SESSIONE 2 CAR-T nel linfoma follicolare e mantellare

ALGORITMO DI TRATTAMENTO NEL LINFOMA MANTELLARE

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Università di Torino

CAR-T:

e la storia continua... migliorando

Milano, 6 febbraio 2025

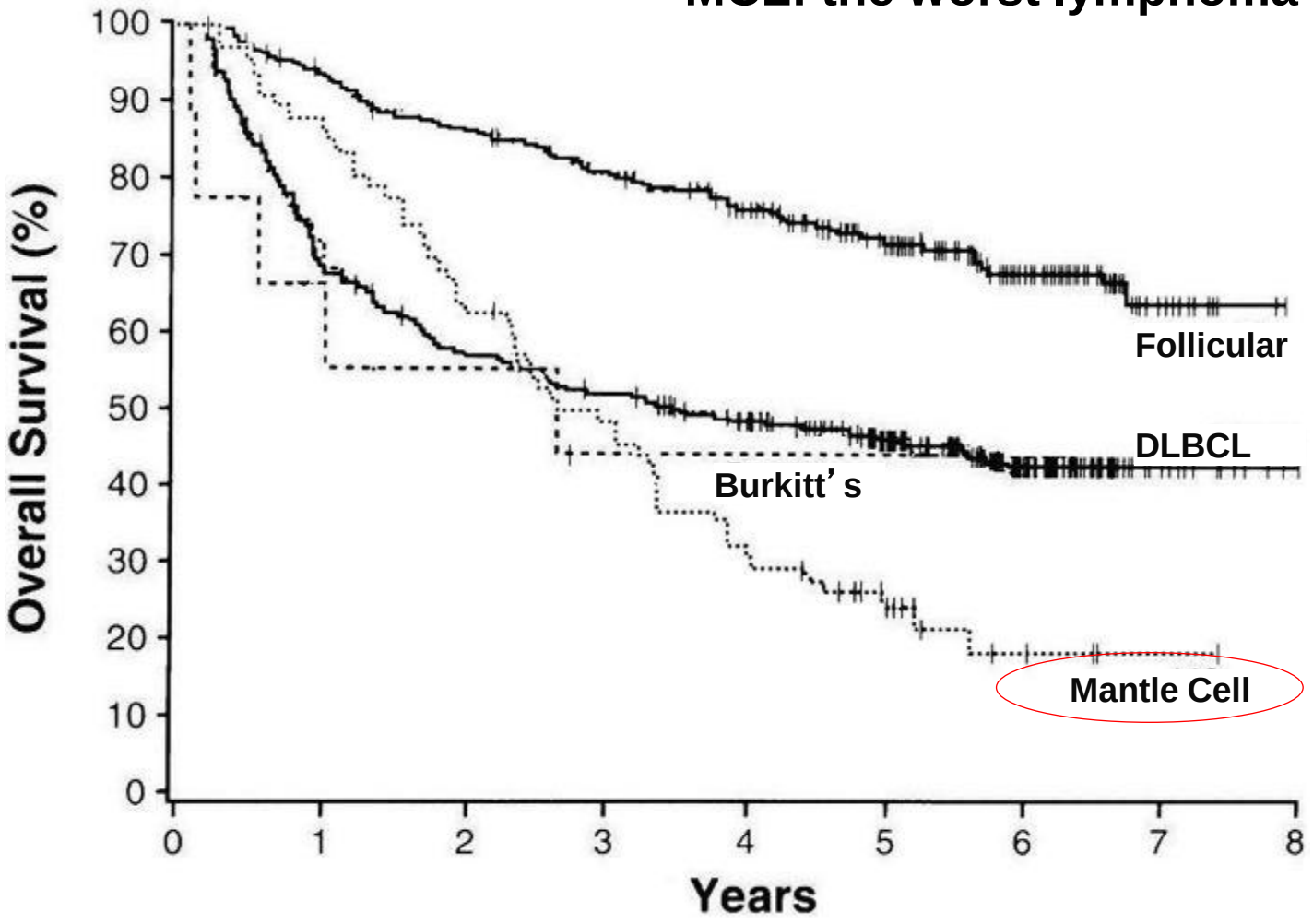
Starhotels E.C.HO.

Disclosures of Simone Ferrero

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other (travel expenses)
Janssen	x		x		x	x	
EUSA Pharma			x		x	x	
Morphosys	x						
Incyte	x					x	
Gilead	x				x		
Abbvie			x			x	
Roche					x	x	
Eli Lilly					x		x
Astra Zeneca						x	
Gentili					x		
Italfarmaco						x	
Sandoz			x		x		
Beigene					x		
Recordati			x		x	x	
Novartis					x		x
Takeda							x

NHL: clinical outcome in the **Nineties**

MCL: the worst lymphoma to have?



The International Lymphoma Study Group. Blood 1997

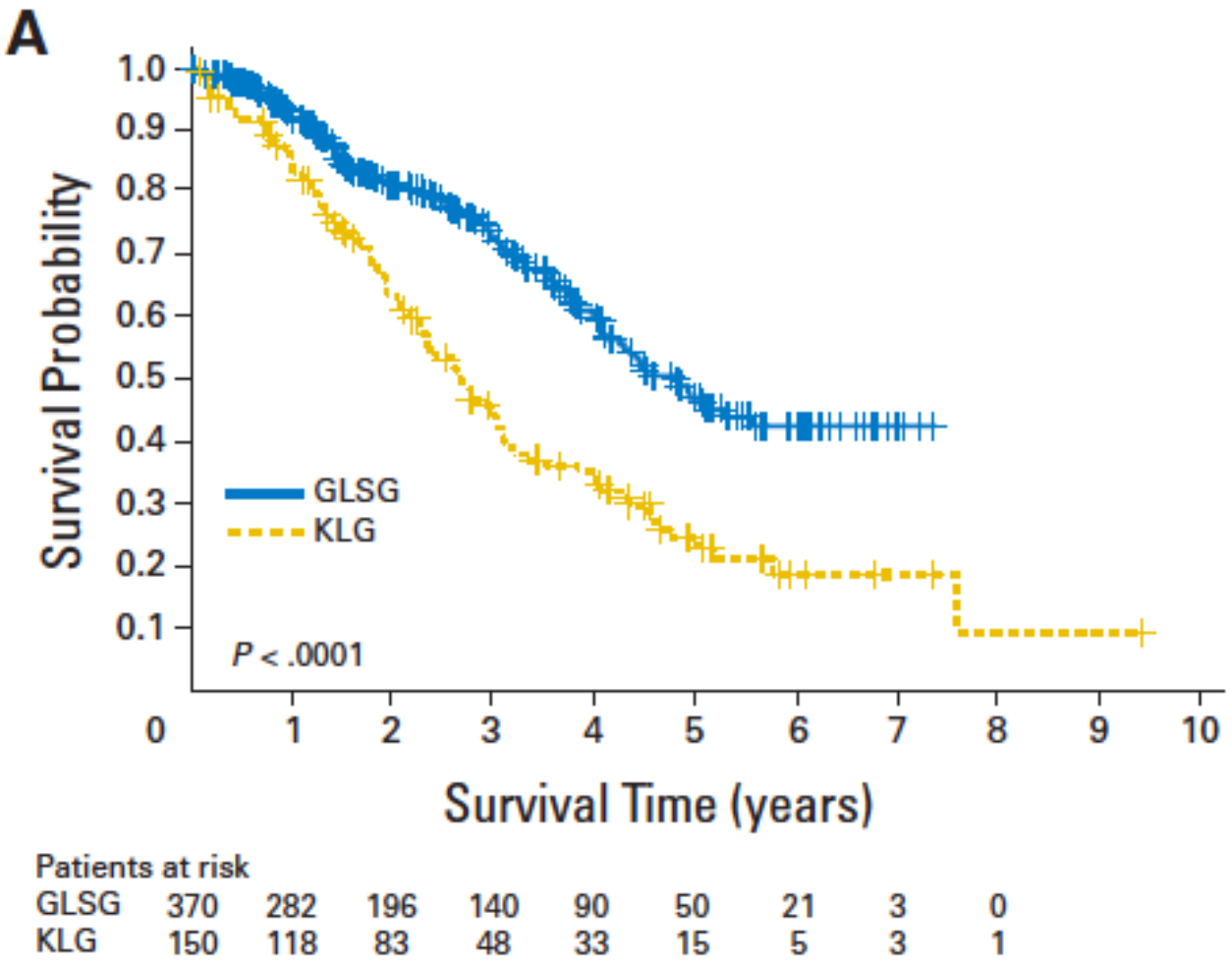
MCL: **improved OS** thanks to rituximab, high-dose ara-c and ASCT

VOLUME 27 · NUMBER 4 · FEBRUARY 1 2009

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

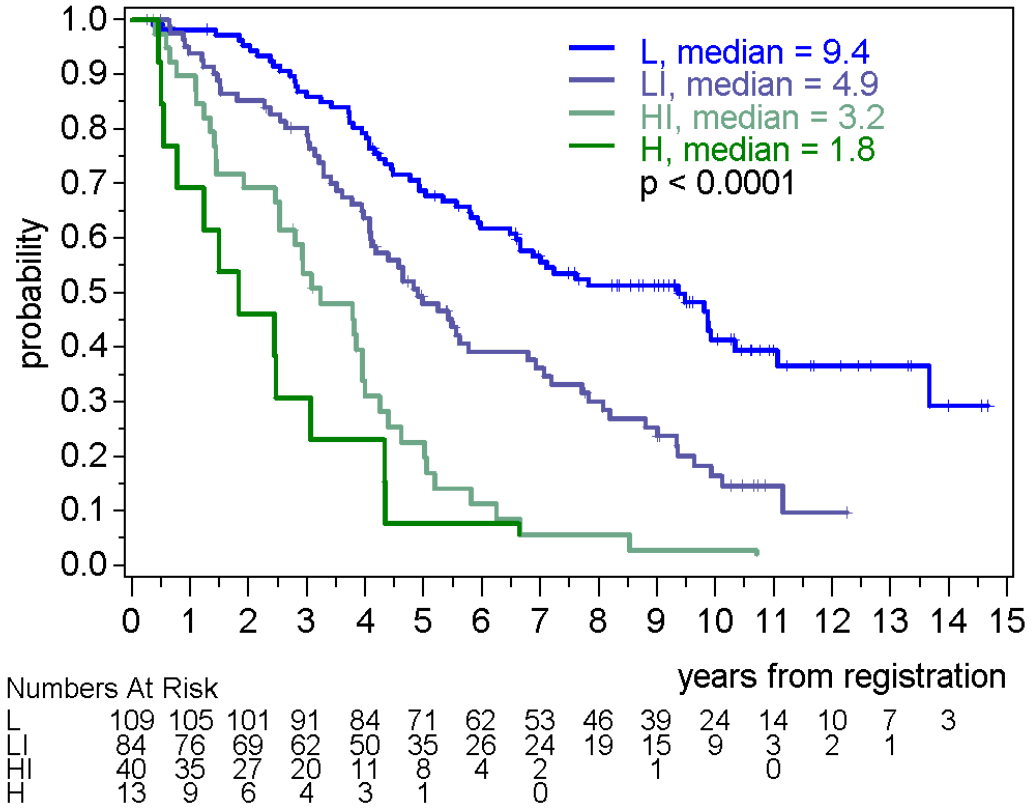
Improvement of Overall Survival in Advanced Stage Mantle Cell Lymphoma

Annina Herrmann, Eva Hoster, Thomas Zwingers, Günter Brittinger, Marianne Engelhard, Peter Meusers, Marcel Reiser, Roswitha Forstpointner, Bernd Metzner, Norma Peter, Bernhard Wörmann, Lorenz Trümper, Michael Pfreundschuh, Hermann Einsele, Wolfgang Hiddemann, Michael Unterhalt, and Martin Dreyling

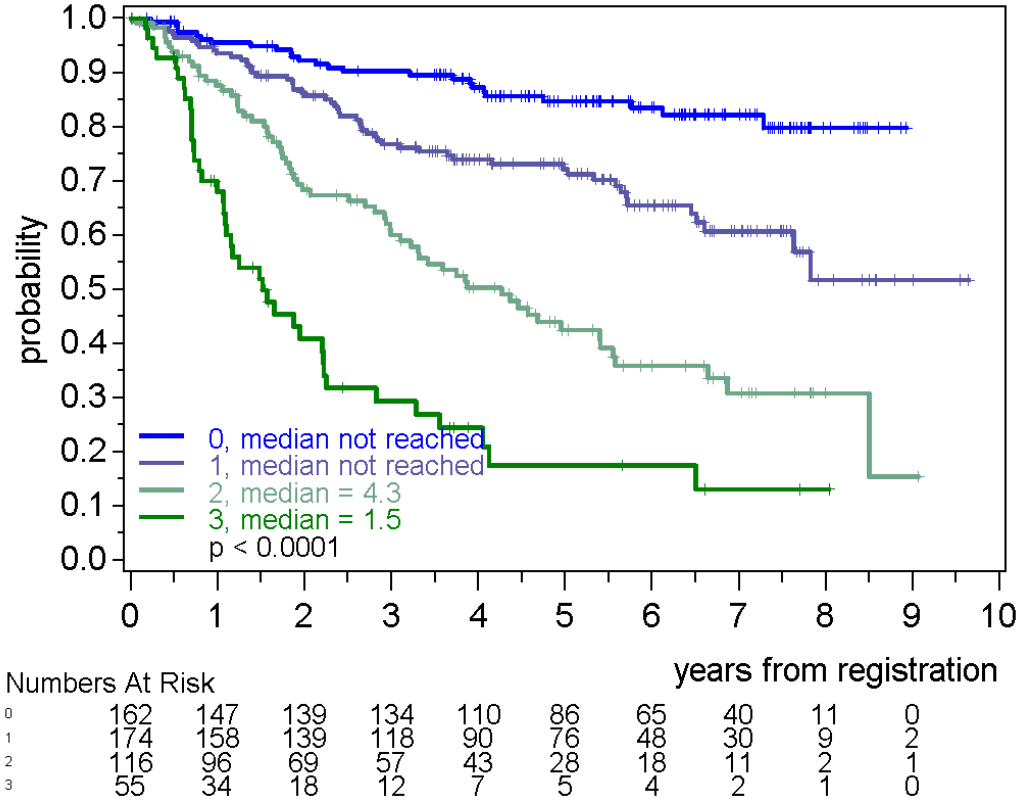


MCL is an heterogeneous disease (**clinics**) -> MIPI-c

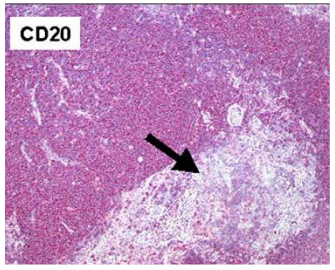
GLSG1996/2000

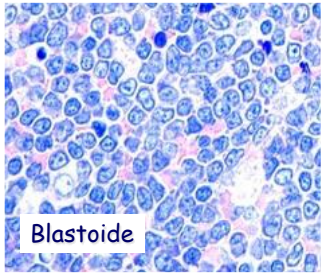


MCL Younger & Elderly



Points	Age, y	ECOG	LDHULN	WBC, 10^9/L
0	<50	0-1	<0.67	< 6.700
1	50-59	—	0.67-0.99	6.700-9.999
2	60-69	2-4	1.000 -1.49	1.000-14.999
3	≥70	—	≥1.5000	≥15000



