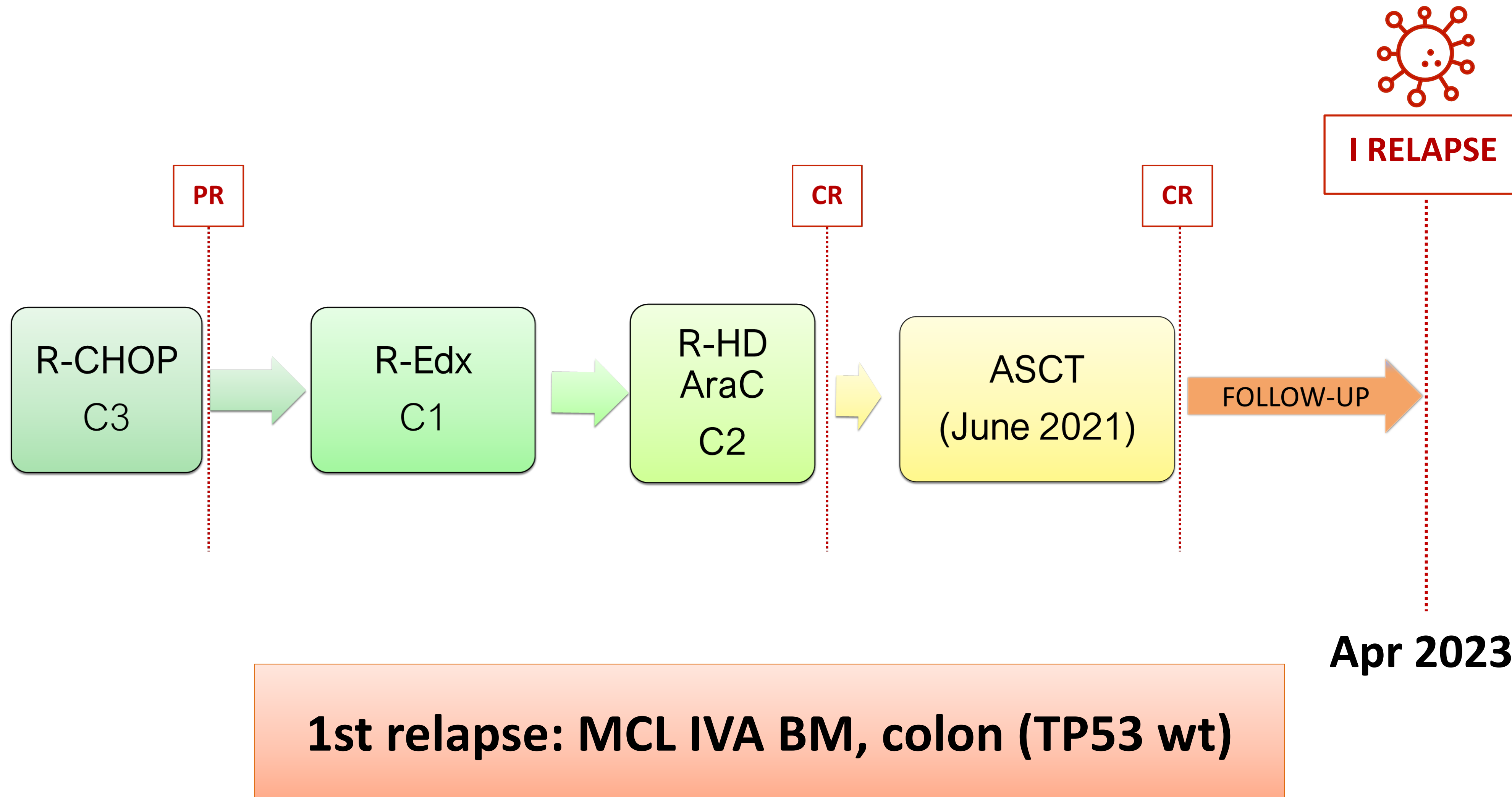
- Generalized lymphadenopathy
- Splenomegaly



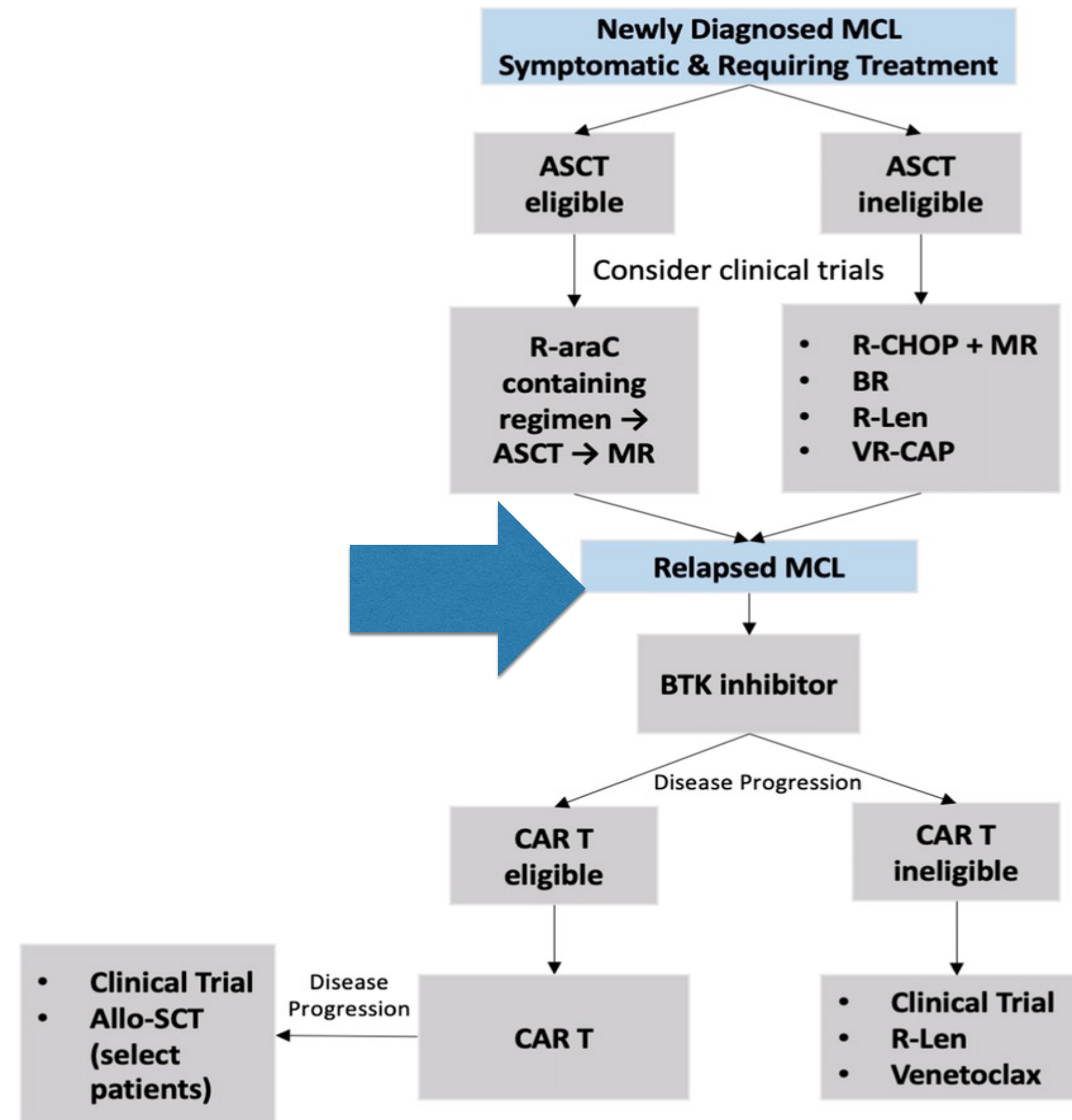
- BM Biopsy:**

Histology: diffuse lymphoid proliferation
Immunophenotype: CD20+, CD5+,
Cyclin D1+
Ki-67: 40%
TP53: wild-type

Diagnosis:
Mantle Cell Lymphoma (Stage IVB, MIPI high-risk)



PRE-TRIANGLE ERA



The NEW ENGLAND
JOURNAL of MEDICINE



CURRENT IS

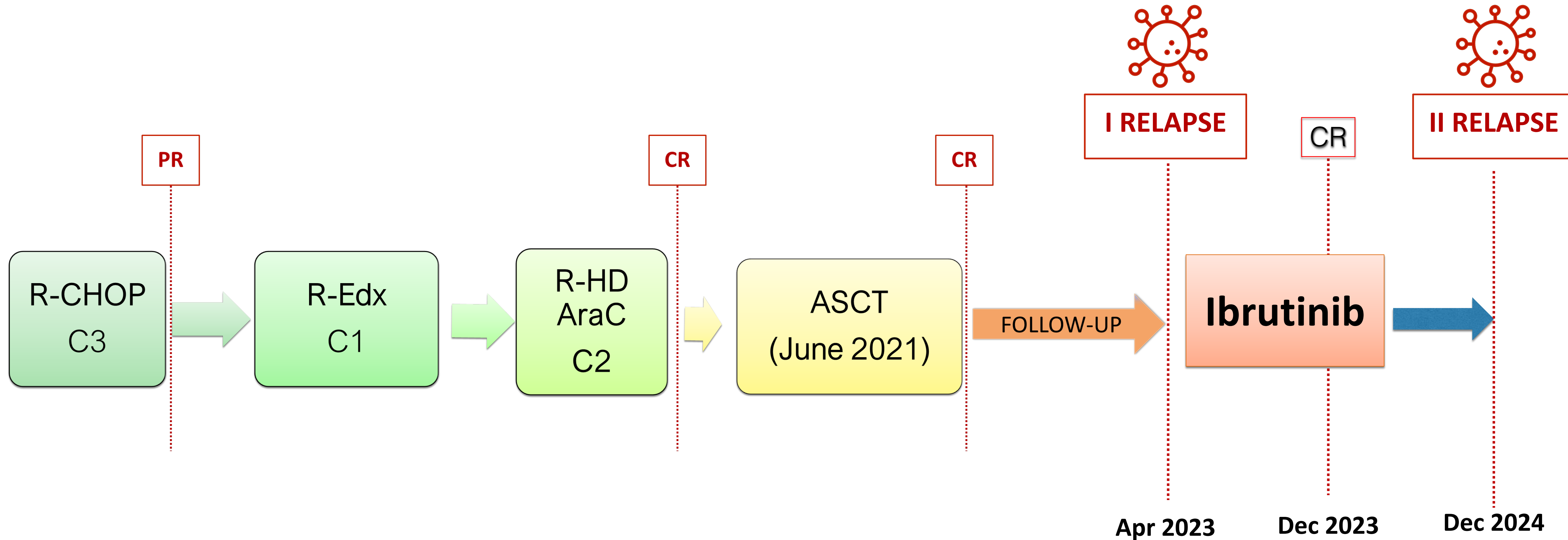
ORIGINAL ARTICLE



Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

Authors: Michael L. Wang, M.D., Simon Rule, M.D., Peter Martin, M.D., Andre Goy, M.D., Rebecca Auer, M.D., Ph.D., Brad S. Kahl, M.D., Wojciech Jurczak, M.D., Ph.D., [+23](#), and Kristie A. Blum, M.D. [Author Info & Affiliations](#)

Published August 8, 2013 | N Engl J Med 2013;369:507-516 | DOI: 10.1056/NEJMoa1306220 | [VOL. 369 NO. 6](#)



What can I do now?