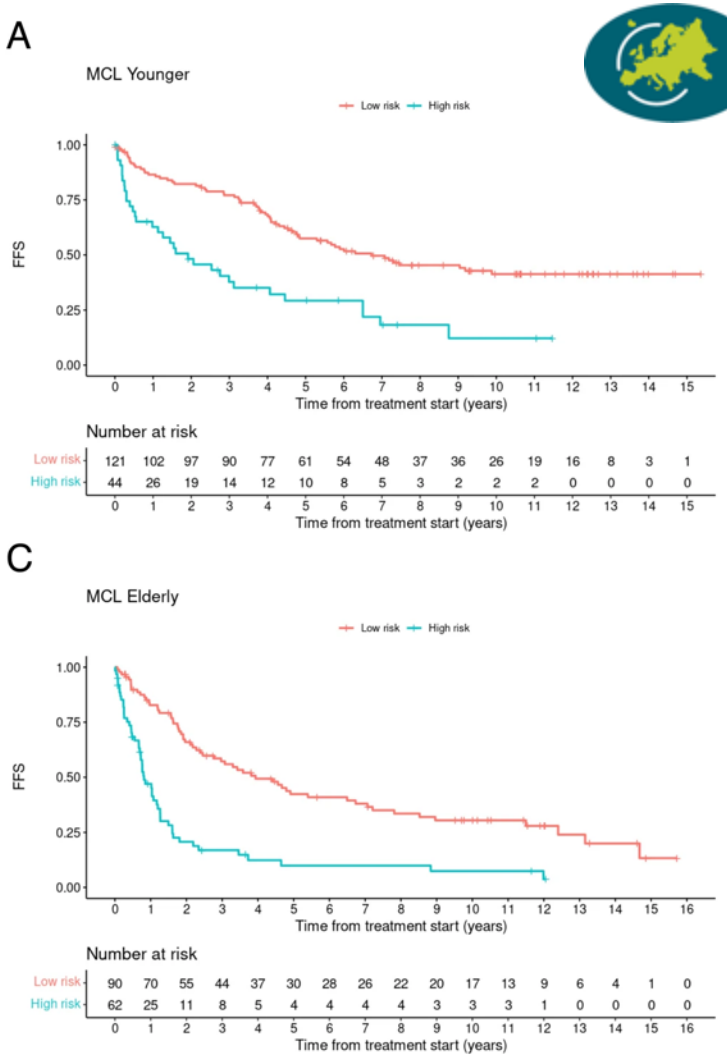


Hoster E. et al, JCO2014

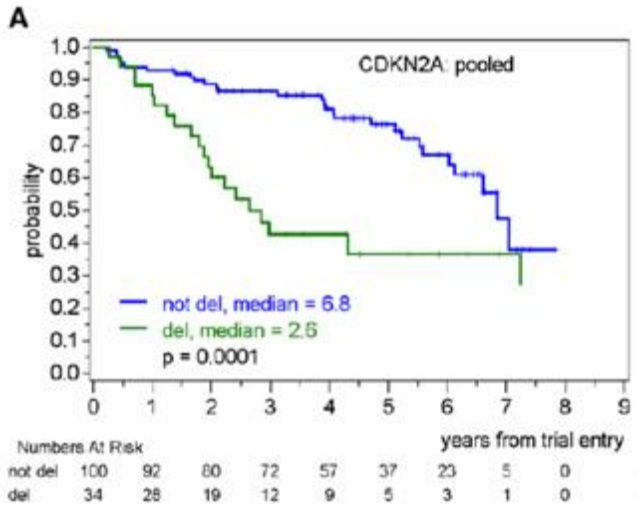
MCL is an heterogeneous disease (**biology**)

Clinical outcome of Mantle Cell Lymphoma patients with high-risk disease (high-risk MIPI-c or high p53 expression)

Gabriel Scheubeck[1✉], Linmiao Jiang[2], Olivier Hermine[3], Hanneke C. Kluin-Nelemans[4], Christian Schmidt[1], Michael Unterhalt[1], Andreas Rosenwald[5], Wolfram Klapper[6], Andrea Evangelista[7], Marco Ladetto[8], Mats Jerkeman[9], Simone Ferrero[10], Martin Dreyling[1,11] and Eva Hoster[1,2,11]

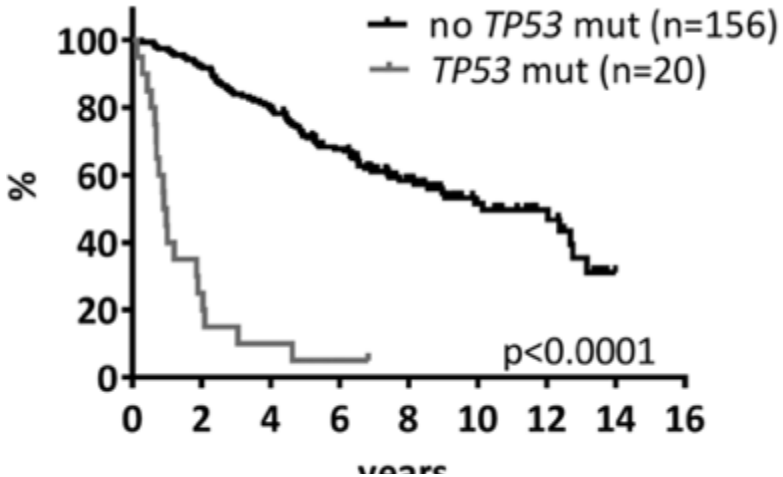


EUROPEAN MCL NETWORK



NORDIC LYMPHOMA GROUP
DEDICATED TO PROMOTING RESEARCH IN TREATMENT, BIOLOGY AND EPIDEMIOLOGY OF MALIGNANT LYMPHOMAS IN THE NORDIC COUNTRIES

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



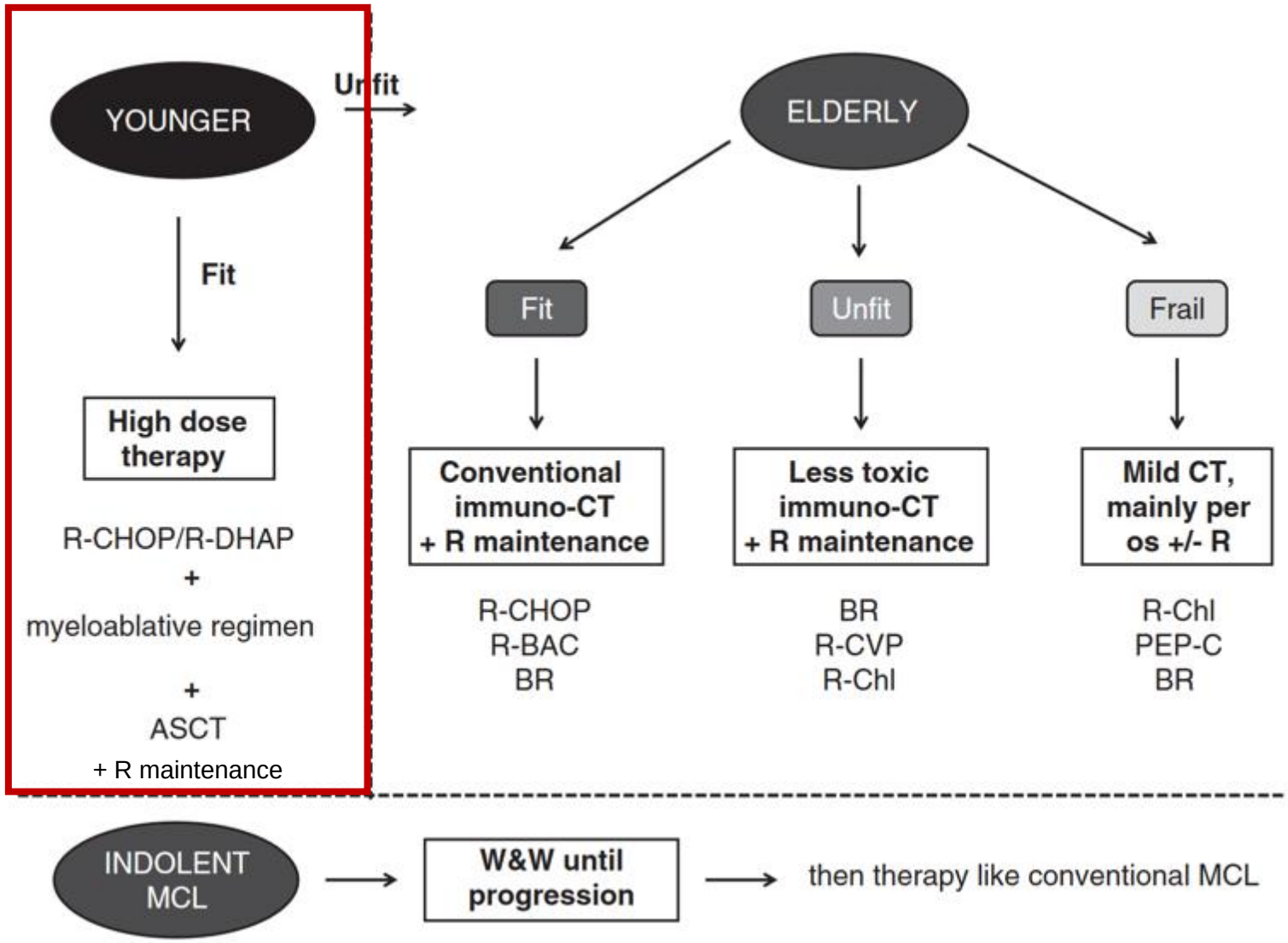
blood
2015 126: 604-611
doi:10.1182/blood-2015-02-628792 originally published online May 28, 2015

European MCL Network

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

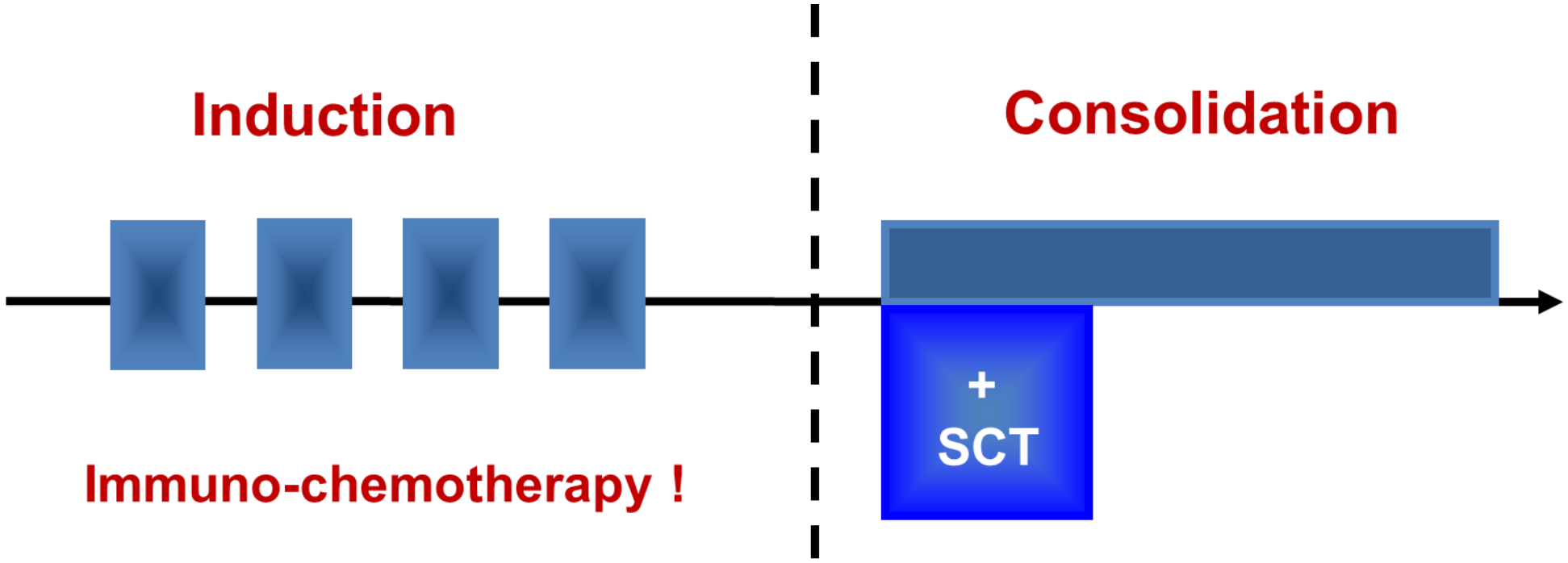
Marie-Hélène Delfau-Larue, Wolfram Klapper, Françoise Berger, Fabrice Jardin, Josette Briere, Gilles Salles, Olivier Casasnovas, Pierre Feugier, Corinne Haioun, Vincent Ribrag, Catherine Thieblemont, Michael Unterhalt, Martin Dreyling, Elizabeth Macintyre, Christiane Pott, Olivier Hermine and Eva Hoster

Therapeutic algorithm for first-line MCL patients: **younger patients**



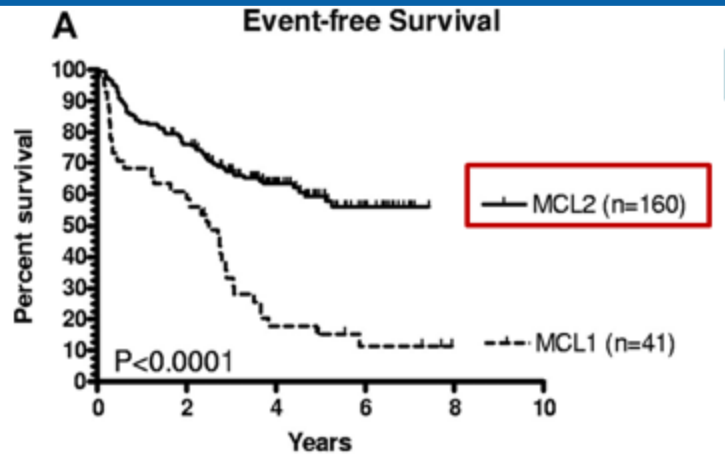
Modified from M Dreyling, S Ferrero and O Hermine, Leukemia 2014

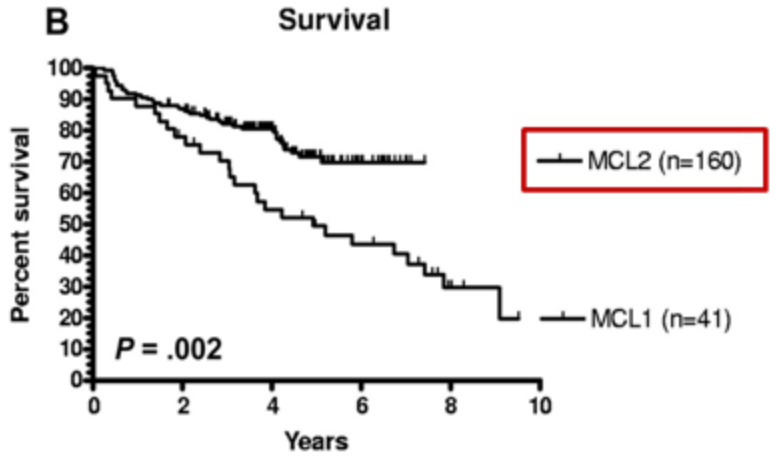
Therapeutic strategies in MCL **younger fit patients** (< 65 y.o)

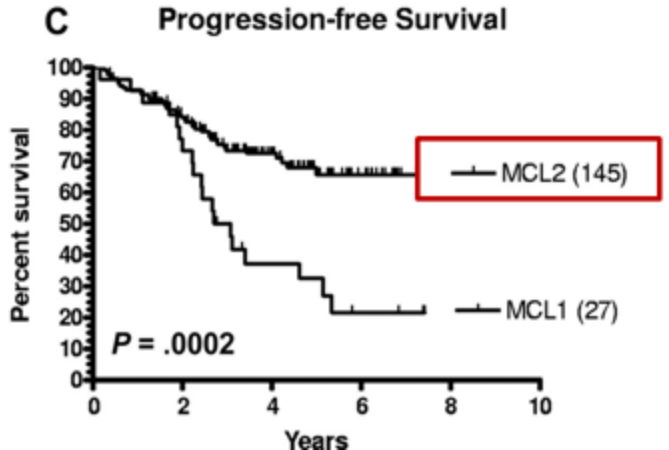


+ maintenance….

Nordic Lymphoma Study Group
MCL1 vs MCL2





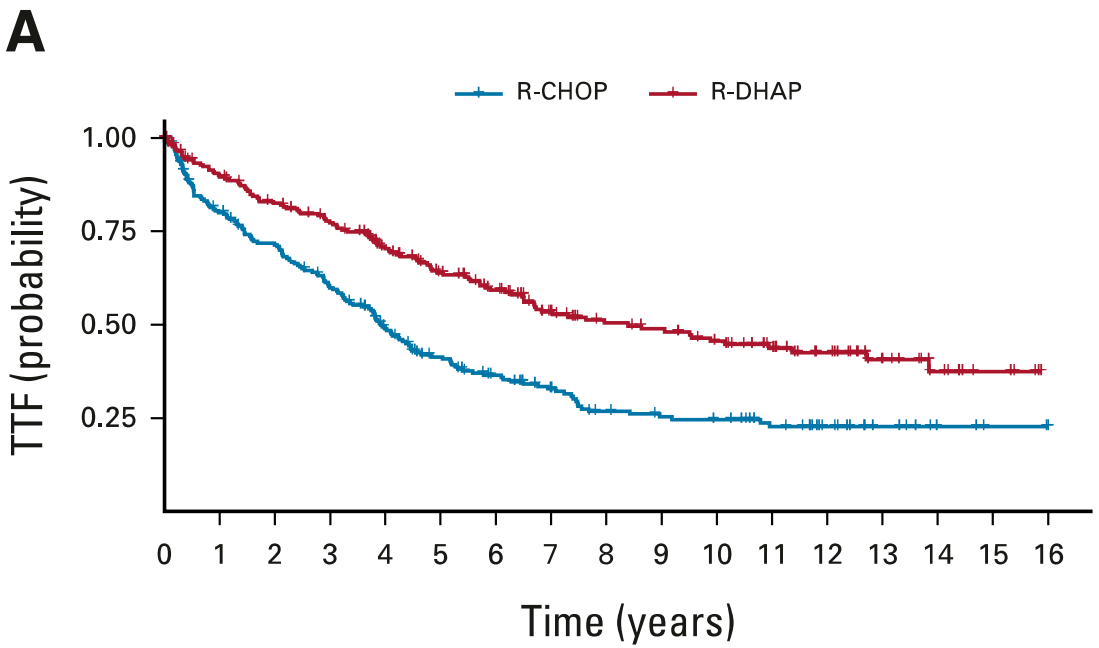


	No Ara-C	R-Ara-C
NORDIC MCL PROTOCOL #	MCL1 (1996-2000) (-CHOP⇒ASCT)	MCL2 (2000-2006)
Number of cases included	41	160
ORR pre-transplant	76%	96%
CR/CRu pre-transplant	27%	54%

Geisler et al, Blood. 2008

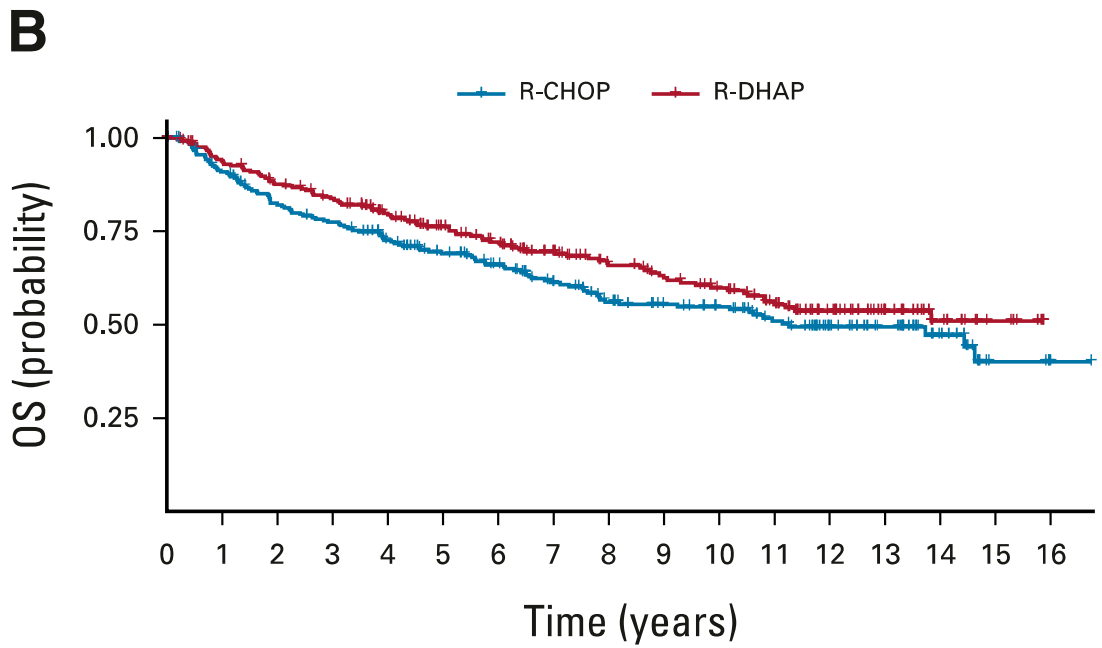
Intensive schemes including ASCT in MCL patients

MCL Network Younger Trial



No. at risk:

R-CHOP	234	178	156	129	100	77	62	50	38	34	32	24	16	9	4	2	1
R-DHAP	232	194	175	160	135	115	100	77	65	61	53	42	32	19	11	5	0

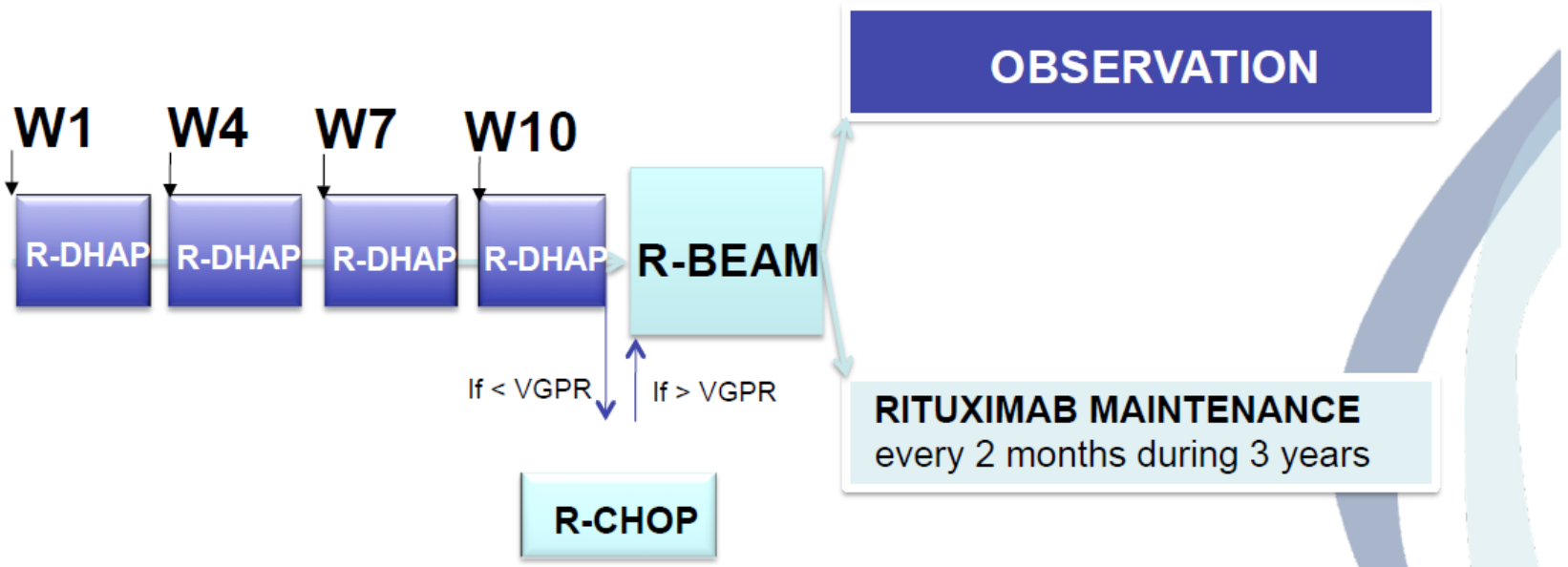


No. at risk:

R-CHOP	249	219	194	182	163	145	130	111	94	85	78	64	46	35	19	5	2
R-DHAP	248	227	209	196	174	155	141	121	103	94	85	70	51	31	16	7	0

Hermine O, et al. Lancet 2016: JCO 2023

Rituximab maintenance after R-DHAP and ASCT in young untreated MCL: **LyMa trial**



R-DHAP: Rituximab 375mg/m2; aracytine 2g/m2 x2 IV 3 hours injection 12hours interval; dexamethasone 40mg d1-4; Cisplatin 100mg/m2 d1 (or oxaliplatin or carboplatin)

R-BEAM: Rituximab 500mg/m2 d-8; BCNU 300mg/m2 d-7; Etoposide 400mg/m2/d d-6 to -3; aracytine 400mg/m2/d d-6 to d-3; melphalan 140mg/m2 d-2

Le Gouill S, et al. NEJM 2017

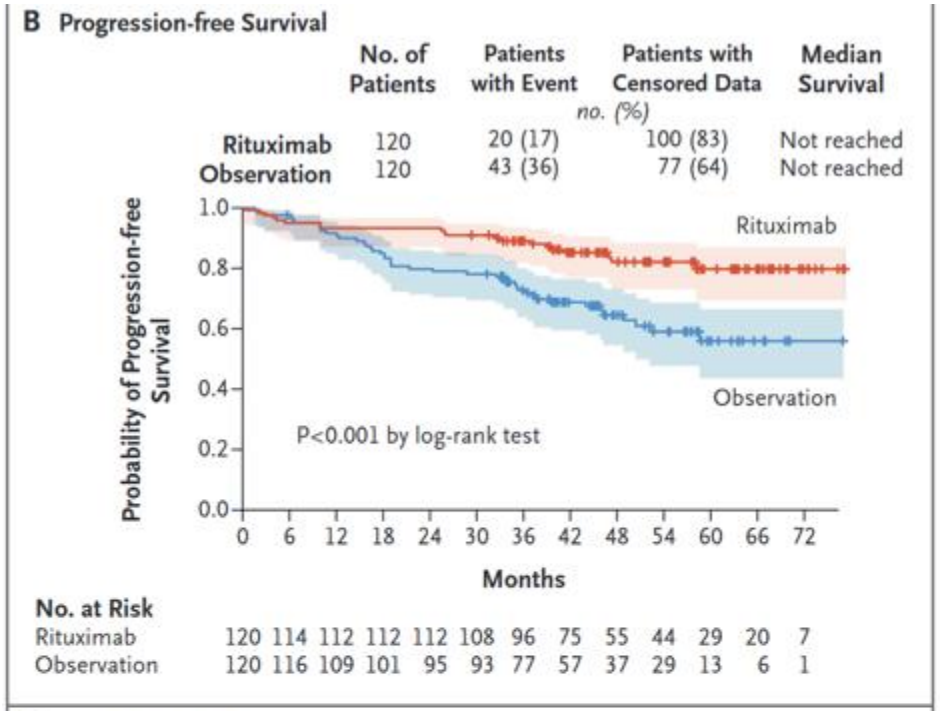
The NEW ENGLAND JOURNAL of MEDICINE
N ENGL J MED 377;13 NEJM.ORG SEPTEMBER 28, 2017

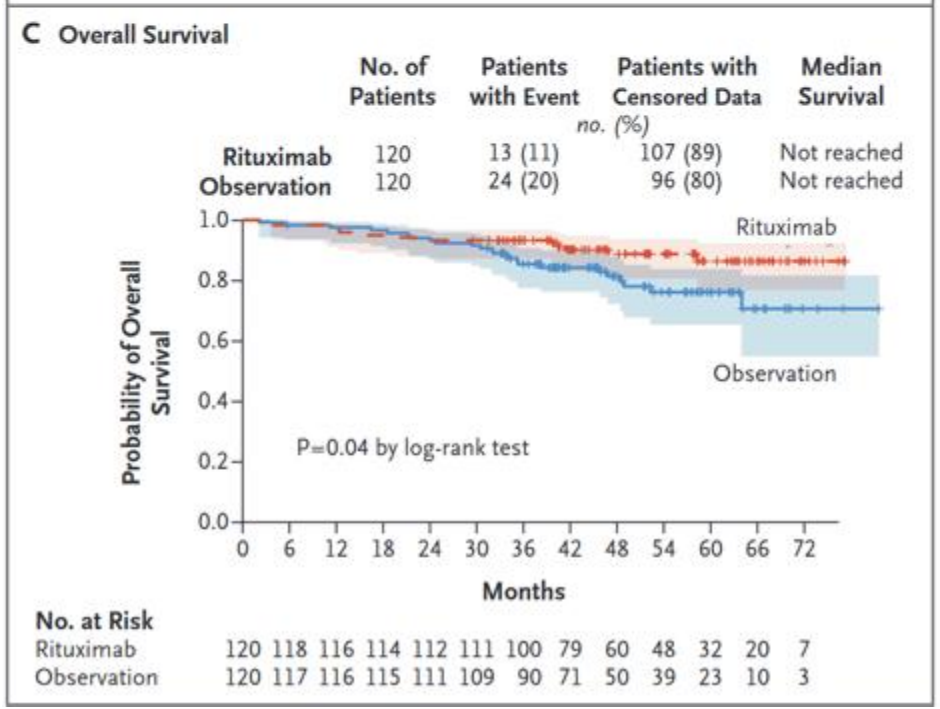
ORIGINAL ARTICLE

Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma

S. Le Gouill, C. Thieblemont, L. Oberic, A. Moreau, K. Bouabdallah, C. Dartigeas, G. Damaj, T. Gastinne, V. Ribrag, P. Feugier, O. Casasnovas, H. Zerazhi, C. Haioun, H. Maisonneuve, R. Houot, F. Jardin, E. Van Den Neste, O. Tournilhac, K. Le Dû, F. Morschhauser, G. Cartron, L.-M. Fornecker, D. Canioni, M. Callanan, M.C. Béné, G. Salles, H. Tilly, T. Lamy, R. Gressin, and O. Hermine, for the LYSA Group*

- 299 patients younger than 66 years of age enrolled at MCL diagnosis
- Overall response rate = 89%,
- Complete response rate = 77%.
- ASCT performed in 257 patients.





Le Gouill S, et al. NEJM 2017

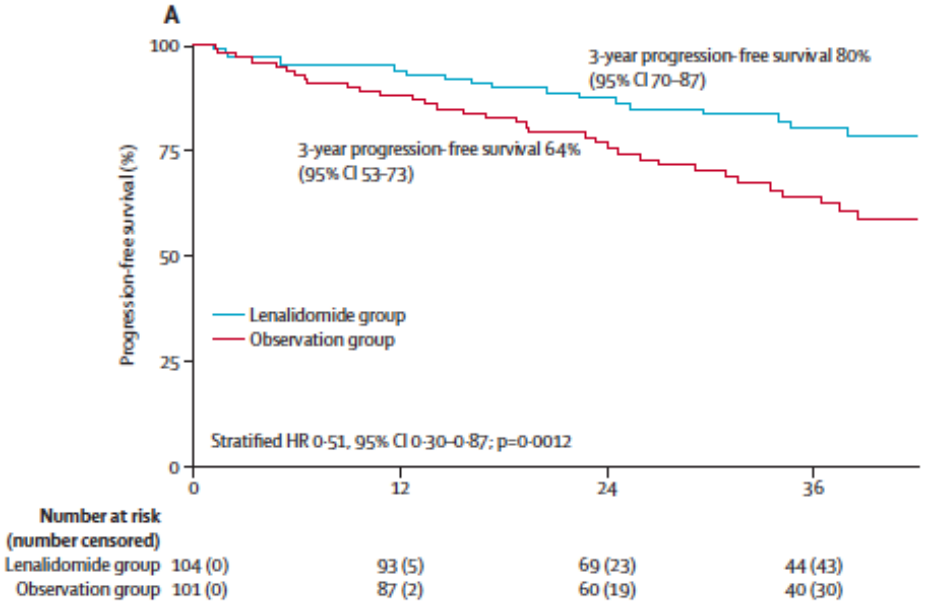
Lenalidomide maintenance after ASCT: the FIL MCL0208 phase III trial

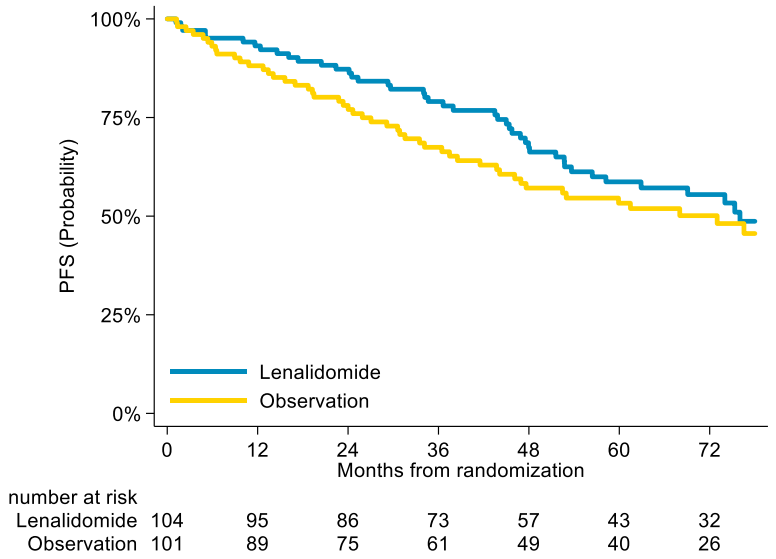
THE LANCET Haematology

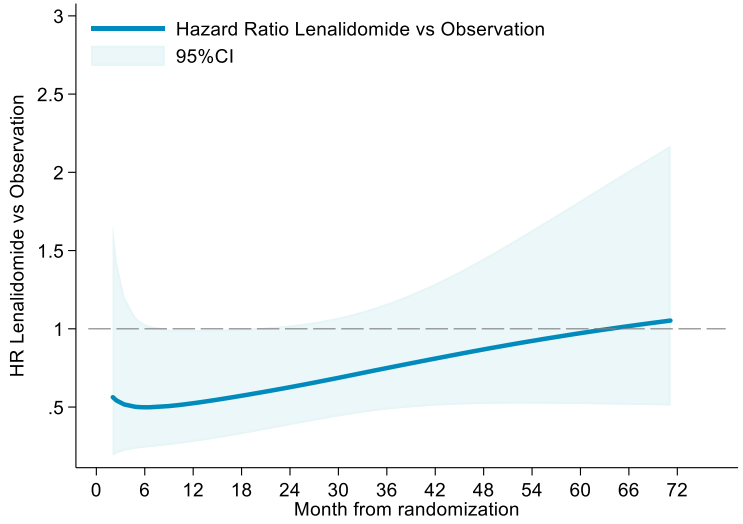
Lancet Haematol 2021; 8: e34-44

Lenalidomide maintenance after autologous haematopoietic stem-cell transplantation in mantle cell lymphoma: results of a Fondazione Italiana Linfomi (FIL) multicentre, randomised, phase 3 trial