What to do after BTK inhibitor failure?

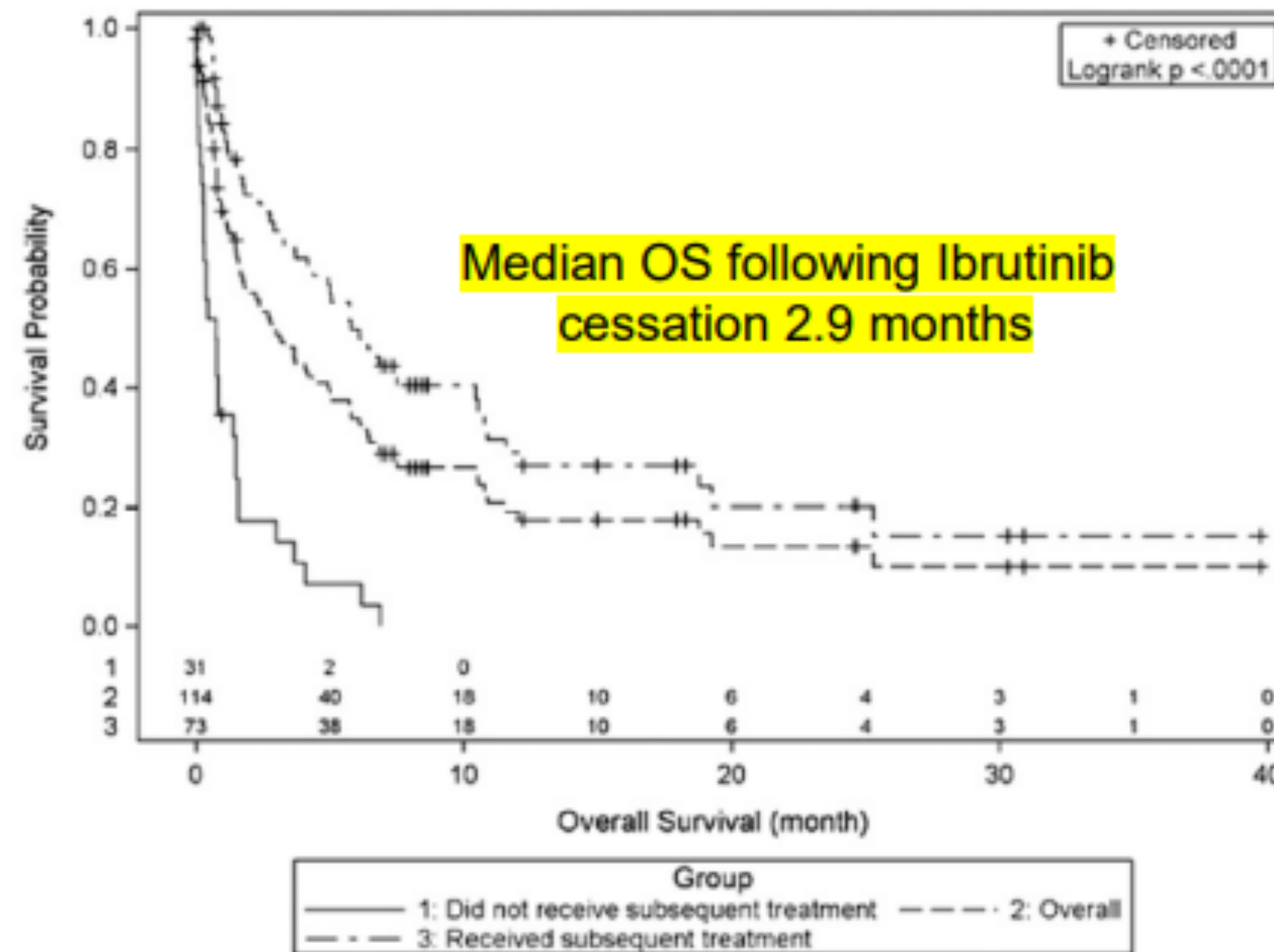
What are the treatment options after BTK inhibitor failure?

What are the available treatment options after BTK inhibitor failure?



What alternative therapies are available?