Marco Ladetto, Sergio Cortelazzo*, Simone Ferrero, Andrea Evangelista, Michael Mian, Rita Tavarozzi, Manuela Zanni, Federica Cavallo, Alice Di Rocco, Vittorio Stefoni, Chiara Pagani, Alessandro Re, Annalisa Chiappella, Monica Balzarotti, Vittorio R Zilioli, Maria Gomes da Silva, Luca Arcaini, Anna L Molinari, Filippo Ballerini, Andrés J M Ferreri, Benedetta Puccini, Fabio Benedetti, Piero M Stefani, Franco Narni, Ivana Casaroli, Caterina Stelitano, Giovannino Ciccone, Umberto Vitolo, Maurizio Martelli*







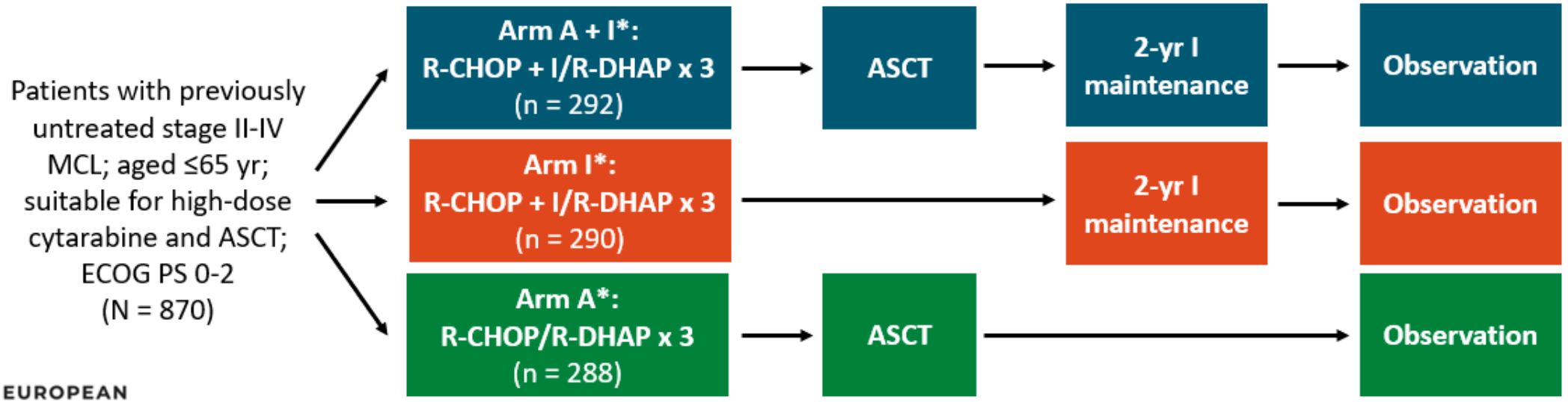
Ladetto M, et al. Lancet Haematol 2021

median follow-up: 74 months

Ladetto M, et al. EHA 2023

TRIANGLE: phase III Trial of Ibrutinib + CIT

- Randomized, open-label, 3-arm phase III trial



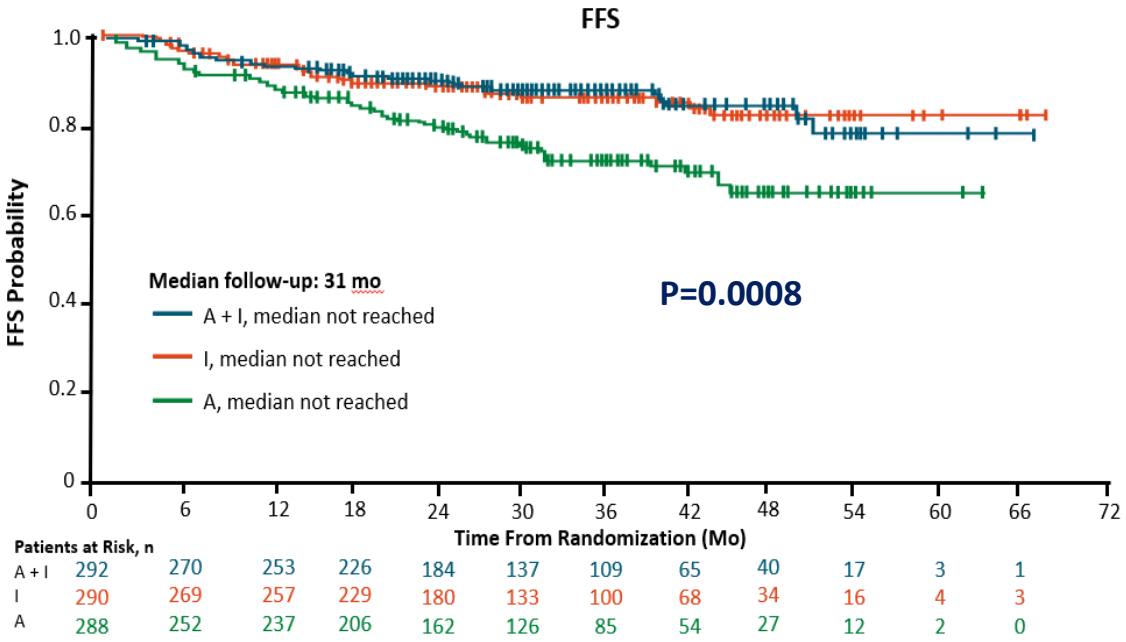
*R maintenance was added following national guidelines in all 3 arms (arm A + I: 57%; arm I: 54%; arm A: 58%).

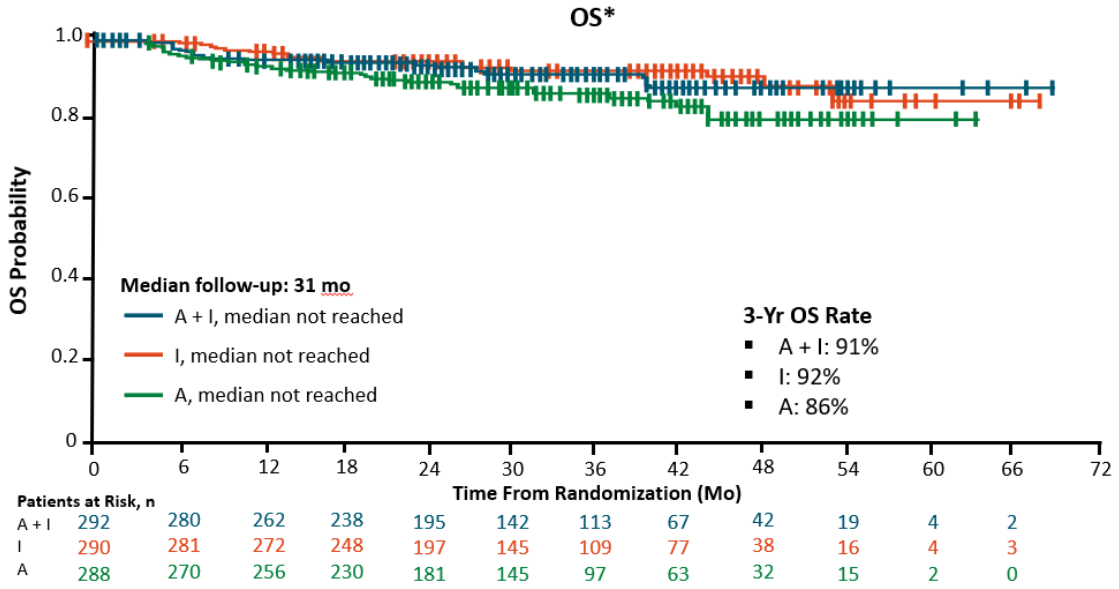
Primary endpoint: FFS

Secondary endpoints: response rates, PFS, RD, OS, safety

Dreyling M et al., Lancet 2024

TRIANGLE trial: FFS (Primary Endpoint) and OS





Test A+I vs I ongoing

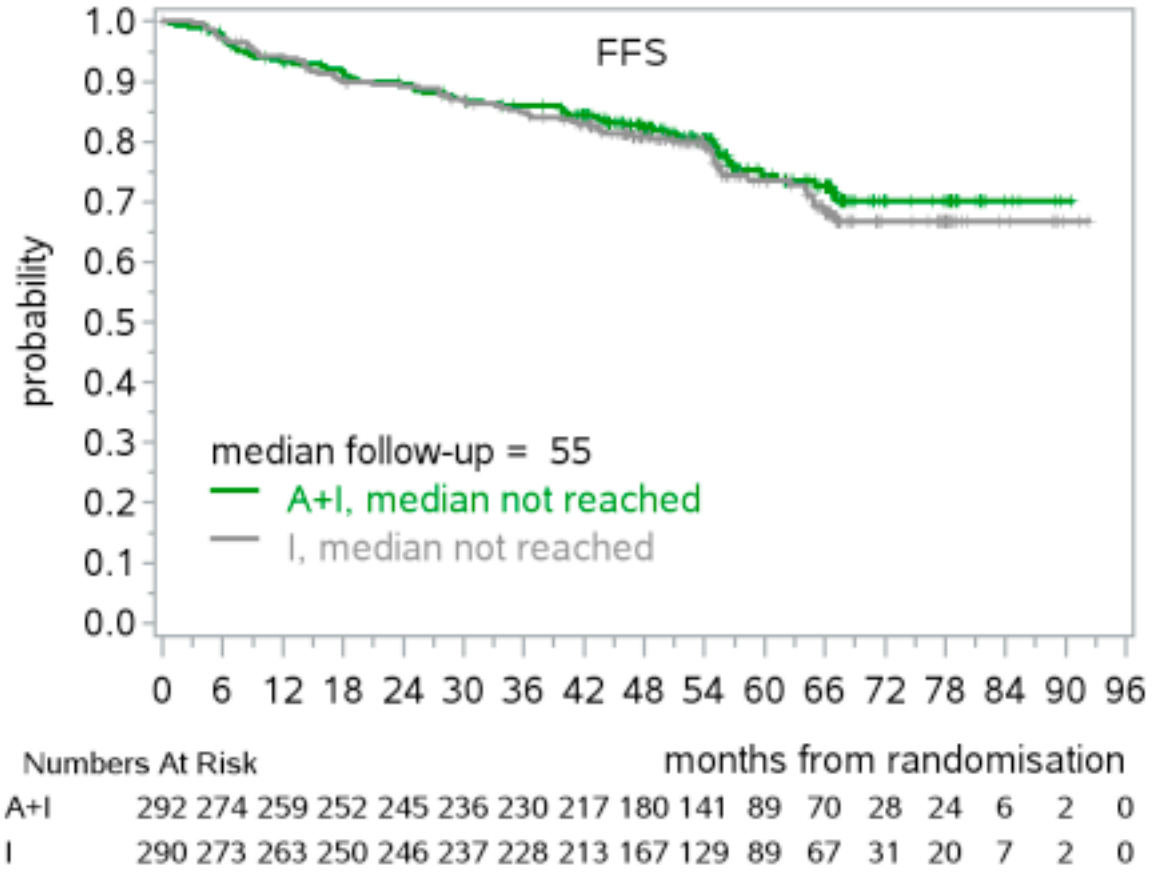
Data still premature to evaluate statistical significance for OS

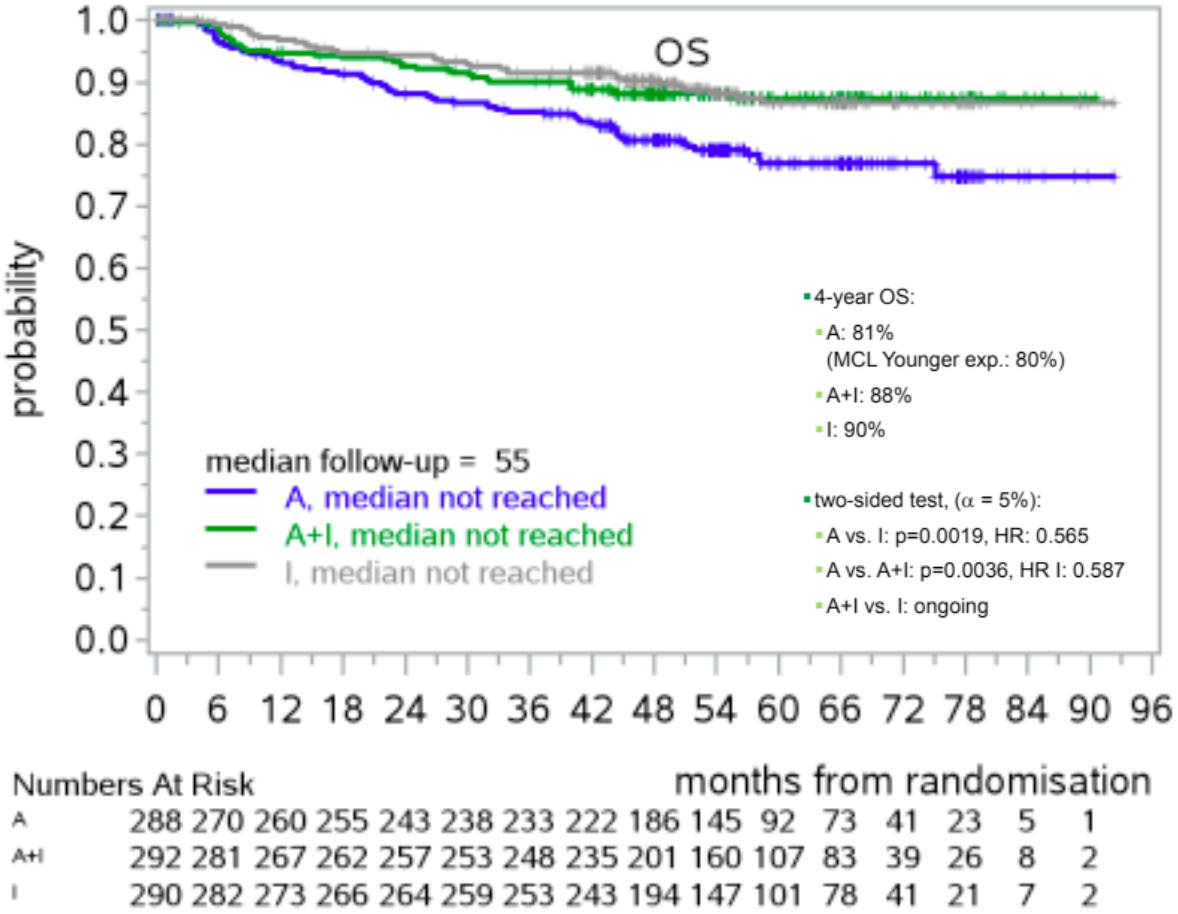
EUROPEAN MCL NETWORK

Dreyling M et al., Lancet 2024

TRIANGLE trial updated: FFS (comparison experimental arms) and OS

« […] Arm I (A+I) may represent the preferred first-line treatment in younger MCL patients […]»





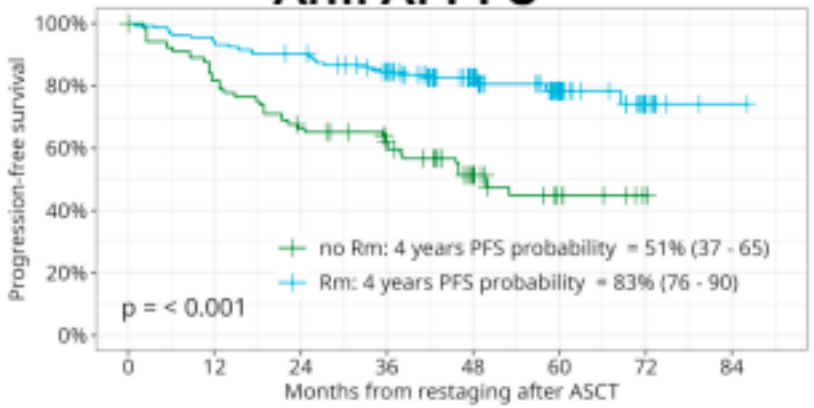
longer follow-up (from 31 to 55 months)