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



NON C'E' NOTTE TANTO LUNGA E
BUIA DA NON PERMETTERE AL
SOLE DI RISORGERE

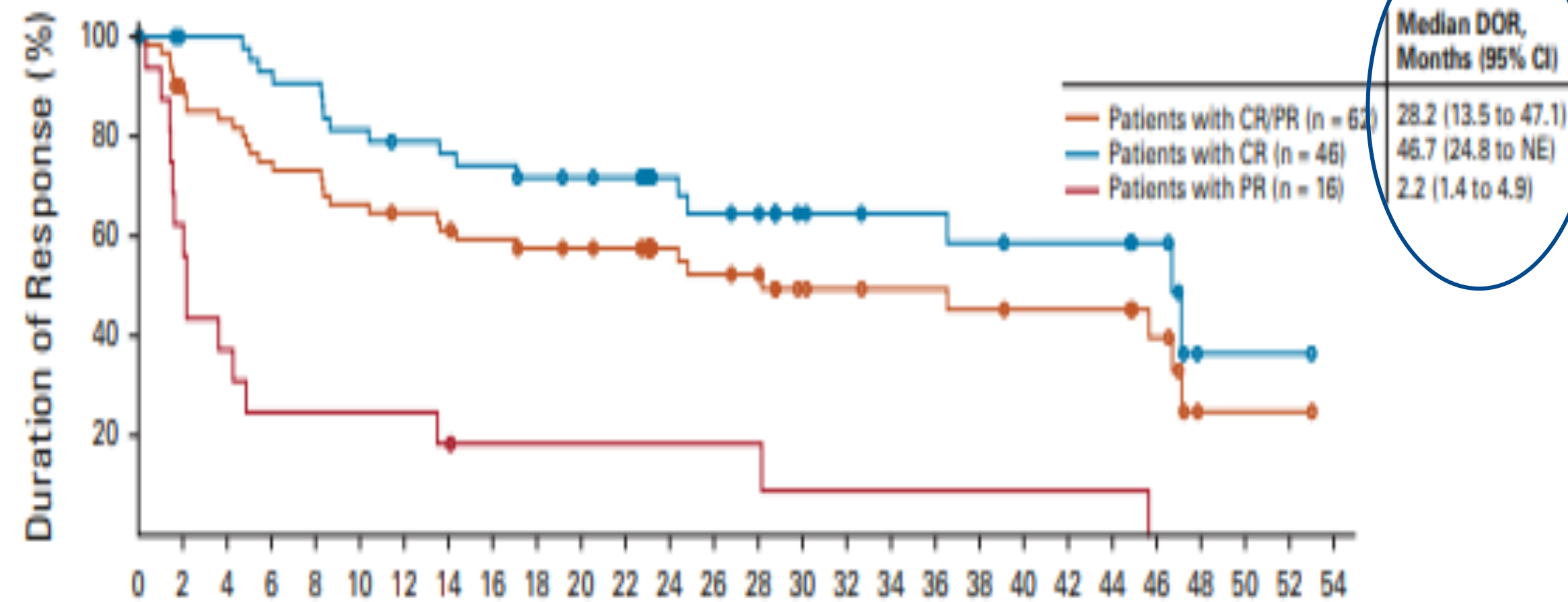
Jim Morrison

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



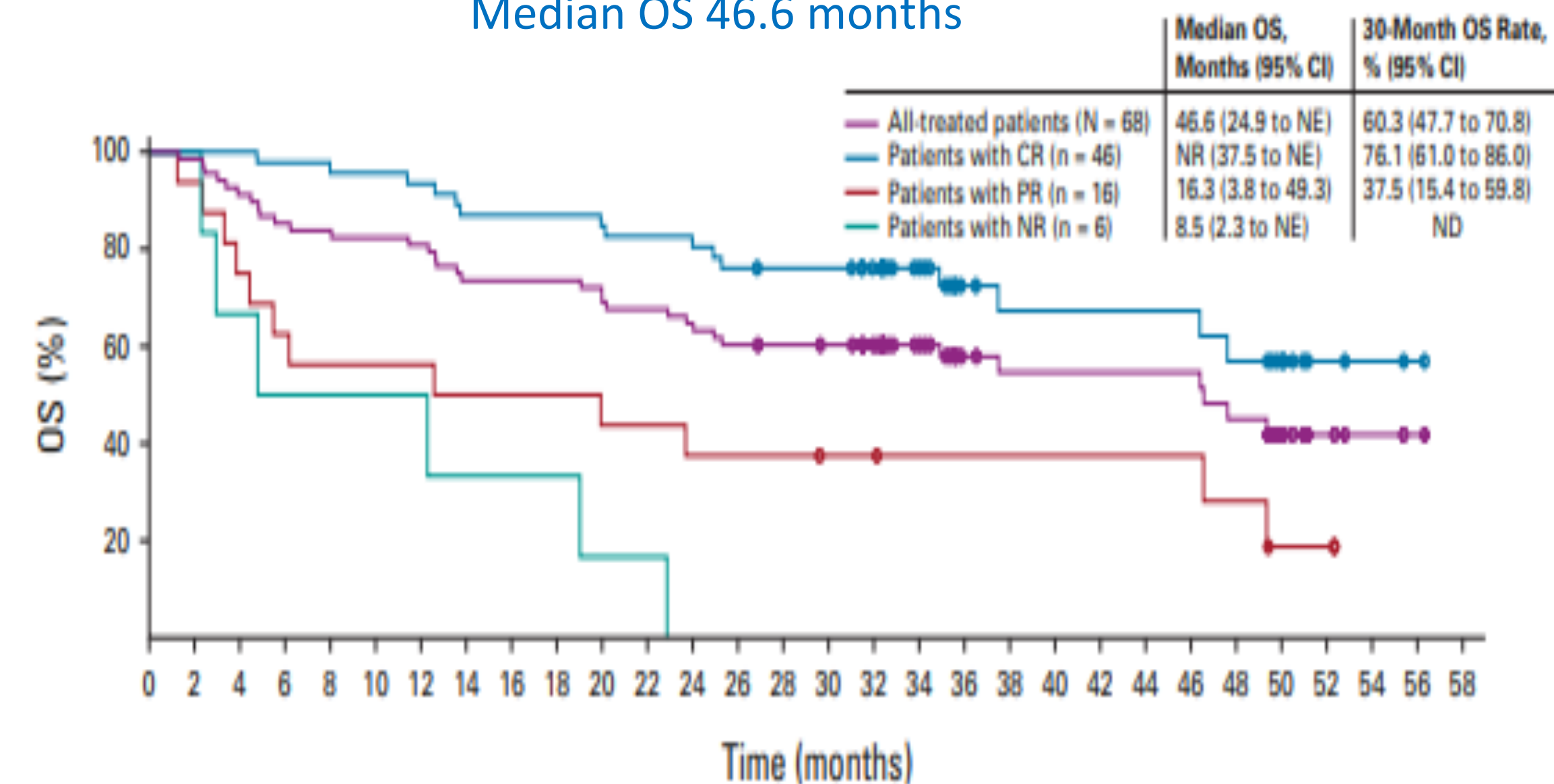
A

Median DOR 28.2 months



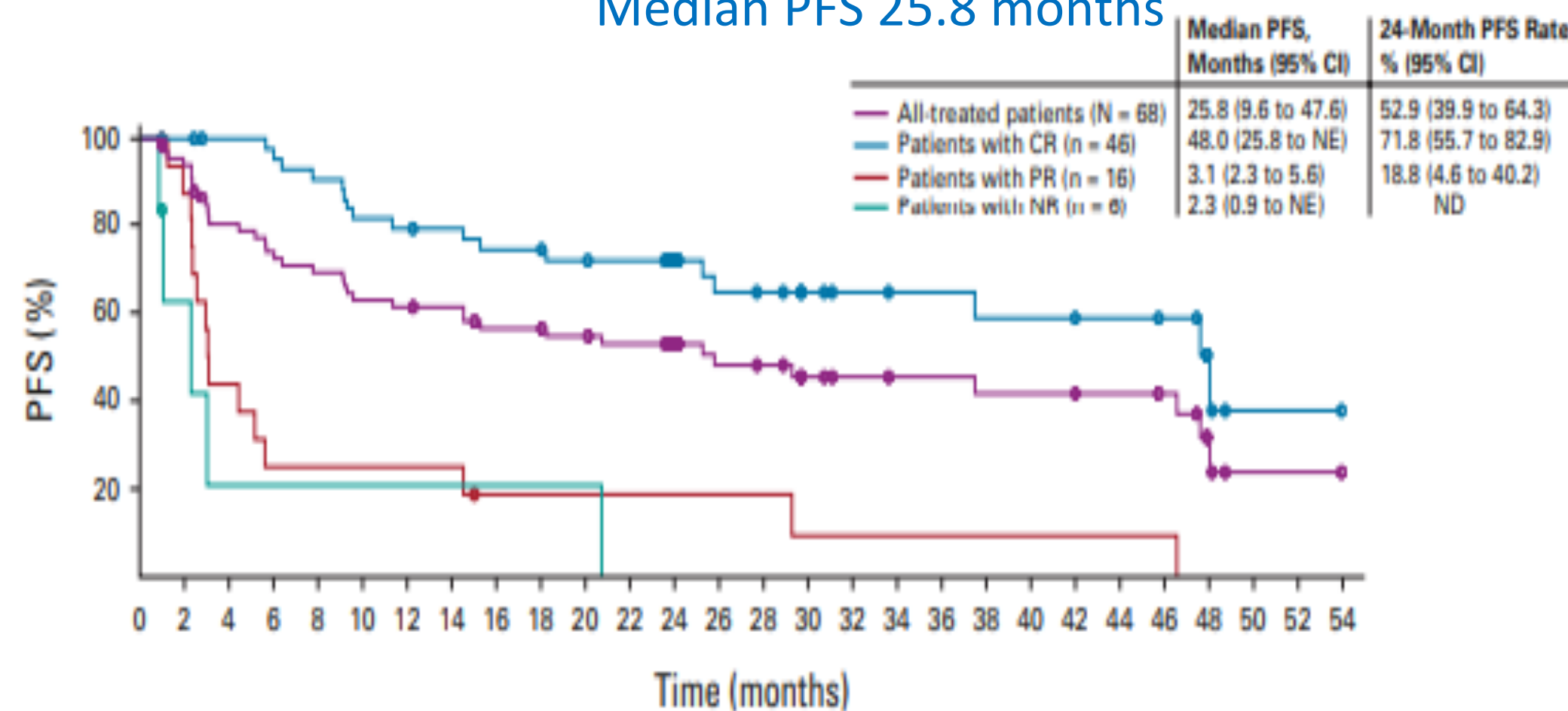
C

Median OS 46.6 months



B

Median PFS 25.8 months



Associations with long-term benefits of KTE-X19:

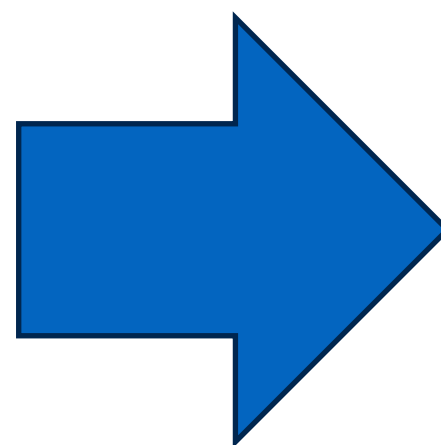
- ✓ high-peak CAR T-cell expansion in responders
- ✓ predictive value of minimal residual disease for relapse

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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
<i>N</i>					
# 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).



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

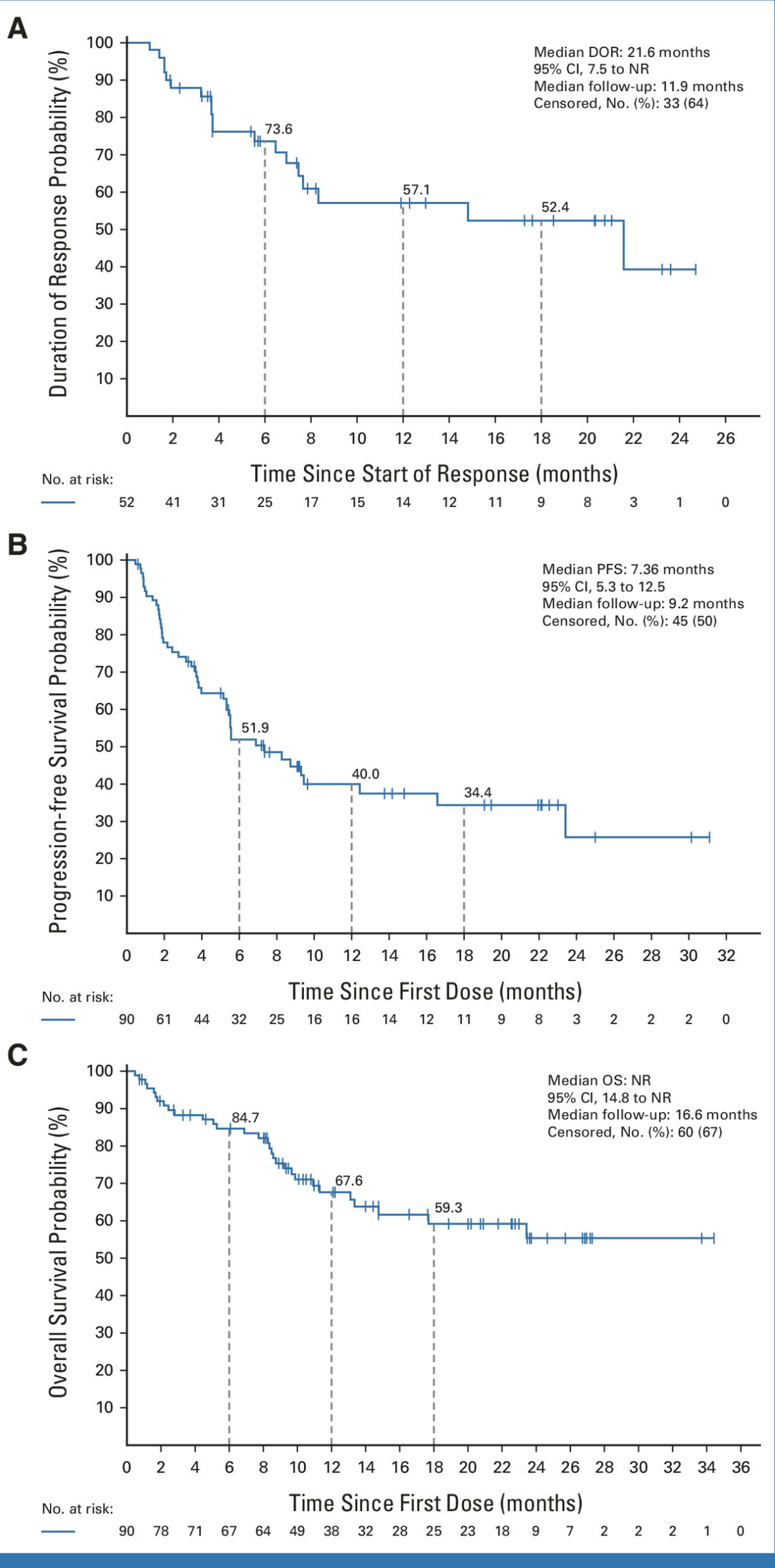
NOTE. Overall response and best response were determined according to the 2014 Lugano criteria²⁰ and on the basis of independent review committee assessment.

Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; DC, duration of response; MCL, mantle-cell lymphoma; NR, not reached; overall survival; PFS, progression-free survival.

^aPatients without postbaseline disease assessment were not included in the analysis.

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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 & CONTACTS](#)

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

Adverse Event	MCL Safety Population (n = 164)			
	TEAE, (≥10%), No. (%)		TRAЕ, No. (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
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 pneumonia, COVID-19 pneumonia, multiple organ dysfunction syndrome, cardiac arrest, hemorrhage, malignant pleural effusion, mucormycosis, streptococcal infection, and sudden death).

Abbreviations: cBTKi, covalent Bruton tyrosine kinase inhibitor; MCL, mantle cell lymphoma; TEAE, treatment-emergent adverse event; TRAЕ, treatment-related adverse event.

^aAdverse events of special interest are those that were previously associated with cBTKi and are all composite terms.

^bCombines neutrophil count decreased, neutropenia, febrile neutropenia, and neutropenic sepsis.

^cBruising includes contusion, petechia, ecchymosis, and increased tendency to bruise.

Qual è un criterio clinico che può influenzare la scelta tra CAR-T e trattamenti farmacologici alternativi?

- A) Età del paziente**
- B) Stato mutazionale**
- C) Comorbidità**
- D) Tutti i precedenti**

FUTURE PERSPECTIVES



- Novel BTK Inhibitor Platforms
 - Bispecific : GLOFITAMAB
- Novel CAR-T product : LISO-CEL
 - Clinical trials

Novel CAR-T product : *LISO-CEL*

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

Key inclusion criteria

- MCL
- ≥2 lines of therapy (BTKi, alkylator, or CD20-targeted agent)
- Secondary CNS lymphoma or prior auto- or allo-HSCT permitted
- ECOG PS 0-1 (n=104)

Bridging therapy

Lymphodepletion:
fludarabine 30 mg/m²
+ cyclophosphamide
300 mg/m² x 3 days

Liso-cel
DL1: 50 x 10⁶
CAR⁺ T cells
DL2: 100 x 10⁶
CAR⁺ T cells
(n=88)

Efficacy analysis set

- Treated at DL1 + DL2 (n=83)

Primary analysis set

- Treated at DL2
- ≥2 lines of therapy (n=74)

Primary endpoint

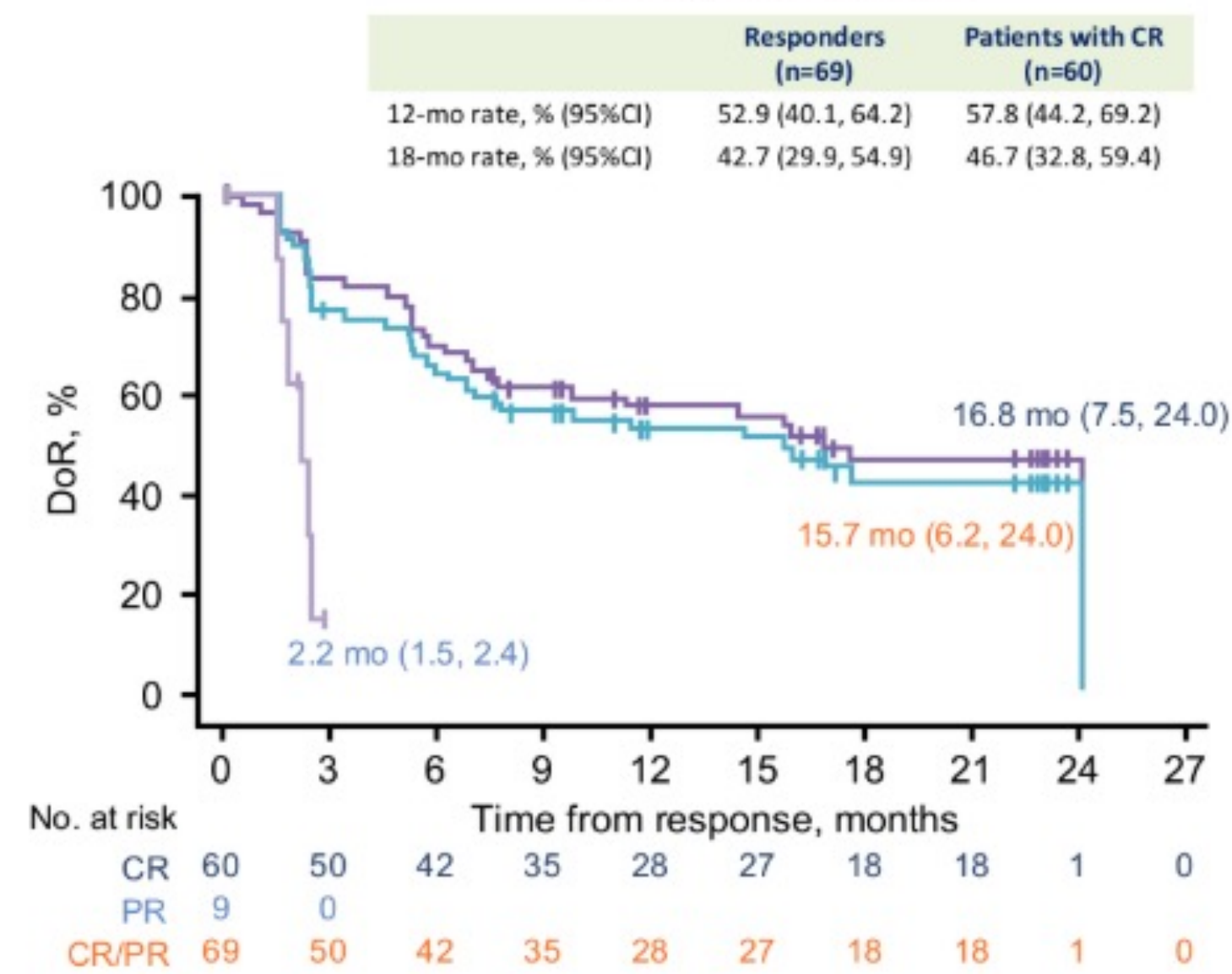
- Safety, ORR (IRC)

Secondary endpoints

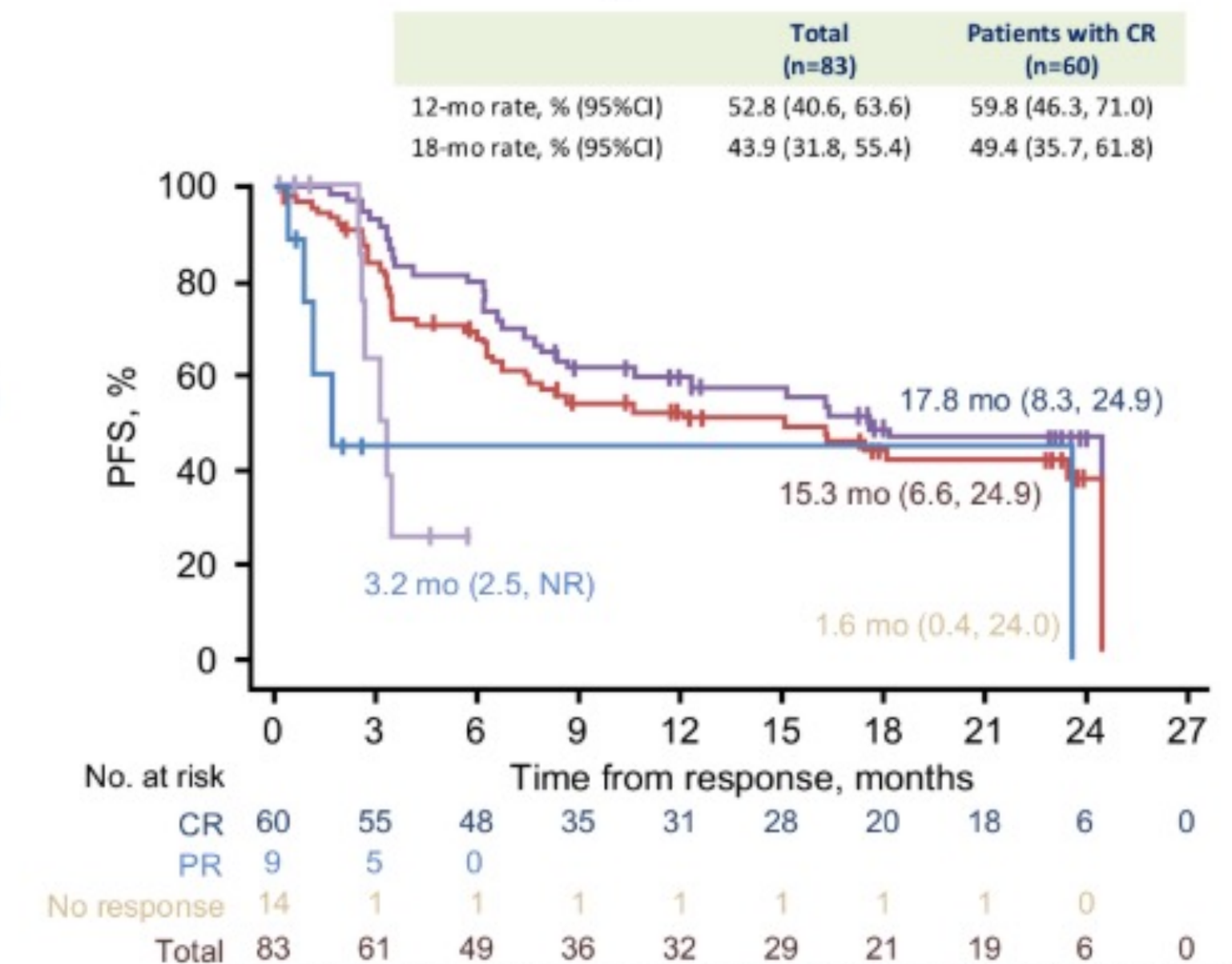
- CR rate, DoR, PFS, OS, cellular kinetics