EUROPEAN MCL NETWORK

Dreyling M et al., ASH 2024

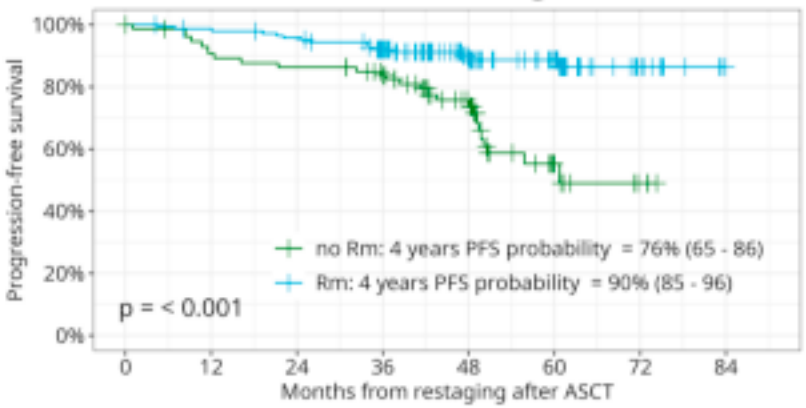
TRIANGLE trial updated: impact of rituximab maintenance

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



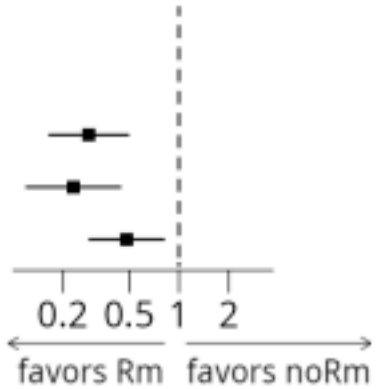
noRm group								
At risk	85.3	75.1	71.6	63.8	41	12.9	6	0
Event	0	8.1	11.5	13.5	19.5	28.7	29.7	29.7
Rm group								
At risk	151.8	146.9	142.1	125.8	85.7	63	24.5	0
Event	0	3.1	6.9	12.8	14.6	15.5	16.6	16.6

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

Endpoint PFS from end of induction/ASCT

Variables	HR (95% CI)
Adjusted for MIPI, Ki67, cytology response after induction/ASCT	
Rm vs. noRm in A	0.29 (0.17 - 0.49)
Rm vs. noRm in A+I	0.23 (0.12 - 0.44)
Rm vs. noRm in I	0.48 (0.29 - 0.81)



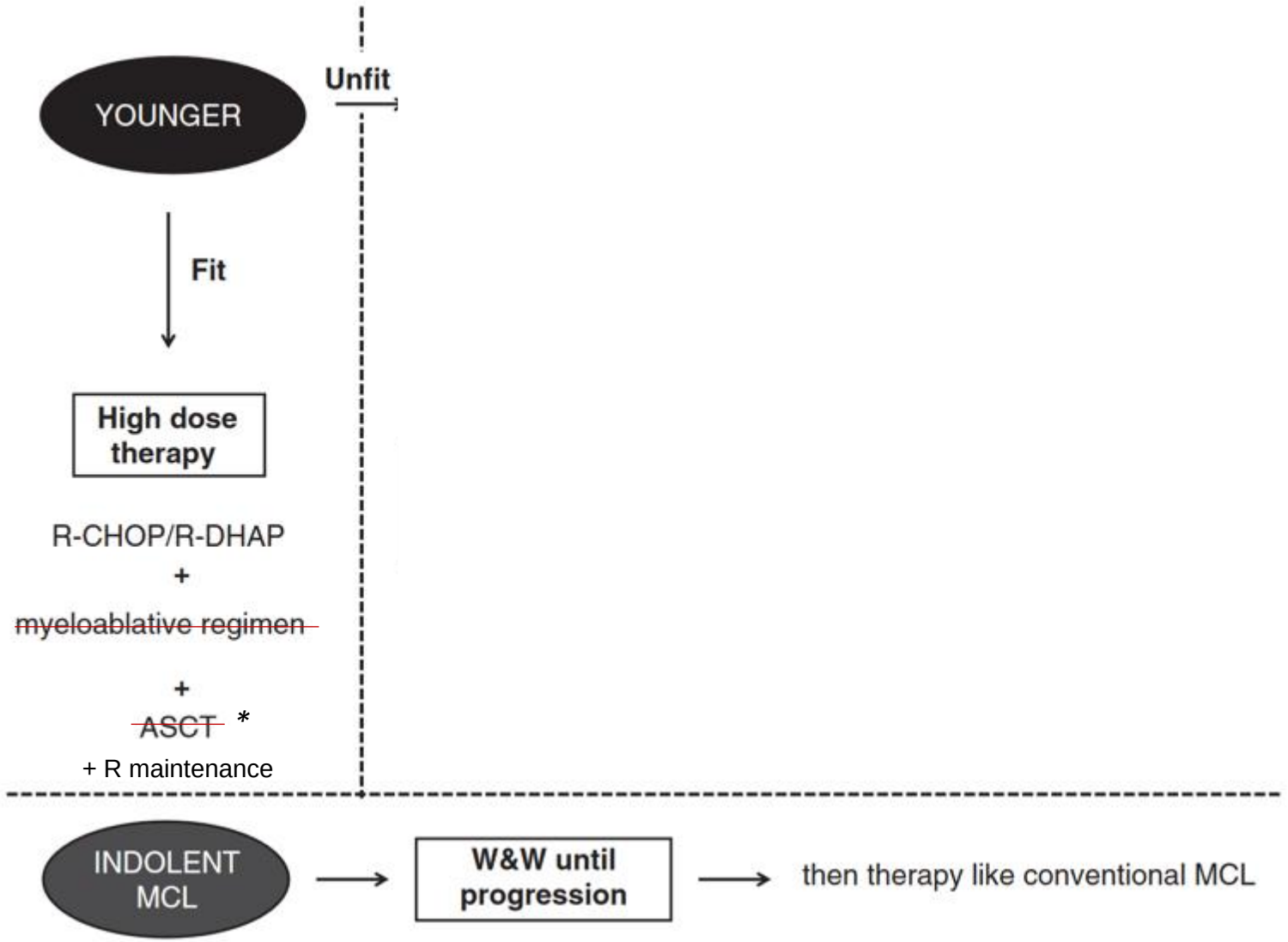
EUROPEAN MCL NETWORK

Ladetto M et al., ASH 2024

Therapeutic algorithm for first-line MCL patients: **younger patients**

up to 70 years old?

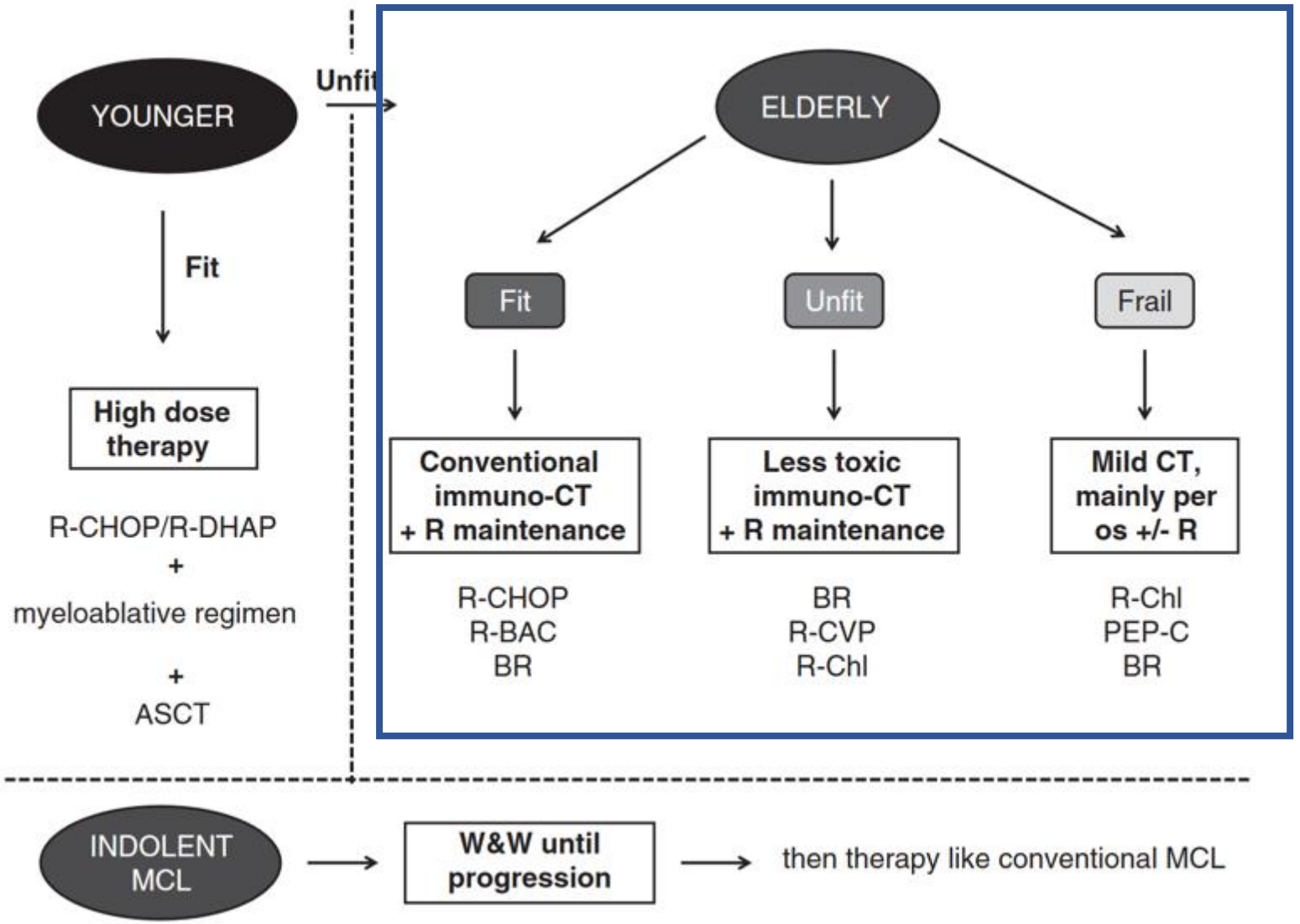
+ ibrutinib (induction and maintenance)
OFF-LABEL (648?)



*(*A+I displays a superiority trend in HR groups but has a worse toxicity profile than I)*

Modified from M Dreyling, S Ferrero and O Hermine, Leukemia 2014

Therapeutic algorithm for first-line MCL patients: **elderly patients**



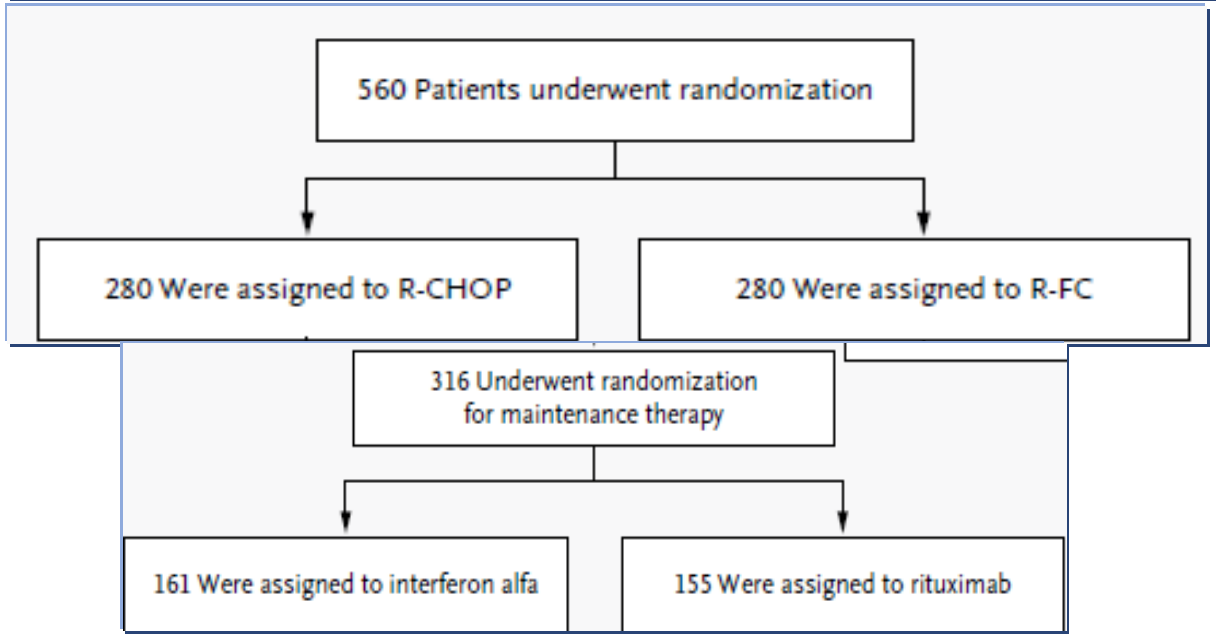
M Dreyling, S Ferrero and O Hermine, Leukemia 2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Treatment of Older Patients with Mantle-Cell Lymphoma

H.C. Kluin-Nelemans, E. Hoster, O. Hermine, J. Walewski, M. Trneny, C.H. Geisler, S. Stilgenbauer, C. Thieblemont, U. Vehling-Kaiser, J.K. Doorduijn, B. Coiffier, R. Forstpointner, H. Tilly, L. Kanz, P. Feugier, M. Szymczyk, M. Hallek, S. Kremers, G. Lepeu, L. Sanhes, J.M. Zijlstra, R. Bouabdallah, P.J. Lugtenburg, M. Macro, M. Pfreundschuh, V. Procházka, F. Di Raimondo, V. Ribrag, M. Uppenkamp, M. André, W. Klapper, W. Hiddemann, M. Unterhalt, and M.H. Dreyling



EUROPEAN MCL NETWORK

MCL Network Elderly Trial

≥60 years

1st: is Flu-regimen better than CHOP?

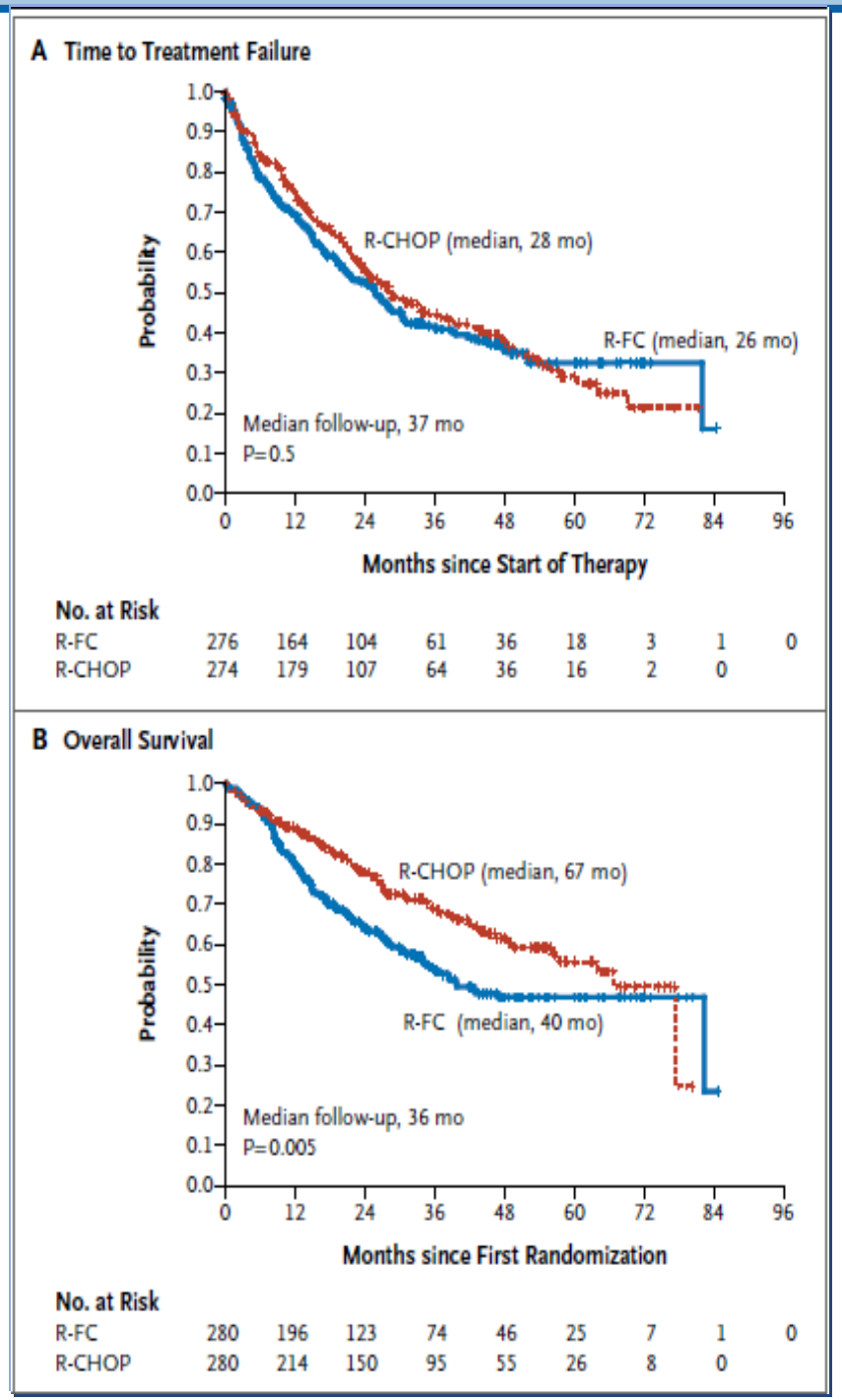
2nd: does **maintenance with Rituximab** (vs IFN) prolong remission?

R-CHOP vs R-FC in elderly patients with MCL

	ORR (%)	CR (%)
R-CHOP	86	34
R-FC	78	40
	P=0.06	P=0.10

MCL Network Elderly Trial

Cause of death	R-FC	R-CHOP
Died in CR/PR	10%	4%
Infections	7%	4%
Second cancer	3%	1%



Kluin-Nelemans HC et al. NEJM 2012;367:520-31

EUROPEAN mcl NETWORK

original reports

Treatment of Older Patients With Mantle Cell Lymphoma (MCL): Long-Term Follow-Up of the Randomized European MCL Elderly Trial

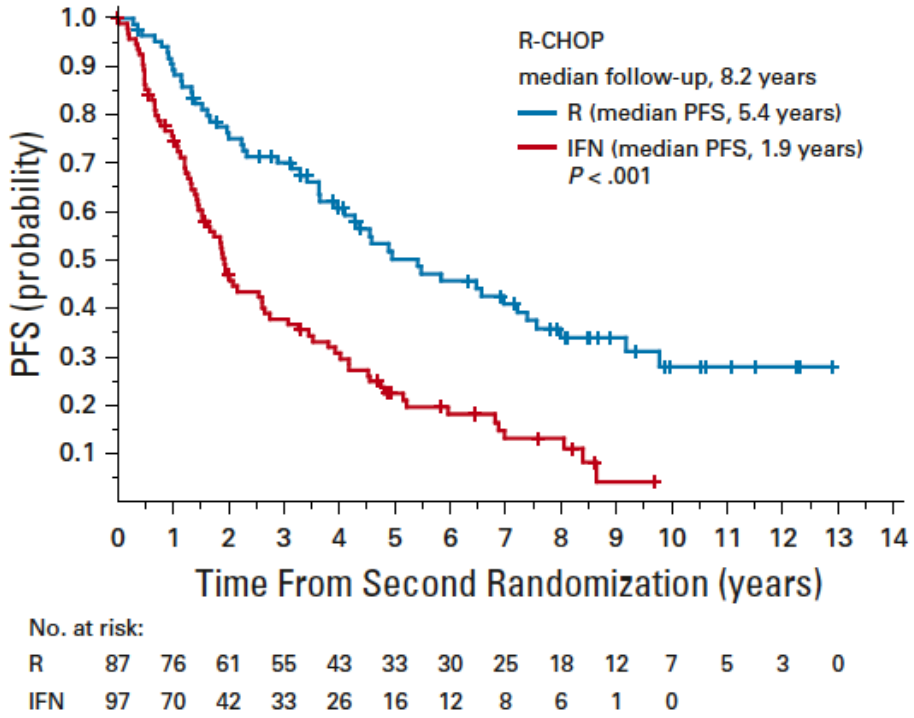
Hanneke C. Kluin-Nelemans, MD, PhD[1]; Eva Hoster, PhD[2]; Olivier Hermine, MD, PhD[3]; Jan Walewski, MD, PhD, DSc[4]; Christian H. Geisler, MD, PhD[5]; Marek Trneny, MD, PhD[6]; Stephan Stilgenbauer, MD[7]; Florian Kaiser, MD[8]; Jeanette K. Doorduijn, MD, PhD[9]; Gilles Salles, MD, PhD[10]; Michal Szymczyk, MD[4]; Hervé Tilly, MD[11]; Lothar Kanz, MD[12]; Christian Schmidt, MD[2]; Pierre Feugier, MD[13]; Catherine Thieblemont, MD, PhD[14]; Josée M. Zijlstra, MD, PhD[15]; Vincent Ribrag, MD[16]; Wolfram Klapper, MD[17]; Christiane Pott, MD, PhD[18]; Michael Unterhalt, MD, PhD[2]; and Martin H. Dreyling, MD, PhD[2]

MCL Network Elderly Trial

EUROPEAN MCL NETWORK

J Clin Oncol 37. © 2019 by American Society of Clinical Oncology

A



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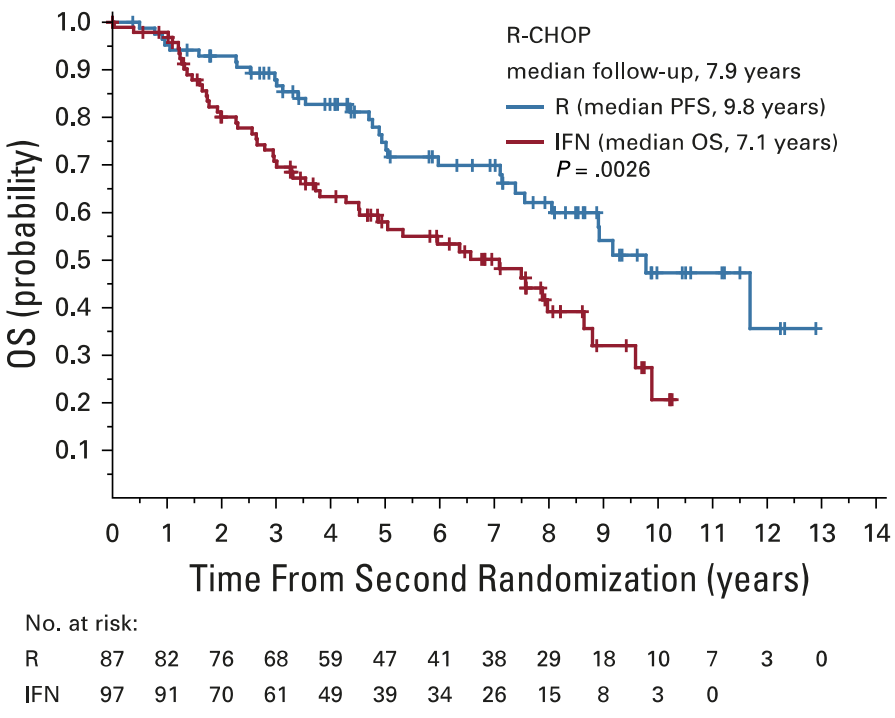
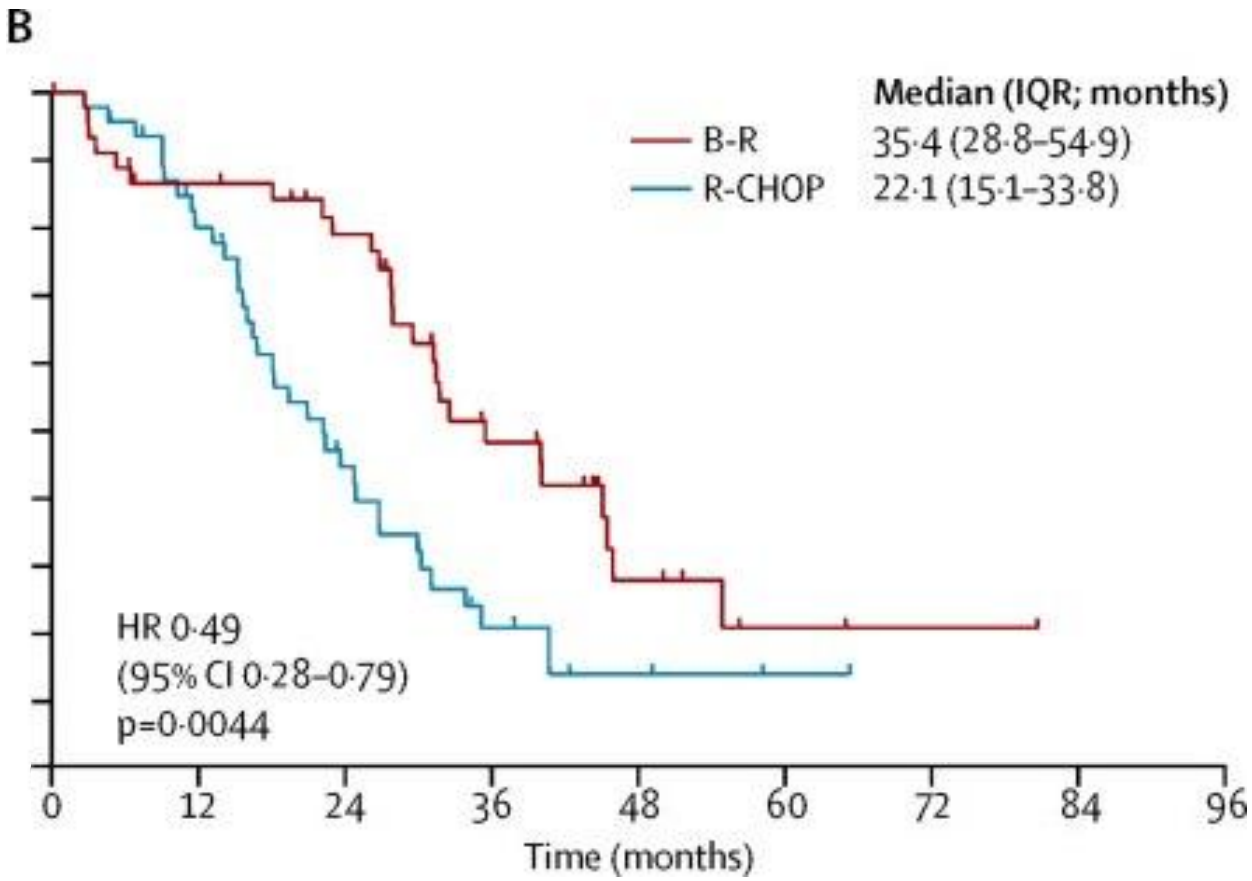


R-chemo + R maintenance

Bendamustine plus Rituximab vs CHOP plus Rituximab

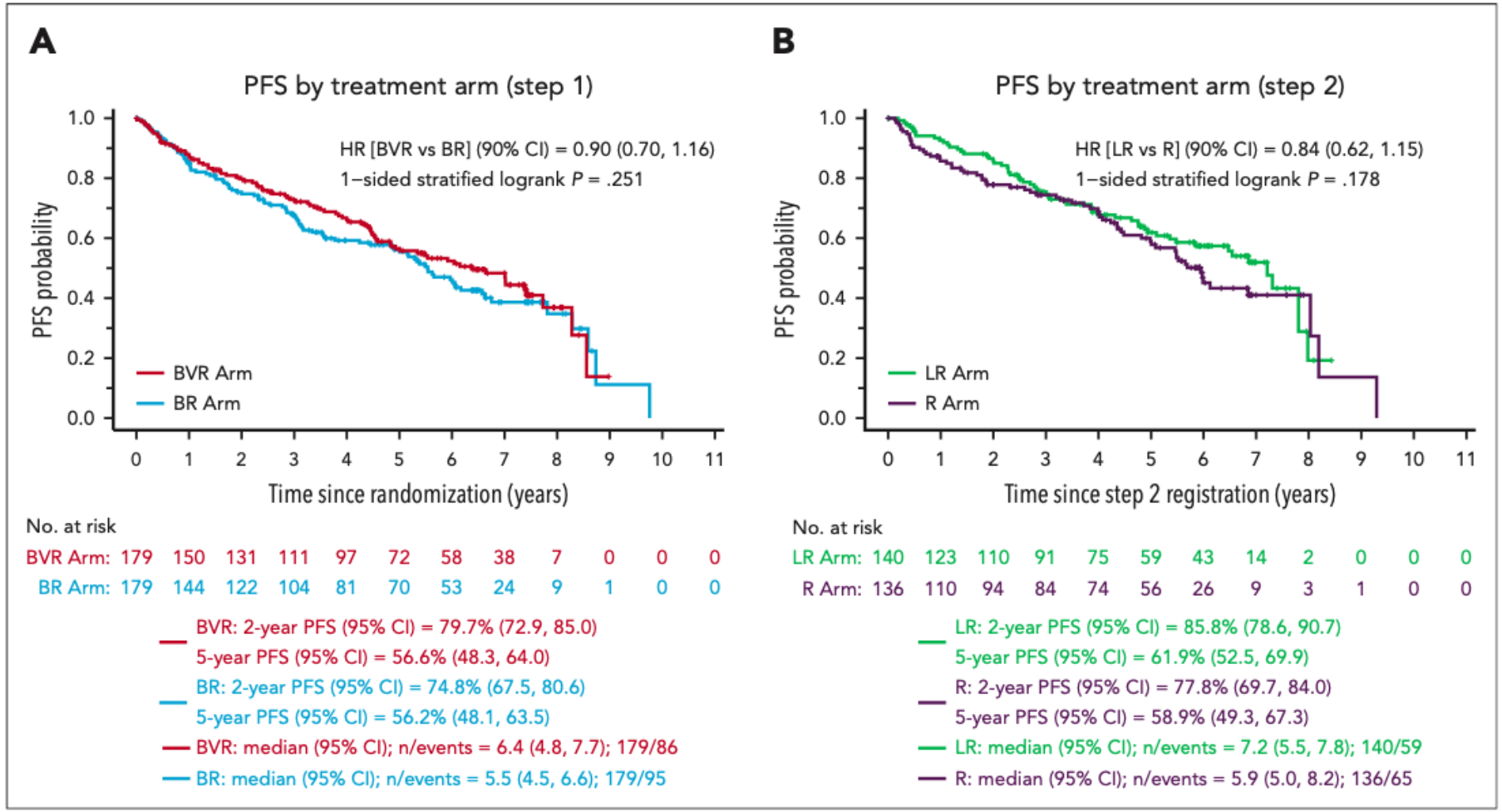
	Grade 3–4	
	R-CHOP	B-R
Leucocytopenia	181 (72%)*	98 (37%)*
Neutropenia	173 (69%)*	77 (29%)*
Lymphocytopenia	106 (43%)	196 (74%)
Anaemia	12 (5%)	8 (3%)
Thrombocytopenia	16 (6%)	13 (5%)

	B-R (n=261)	R-CHOP (n=253)	p value
Alopecia	0	245 (100%)*	<0·0001
Paresthesia	18 (7%)	73 (29%)	<0·0001
Stomatitis	16 (6%)	47 (19%)	<0·0001
Skin (erythema)	42 (16%)	23 (9%)	0·024
Skin (allergic reaction)	40 (15%)	15 (6%)	0·0006
Infectious episodes	96 (37%)	127 (50%)	0·0025
Sepsis	1 (<1%)	8 (3%)	0·019