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



Progression-free survival



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

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

Authors: [Tycel Jovelle Phillips, MD](#) , [Carmelo Carlo-Stella, MD](#) , [Franck Morschhauser, MD, PhD](#) , [Emmanuel Bachy, MD, PhD](#) , [Michael Crump, MD, FRCPC](#), [Marek Trněný, MD](#) , [Nancy L. Bartlett, MD](#) , ... [SHOW ALL](#) ..., and [Michael Dickinson, MBBS, DMedSc](#)  | [AUTHORS INFO & AFFILIATIONS](#)

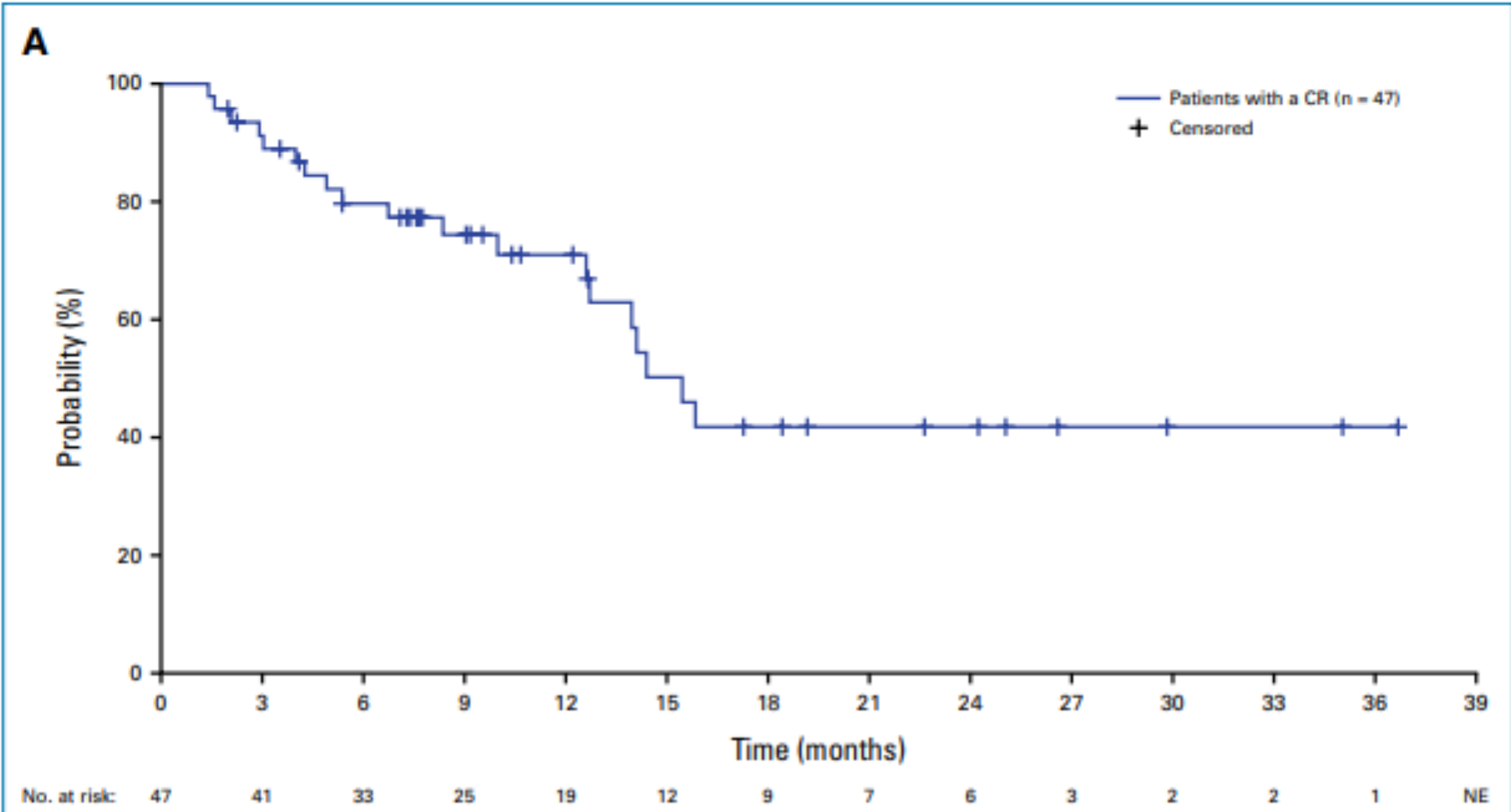
Publication: Journal of Clinical Oncology • Volume 43, Number 3 • <https://doi.org/10.1200/JCO.23.02470>

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)		
95% CI	41.3 to 89.0	67.3 to 91.8	52.0 to 85.0		
Partial response rate					
No. (%)	1 (6.3)	3 (6.8)	1 (3.2)		
95% CI	0.2 to 30.2	1.4 to 18.7	0.1 to 16.0		
Overall response rate					
No. (%)	12 (75.0)	39 (88.6)	23 (74.2)		
95% CI	47.6 to 92.7	75.4 to 96.2	55.4 to 88.0		

TABLE 4. Summary of Safety in the Overall Population and by Cohort (safety-evaluable population)

AE	Glofitamab SUD, No. (%)		
	1,000 mg Gpt Cohort (n = 16)	2,000 mg Gpt Cohort (n = 44)	All Patients (N = 60)
Any AE	16 (100.0)	44 (100.0)	60 (100.0)
Grade 3/4 AE	13 (81.3)	26 (59.1)	39 (65.0)
SAE	15 (93.8)	32 (72.7)	47 (78.3)
AE leading to glofitamab withdrawal ^a	1 (6.3)	3 (6.8)	4 (6.7)
AE leading to glofitamab dose interruption	10 (62.5)	26 (59.1)	36 (60.0)
AE related to glofitamab	16 (100.0)	39 (88.6)	55 (91.7)
AE related to glofitamab leading to glofitamab withdrawal	0	1 (2.3)	1 (1.7)
AE related to glofitamab leading to glofitamab dose interruption	7 (43.8)	15 (34.1)	22 (36.7)
Grade 3/4 AEs related to glofitamab	13 (81.3)	22 (50.0)	35 (58.3)
SAE related to glofitamab	12 (75.0)	24 (54.5)	36 (60.0)
Grade 5 AE	2 (12.5)	7 (15.9)	9 (15.0)
Grade 5 AE related to glofitamab	0	0	0

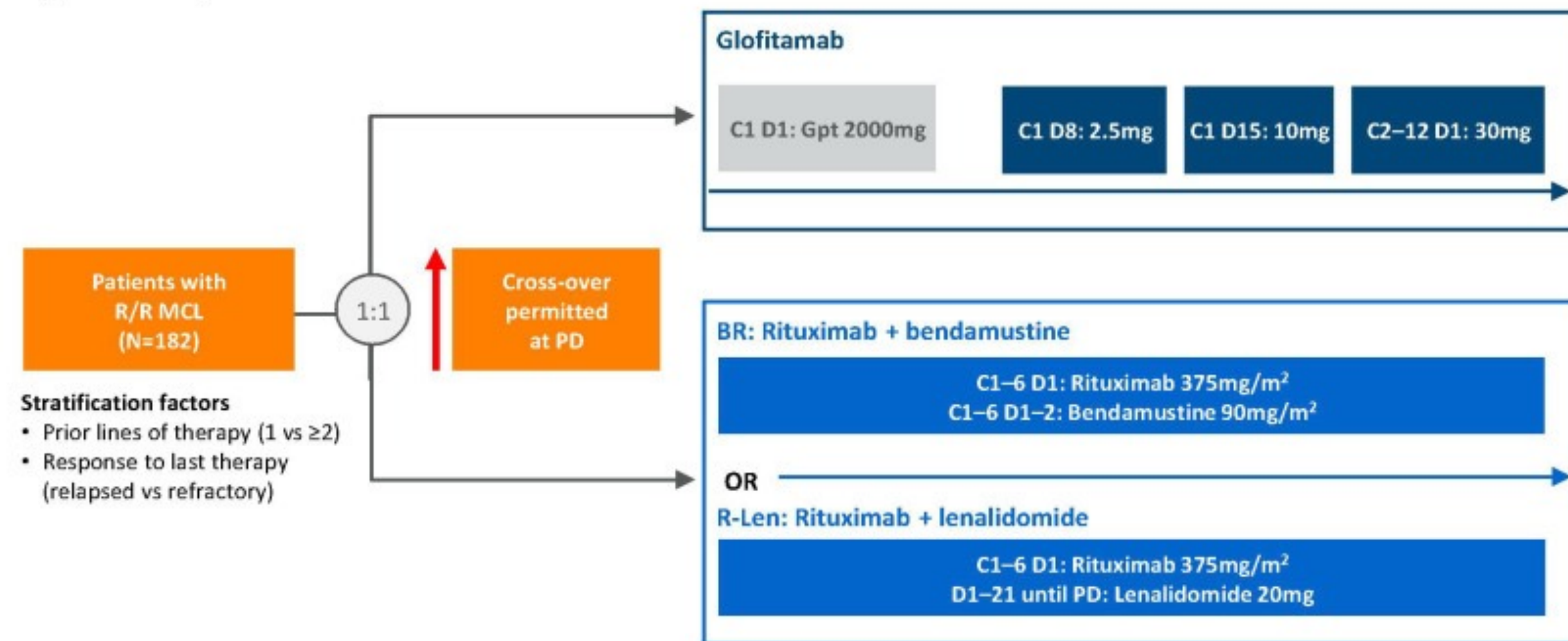


GLOBRYTE: A Phase III, Open-Label, Multicenter, Randomized Trial Evaluating Glofitamab Monotherapy in Patients with Relapsed or Refractory Mantle Cell Lymphoma

MD01-01_I01_PFIL06



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 failure to achieve a partial response or complete response to the last regimen.