Rummel MJ et al. Lancet 2013;381:1203-10

BR + R maintenance (L648) is an effective induction regimen in MCL



blood® 5 SEPTEMBER 2024 | VOLUME 144, NUMBER 10 1089

More is not always better

Carlo Visco | University of Verona

BR + R median PFS = 5.5 years

Smith M et al., Blood 2024

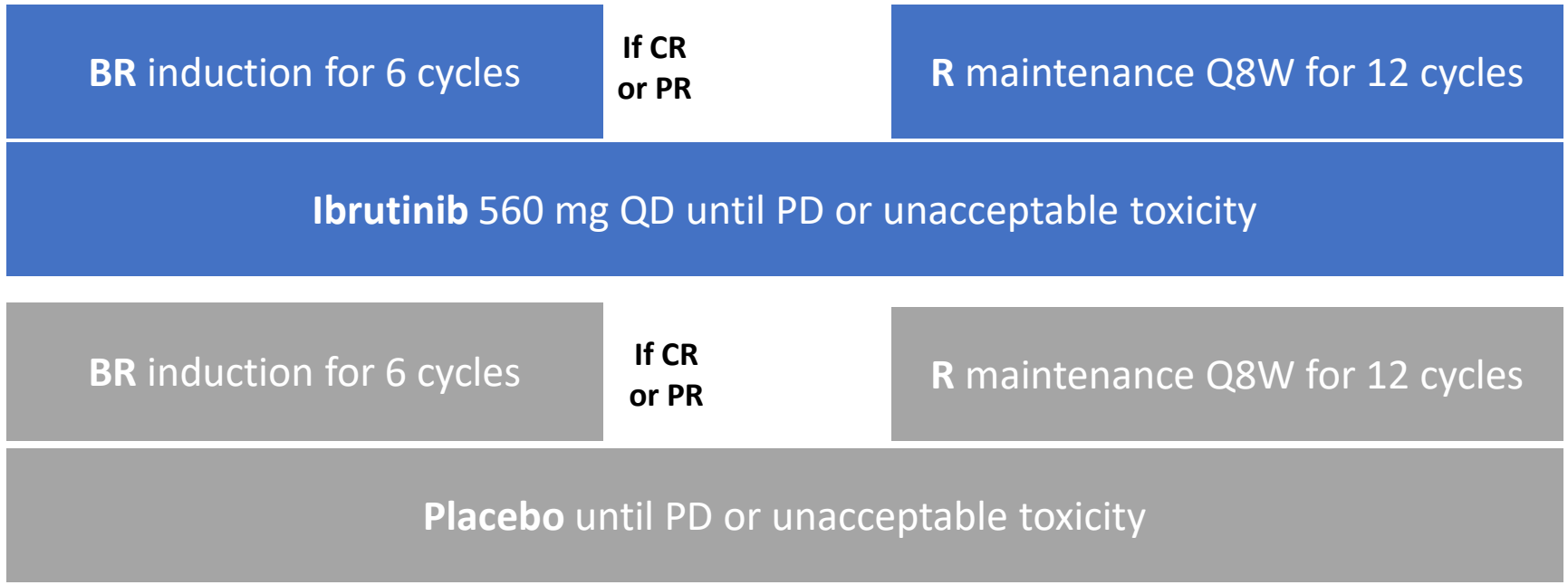
BR vs BR + ibrutinib «SHINE trial»

SHINE: Study Design

- Multicenter, randomized, double-blind, placebo-controlled phase III trial

Stratification by: MIPI score (low vs intermediate vs high)

Patients ≥65 yr of age with previously untreated stage II-IV MCL, no planned SCT (N = 523)



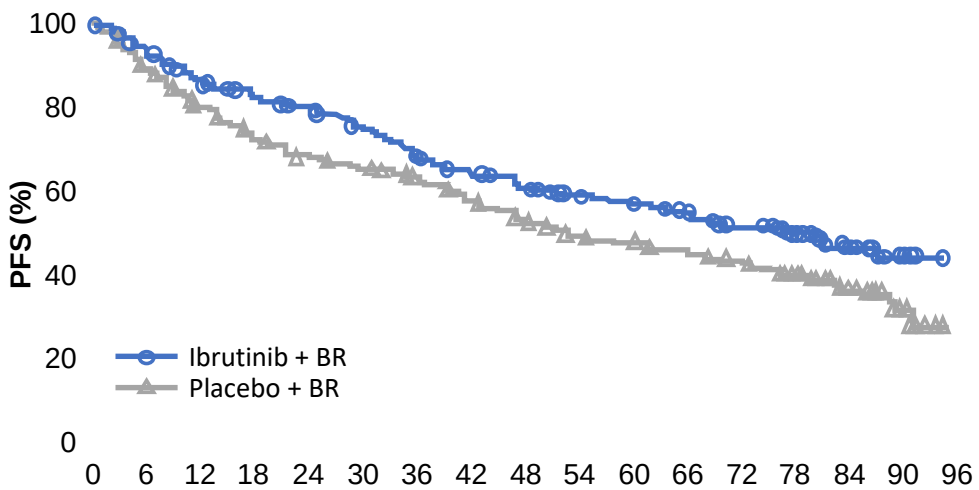
- **Primary endpoint:** investigator-assessed PFS (in ITT)
- **Key secondary endpoints:** ORR, time to next treatment, OS, safety

Wang. ASCO 2022. Abstr LBA7502. Wang. NEJM. 2022

SHINE TRIAL: BR +/- ibrutinib

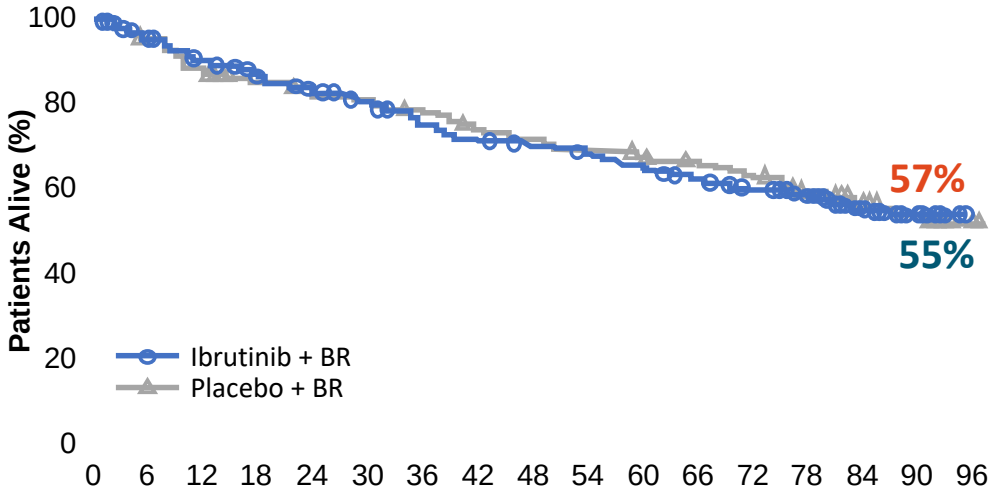
(off-label)

PFS (Primary Endpoint)



Patients at Risk																	
Ibrutinib + BR	261	228	207	191	182	167	152	139	130	120	115	106	95	78	39	11	0
Placebo + BR	262	226	199	177	166	158	148	135	119	109	103	98	90	78	41	11	0

OS (Key Secondary Endpoint)



Patients at Risk																	
Ibrutinib + BR	261	239	221	208	197	187	171	163	158	152	145	138	128	118	70	25	0
Placebo + BR	262	244	223	212	203	197	188	177	171	165	159	154	147	147	90	31	2

- Median follow-up: 84.7 mo (7.1 yr)
- "[…] A 2.3-yr statistically significant and clinically meaningful improvement in median PFS was observed in the ibrutinib arm (**80.6 months**) vs the placebo arm (**52.9 months**) […]"

The NEW ENGLAND JOURNAL of MEDICINE

Wang. ASCO 2022. Abstr LBA7502. Wang. NEJM. 2022

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Combination of Rituximab, Bendamustine, and Cytarabine for Patients With Mantle-Cell Non-Hodgkin Lymphoma Ineligible for Intensive Regimens or Autologous Transplantation

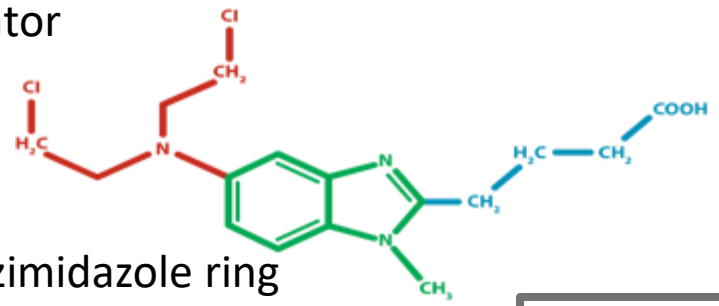
Carlo Visco, Silvia Finotto, Renato Zambello, Rossella Paolini, Andrea Menin, Roberta Zanotti, Francesco Zaja, Gianpietro Semenzato, Giovanni Pizzolo, Emanuele S.G. D'Amore, and Francesco Rodeghiero

	ORR (%)	CR (%)
Untreated	**100**	**95**

Treatment	Day 1	2	3	4
Rituximab 375 mg/m²	↓			
Bendamustine 70 mg/m²		↓	↓	
Ara-C 800 mg/m²		↓	↓	↓

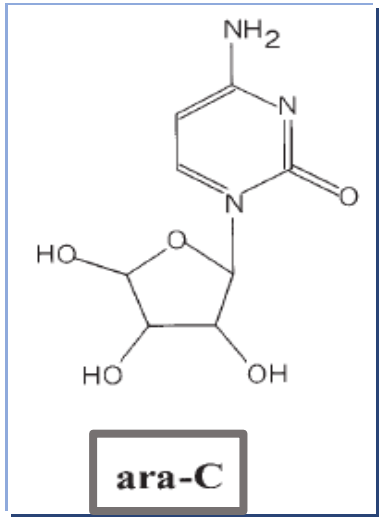
	Overall			
	Cycles (N = 182)		Patients (N = 40)	
Grade 3 or 4 Event	No.	%	No.	%
Leukopenia	87	48	23	57
Neutropenia	56	31	16	40
Febrile neutropenia	7	4	5	12
Thrombocytopenia	138	76	35	87
Anemia	48	26	18	45

Alkylator group



Benzimidazole ring

bendamustine



ara-C

Original R-BAC schedule (800)

blood advances

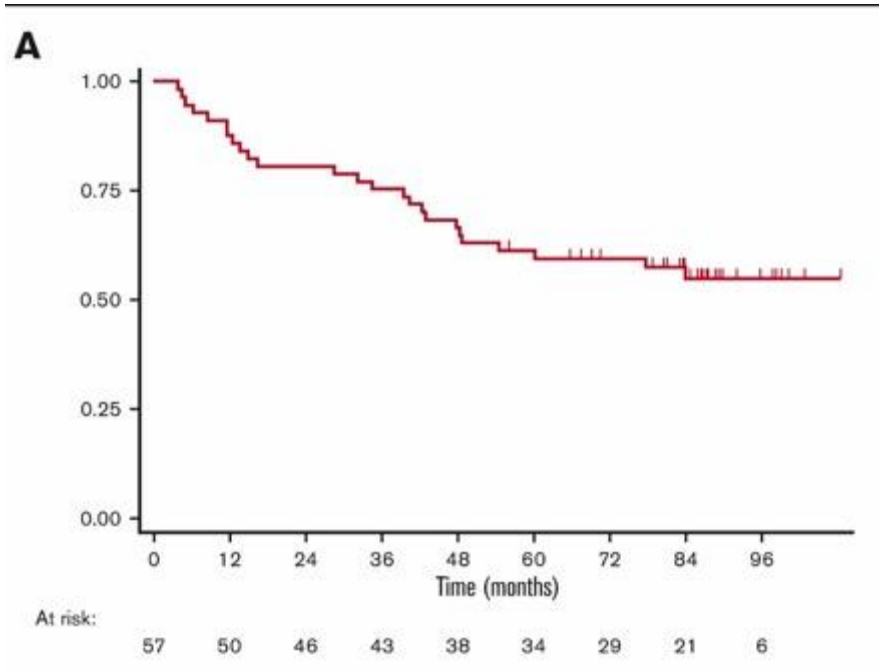
CLINICAL TRIALS AND OBSERVATIONS | JULY 27, 2023

Long-term follow-up of rituximab plus bendamustine and cytarabine in older patients with newly diagnosed MCL

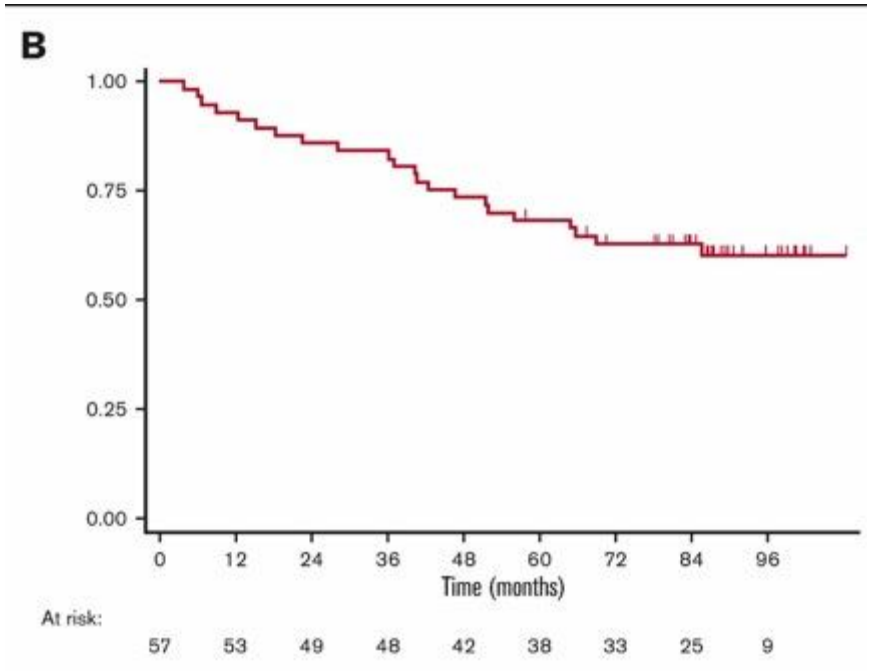
Clinical Trials & Observations

Maria Chiara Tisi, Riccardo Moia, Caterina Patti, Andrea Evangelista, Simone Ferrero, Michele Spina, Monica Tani, Barbara Botto, Melania Celli, Benedetta Puccini, Emanuele Cencini, Alice Di Rocco, Claudio Chini, Chiara Ghiggi, Renato Zambello, Manuela Zanni, Roberta Sciarra, Riccardo Bruna, Martina Ferrante, Stefano Alessandro Pileri, Francesca Maria Quaglia, Caterina Stelitano, Alessandro Re, Stefano Volpetti, Vittorio Ruggero Zilioli, Annalisa Arcari, Francesco Merli, Carlo Visco

PFS of all patients (7-year PFS, 55% [95% CI, 41-67])



OS of all patients (7-year OS, 63% [95% CI, 49-74])



Survival curves at a median follow-up of 86 months

FIL R-BAC 500 trial

blood advances JULY 27, 2023

Long-term follow-up of rituximab plus bendamustine and cytarabine in older patients with newly diagnosed MCL

Maria Chiara Tisi,[1] Riccardo Moia,[2] Caterina Patti,[3] Andrea Evangelista,[4] Simone Ferrero,[5] Michele Spina,[6] Monica Tani,[7] Barbara Botto,[8] Melania Celli,[9] Benedetta Puccini,[10] Emanuele Cencini,[11] Alice Di Rocco,[12] Claudio Chini,[13] Chiara Ghiggi,[14] Renato Zambello,[15] Manuela Zanni,[16] Roberta Sciarra,[17] Riccardo Bruna,[2] Martina Ferrante,[18] Stefano Alessandro Pileri,[19] Francesca Maria Quaglia,[20] Caterina Stelitano,[21] Alessandro Re,[22] Stefano Volpetti,[23] Vittorio Ruggero Zilioli,[24] Annalisa Arcari,[25] Francesco Merli,[26] and Carlo Visco[20]