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)**



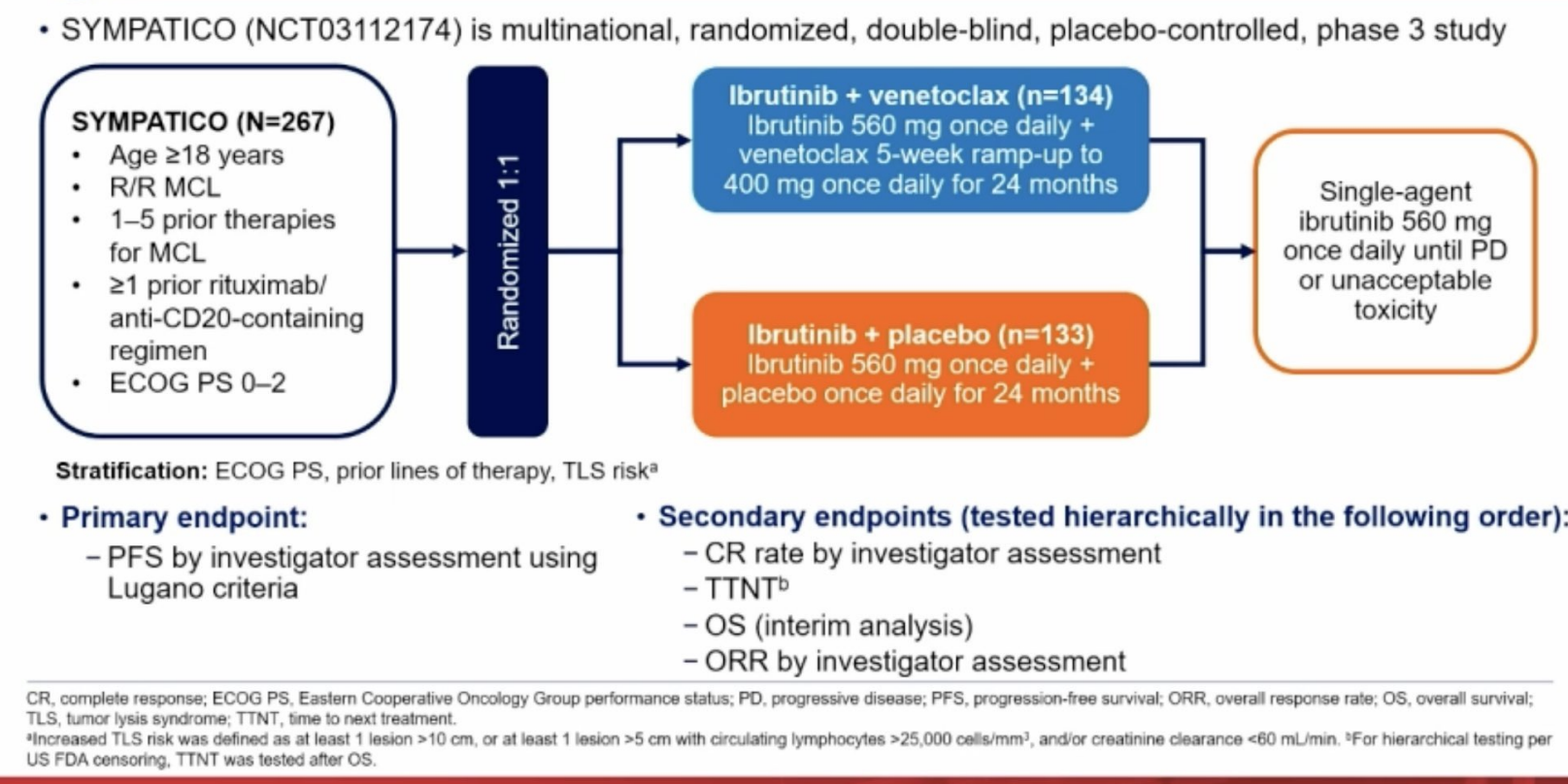


Ibrutinib plus venetoclax in relapsed or refractory mantle cell lymphoma (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

Michael Wang, Wojciech Jurczak, Marek Trnieny, 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



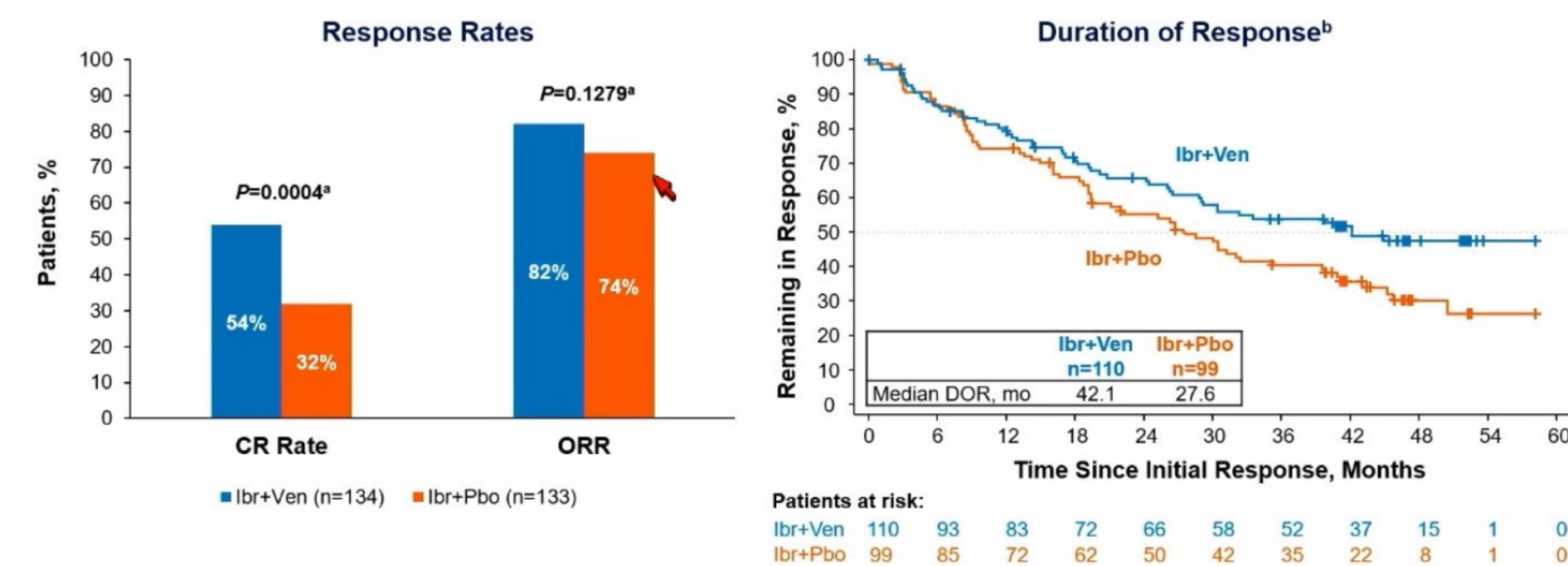
SYMPATICO Study Design



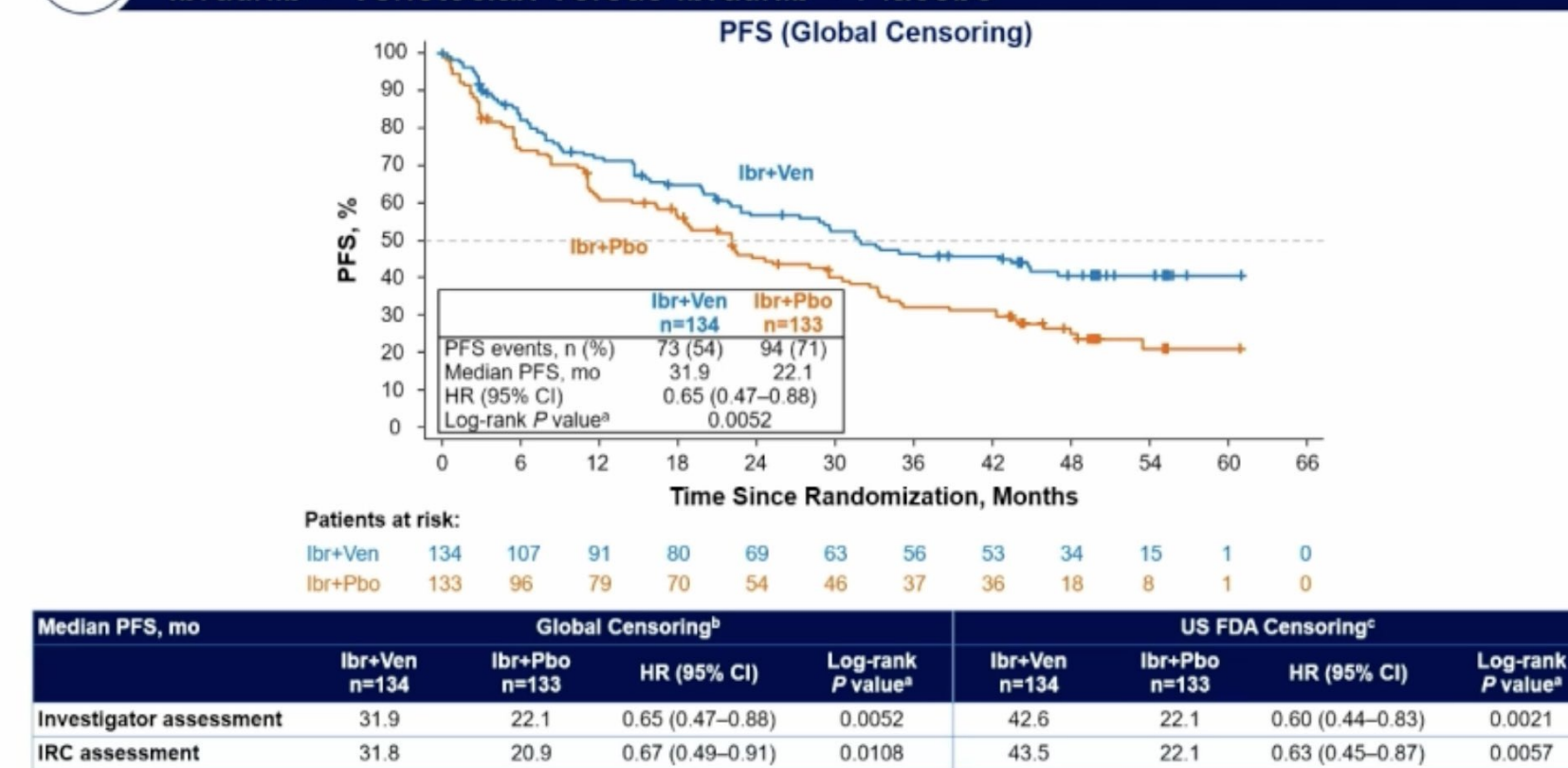
Novel BTK Inhibitor Platforms: Is Rechallenge a Viable Option?



CR Rate Was Significantly Improved With Ibrutinib + Venetoclax



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



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]). ^bCensoring at last non-PD assessment for patients without PD or death. ^cPatients 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.

Michael Wang, et al. Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study. *Blood*, Volume 142, Supplement 2, 2023, Page LBA-2



The young side of LYMPHOMA

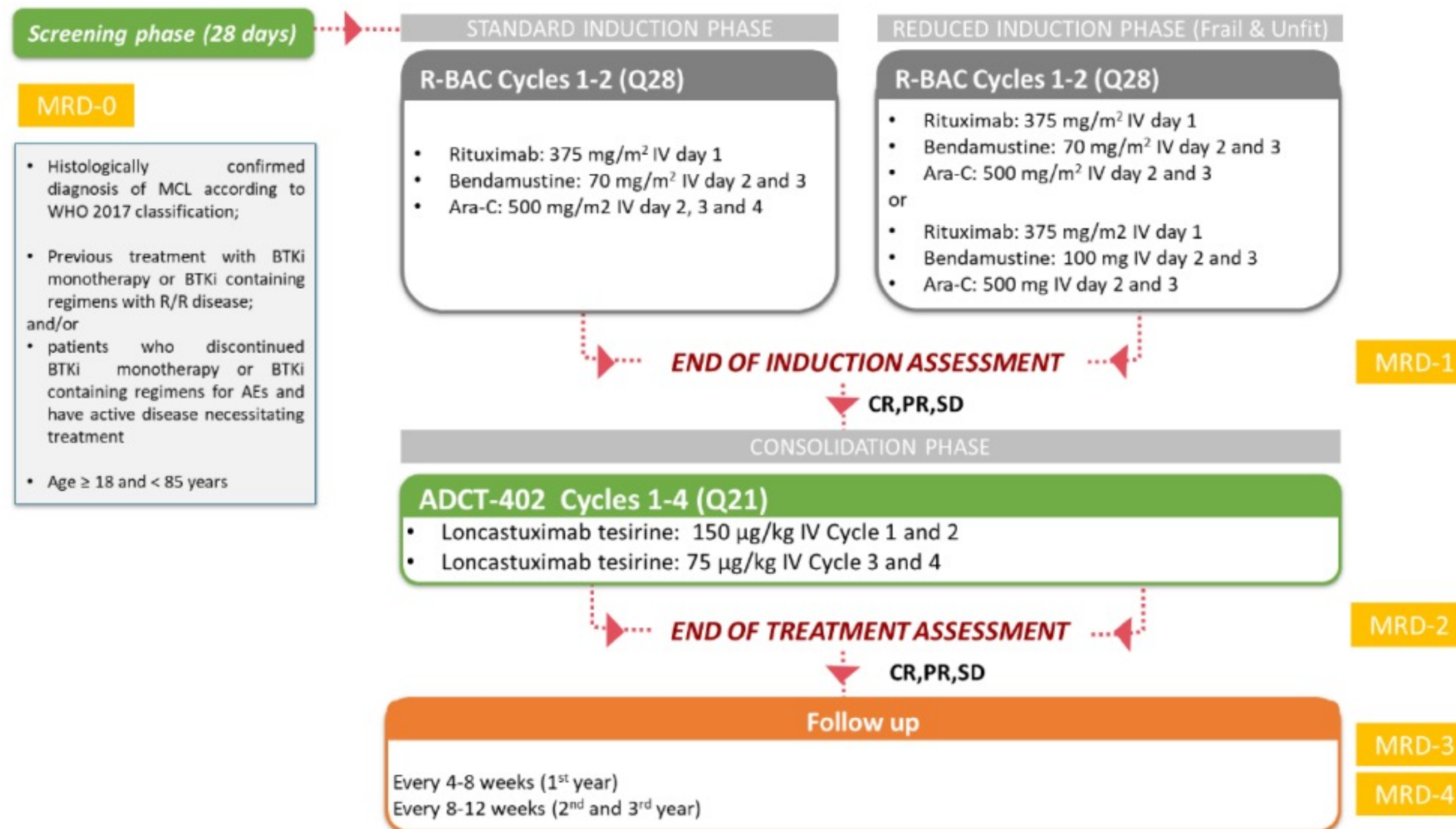
gli under 40 a confronto



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

STUDY COORDINATORS *Marco Ladetto*
Carlo Visco

Verona, 26-27 settembre 2025

Quale combinazione terapeutica è stata studiata molto recentemente nei pazienti con MCL RR?

- A) Lenalidomide + Dexametasone**
- B) Rituximab + CHOP**
- C) Ibrutinib + Venetoclax**
- D) Obinutuzumab + Idelalisib**

Biol Blood Marrow Transplant 19 (2013) 625–631

Allogeneic Hematopoietic Cell Transplantation for Chemotherapy-Unresponsive Mantle Cell Lymphoma: A Cohort Analysis from the Center for International Blood and Marrow Transplant Research



Mehdi Hamadani¹, Wael Saber^{2,*}, Kwang Woo Ahn², Jeanette Carreras²,
Mitchell S. Cairo³, Timothy S. Fenske⁴, Robert Peter Gale⁵, John Gibson⁶,
Gregory A. Hale⁷, Parameswaran N. Hari², Jack W. Hsu⁸, David J. Inwards⁹,
Rammurti T. Kamble¹⁰, Anderas Klein¹¹, Dipnarine Maharaj¹²,
David I. Marks¹³, David A. Rizzieri¹⁴, Bipin N. Savani¹⁵, Harry C. Schouten¹⁶,
Edmund K. Waller¹⁷, Baldeep Wirk⁸, Hillard M. Lazarus¹⁸

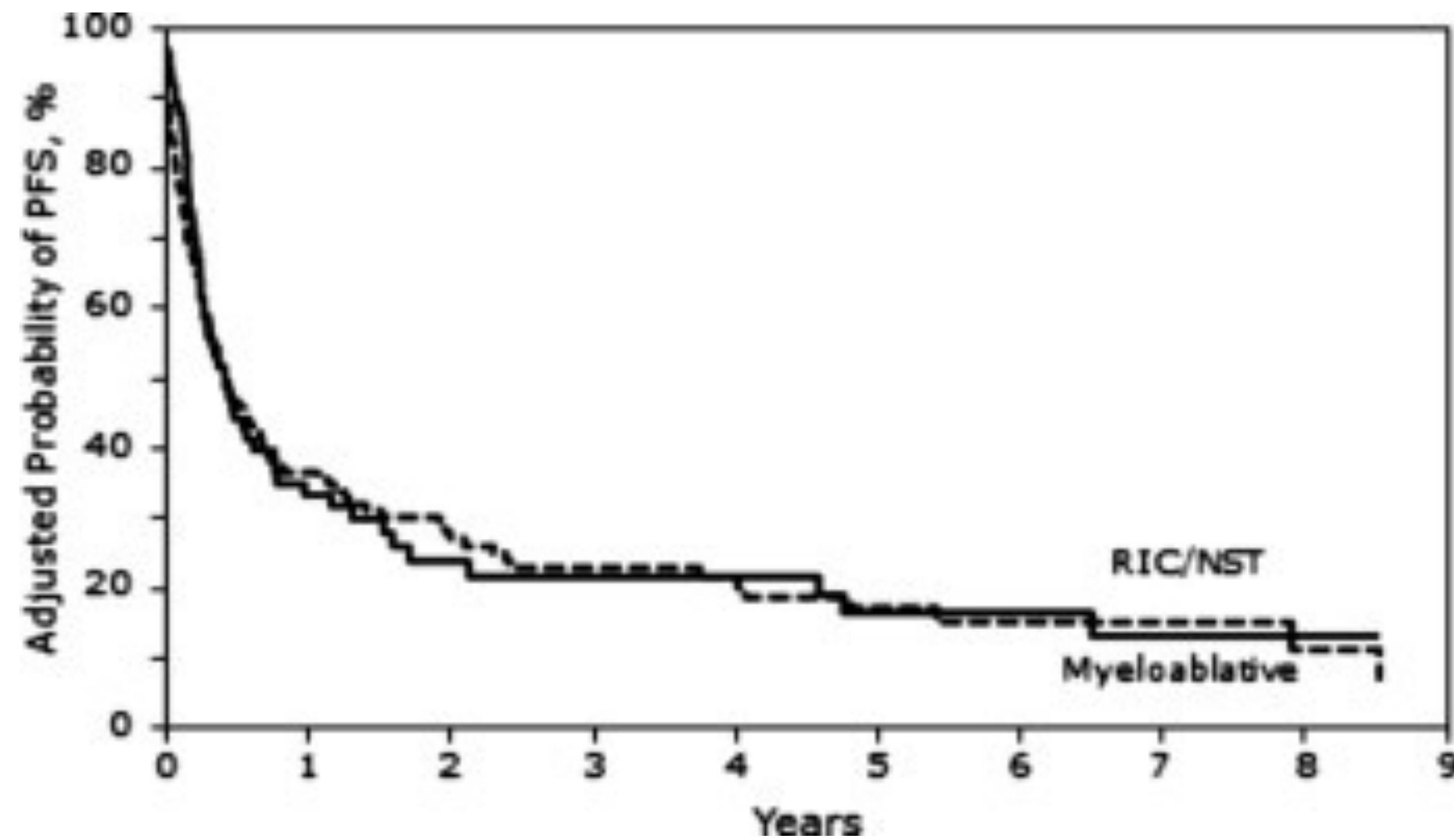
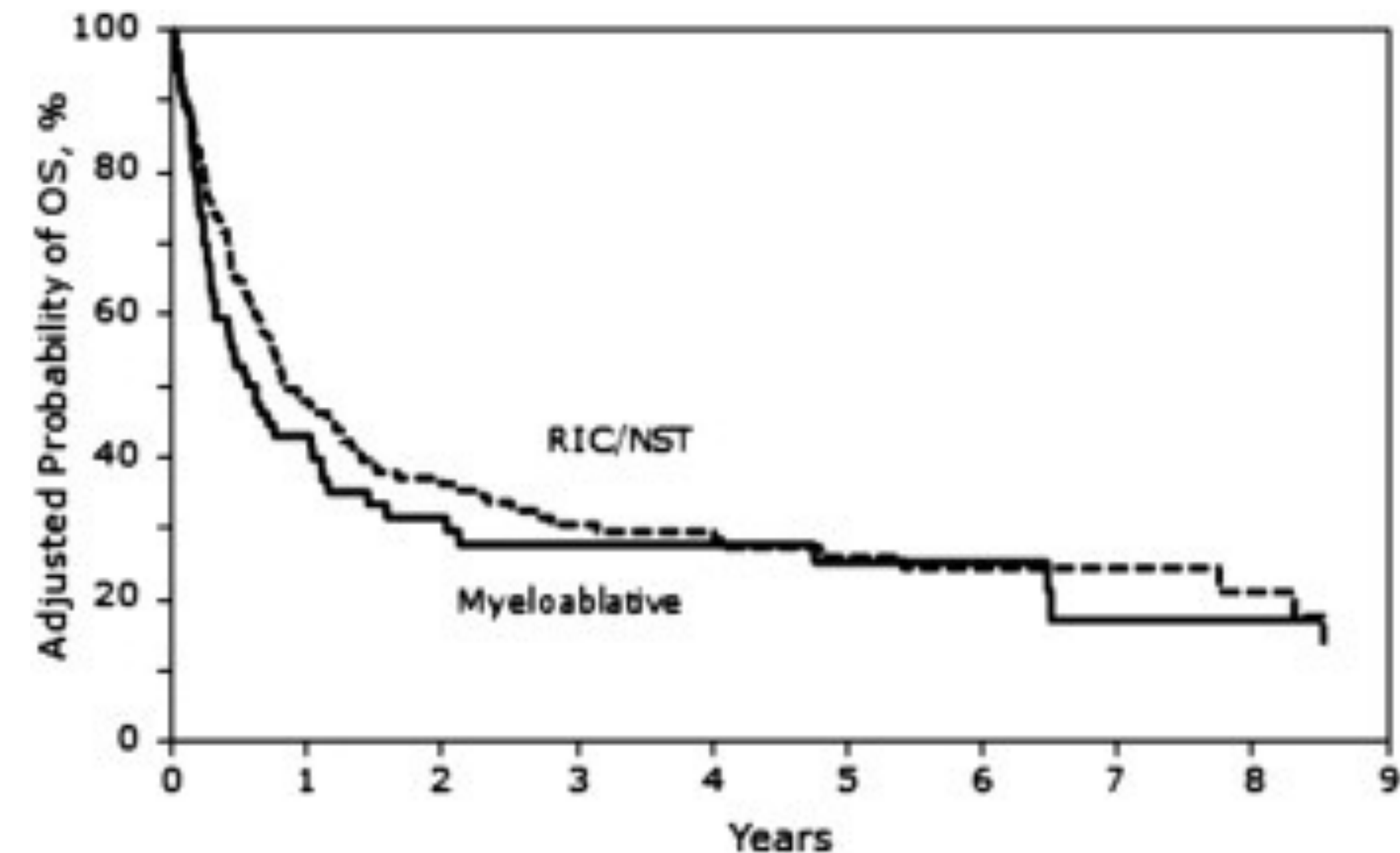


Table 3
Causes of Death

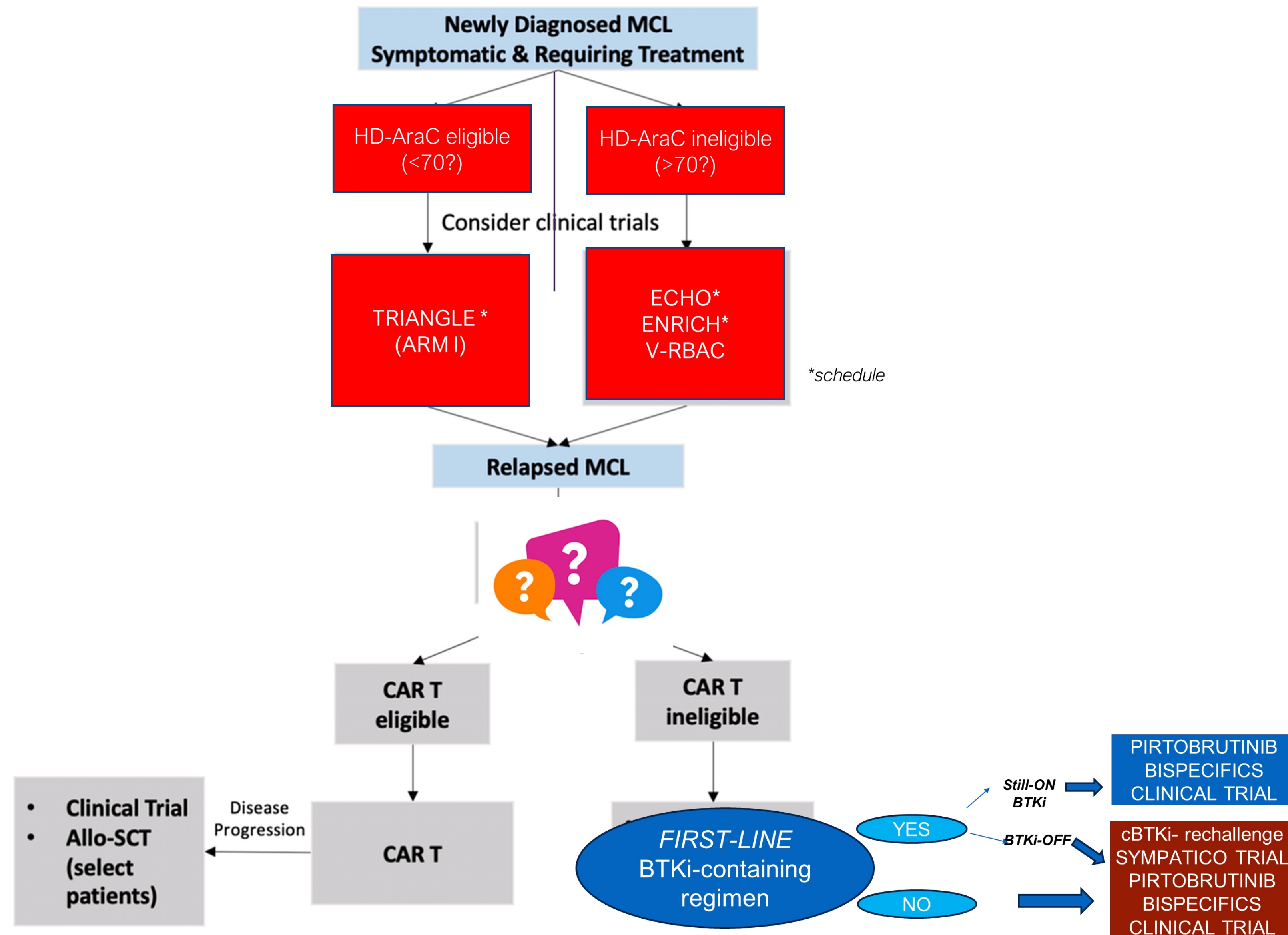
Cause of Death	MA, n (%)	RIC/NST, n (%)
Total number	56	93
Graft rejection	2 (4)	1 (1)
Infection	8 (14)	11 (12)
Pulmonary syndrome	0	2 (2)
Acute respiratory distress syndrome	0	1 (1)
GVHD	3 (5)	12 (13)
Primary disease	22 (39)	39 (42)
Organ failure	7 (13)	8 (9)
2nd malignancy	0	2 (2)
Hemorrhage	3 (5)	2 (2)
Accidental death	0	1 (1)
Vascular	0	1 (1)
Toxicity	2 (4)	3 (3)
Other cause, not specified*	9 (16)	10 (11)

* Six cases reported as "other HSCT related cause."



BTKi ERA

Personal
Opinion



CONCLUSION

- The therapeutic algorithm of MCL is rapidly evolving.
- As BTKi are moving to first line, R/R patient's management will be a critical issue.
- BTKi rechallenge shows promising activity, even after prior BTKi exposure.
- CAR-T cell therapy represents a powerful option after BTKi failure, especially in younger or fit patients, with durable responses.
- Glofitamb is emerging as a promising off-the-shelf immunotherapy, showing high response rates even in heavily pretreated patients post-BTKi.

The young side of LYMPHOMA

gli under 40 a confronto



Verona, 26-27 settembre 2025