Survival curves at a median follow-up of 86 months

R-BAC500

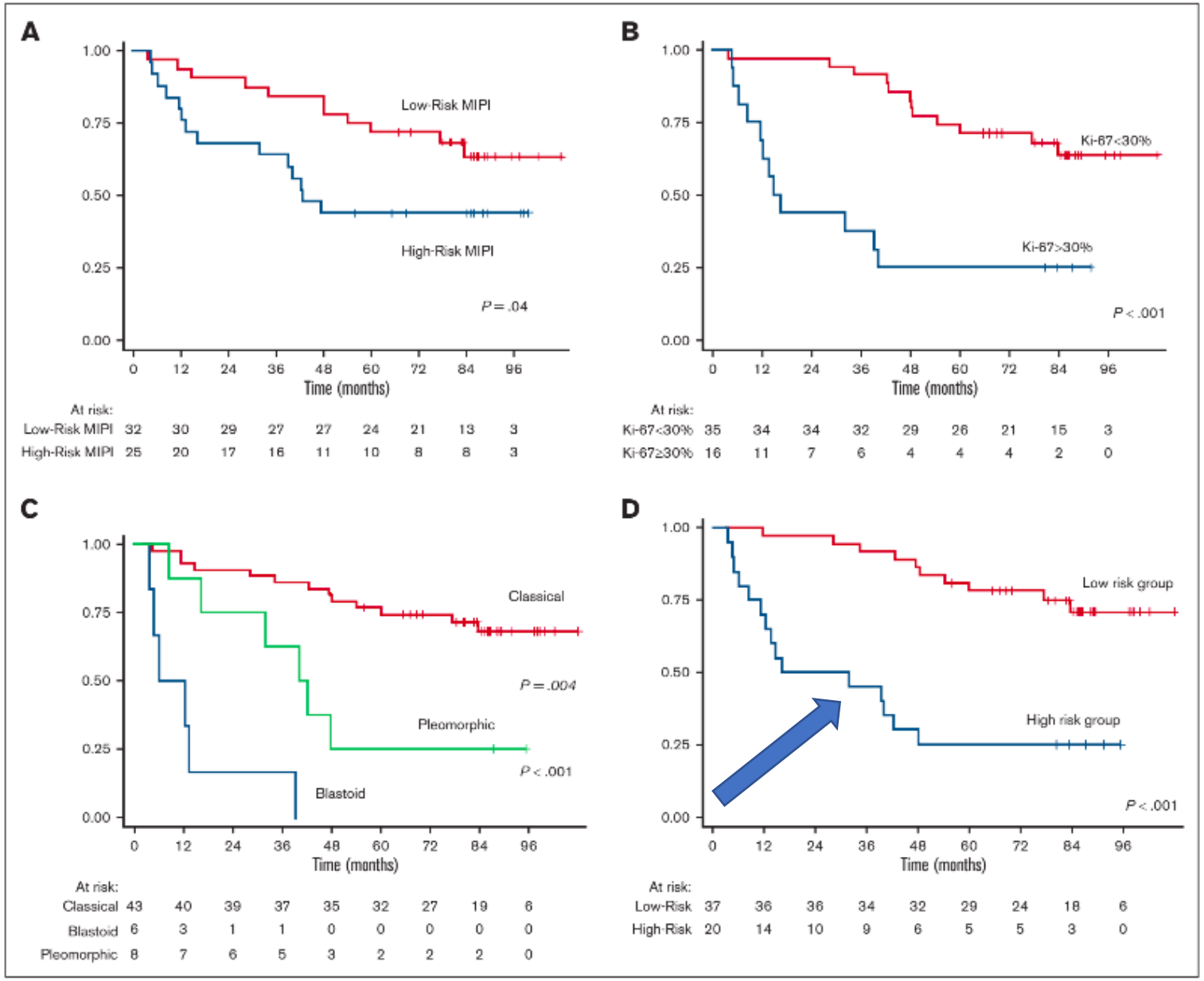
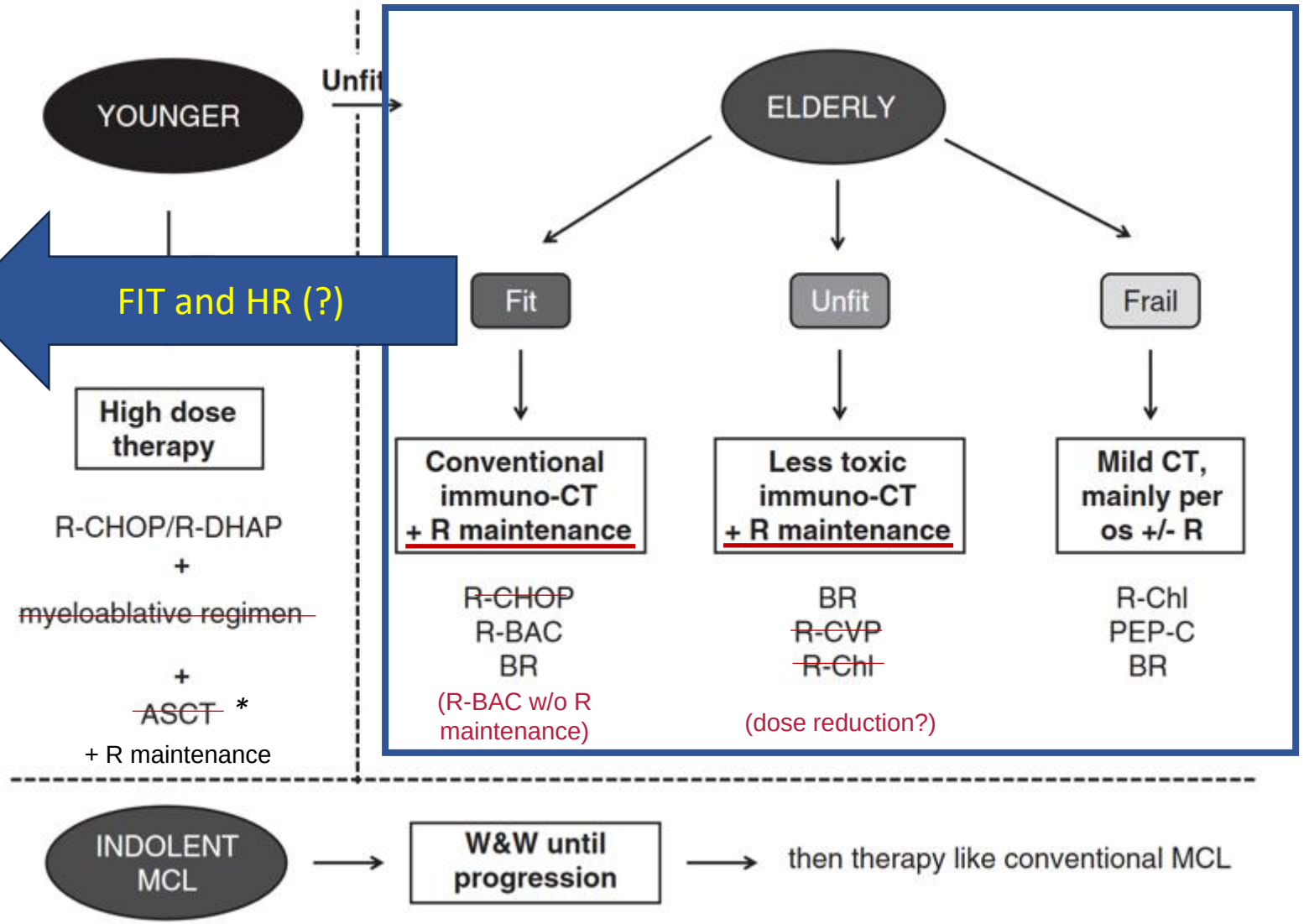


Figure 2. Survival curves for PFS. (A) MIPI score, (B) Ki67 value, (C) morphological variant, (D) or risk group defined as follows: low-risk (Ki67 < 30% and classical morphological variant); high-risk group (Ki67 ≥ 30% and/or blastoid/pleomorphic morphological variant).

Therapeutic algorithm for first-line MCL patients: **elderly patients**

up to 70 years old?

+ ibrutinib (induction and maintenance)
OFF-LABEL (648?)

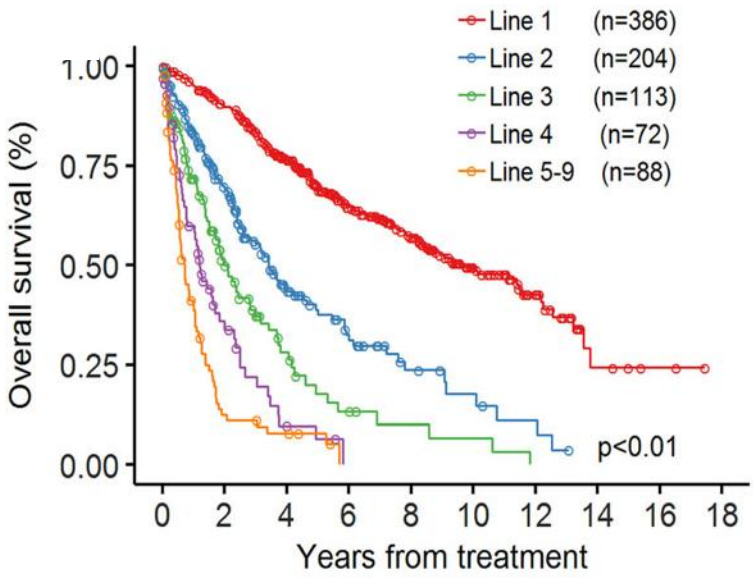


Modified from M Dreyling, S Ferrero and O Hermine, Leukemia 2014

MCL: overall outcome after first line

OS and PFS in Patients with MCL After Multiple Lines of Therapy

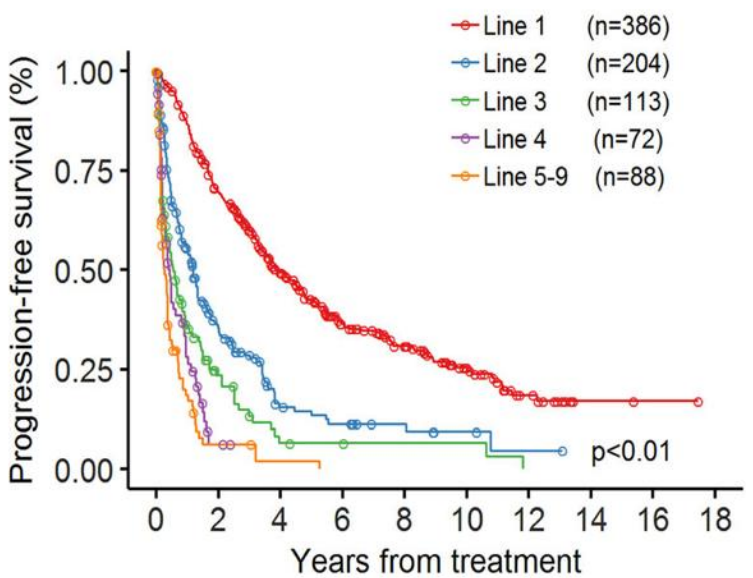
OS



Number at risk

	386	329	242	142	101	53	28	5	2	0
	204	111	45	23	11	6	3	0	0	0
	113	38	15	6	3	2	0	0	0	0
	72	16	4	0	0	0	0	0	0	0
	88	9	5	0	0	0	0	0	0	0

PFS



Number at risk

	386	254	155	86	60	31	13	2	1	0
	204	55	16	11	6	3	1	0	0	0
	113	17	4	3	2	2	0	0	0	0
	72	2	0	0	0	0	0	0	0	0
	88	4	1	0	0	0	0	0	0	0

Treatment outcomes decline with successive lines of therapy, with a progressive shortening in the response duration and survival after each line of therapy

Adapted from Figure 5 in Ref. Kumar A, et al. Blood Cancer J 2019

Current Treatment in Mantle Cell Lymphoma

Preferred First-line Treatment Options

Aggressive Chemotherapy
R-DHAP (cisplatin, or oxaliplatin)
R-CHOP/R-DHAP (alternating)
NORDIC (maxi-CHOP/R + HD cytarabine)

→ **Consolidation and Maintenance**
HDT + ASCT → R maint for 3 yr

Less Aggressive Chemotherapy
BR
R-CHOP
RBAC

→ **Maintenance**
After R-CHOP: R maint until Progression.

Preferred Second-line Treatment Options

Covalent BTK inhibitor
- Ibrutinib

Third-line Treatment

CAR-T
- Brexucabtagene autoleucel (after chemoimmunotherapy and BTK inhibitor – by 3L)

Non covalent BTK inhibitor:
- Pirtobrutinib (after covalent BTK inhibitor)

Rielaborazione grafica dell'esperto -Courtesy of Prof. Maurizio Martelli

Ibrutinib for **relapsed/refractory MCL**

The NEW ENGLAND JOURNAL of MEDICINE

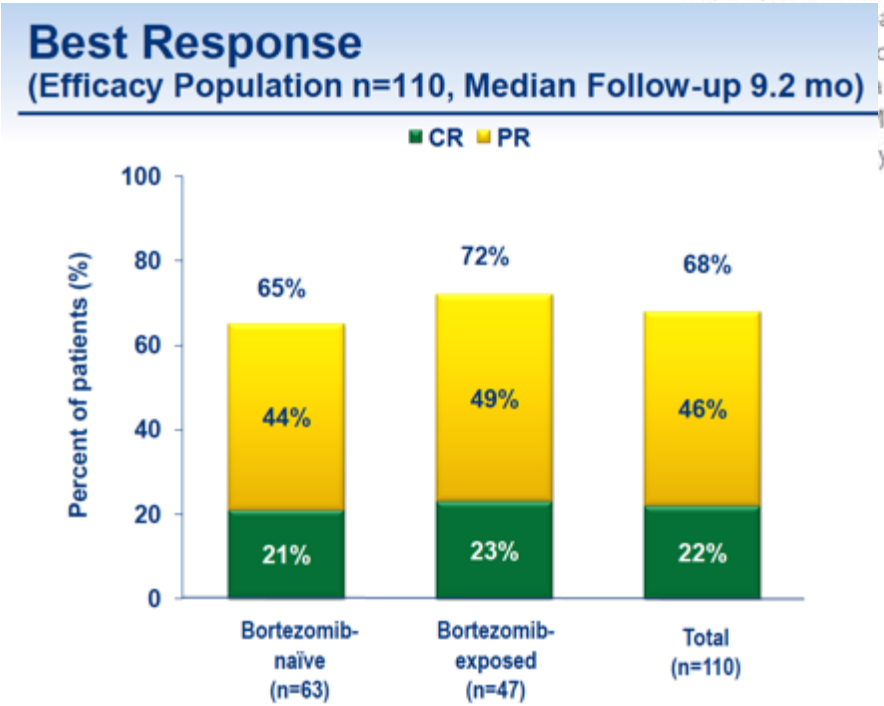
ORIGINAL ARTICLE

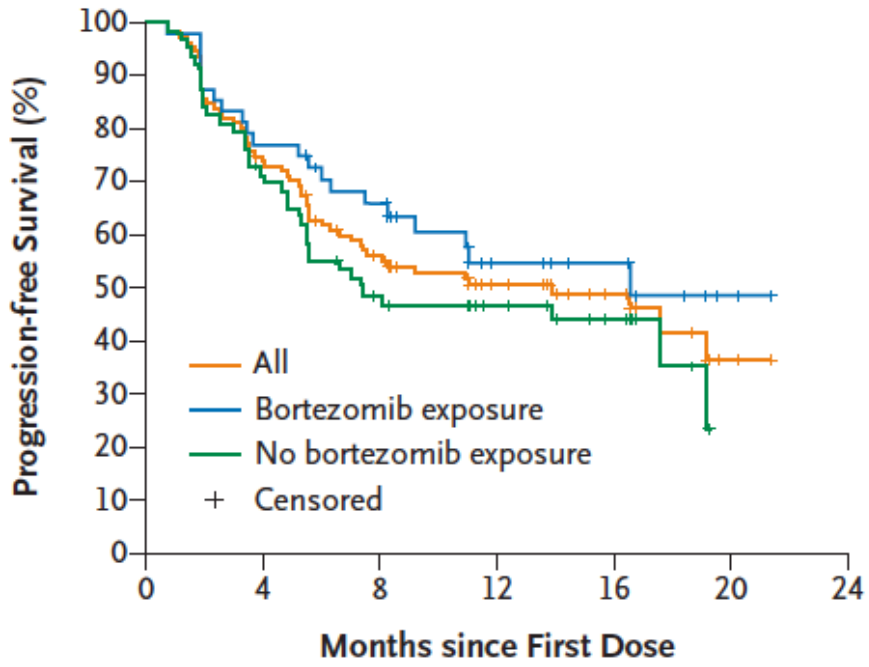
Targeting BTK with Ibrutinib in Relapsed or Refractory Mantle-Cell Lymphoma

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., Ranjana H. Advani, M.D., Jorge E. Romaguera, M.D., Michael E. Williams, M.D., Jacqueline C. Barrientos, M.D., Ewa Chmielowska, M.D., John Radford, M.D., auer, M.D., Martin Dreyling, M.D., Wieslaw Wiktor Jedrzejczak, ohnson, M.D., Stephen E. Spurgeon, M.D., Lei Li, Ph.D., ng, M.D., Ph.D., Kate Newberry, Ph.D., Zhishuo Ou, M.D., .S., Bingliang Fang, Ph.D., Jesse McGreivy, M.D., Fong Clow, y, Ph.D., Betty Y. Chang, Ph.D., Darrin M. Beaupre, M.D., P Lori A. Kunkel, M.D., and Kristie A. Blum, M.D.

This article was published on June 19, 2013, at NEJM.org.

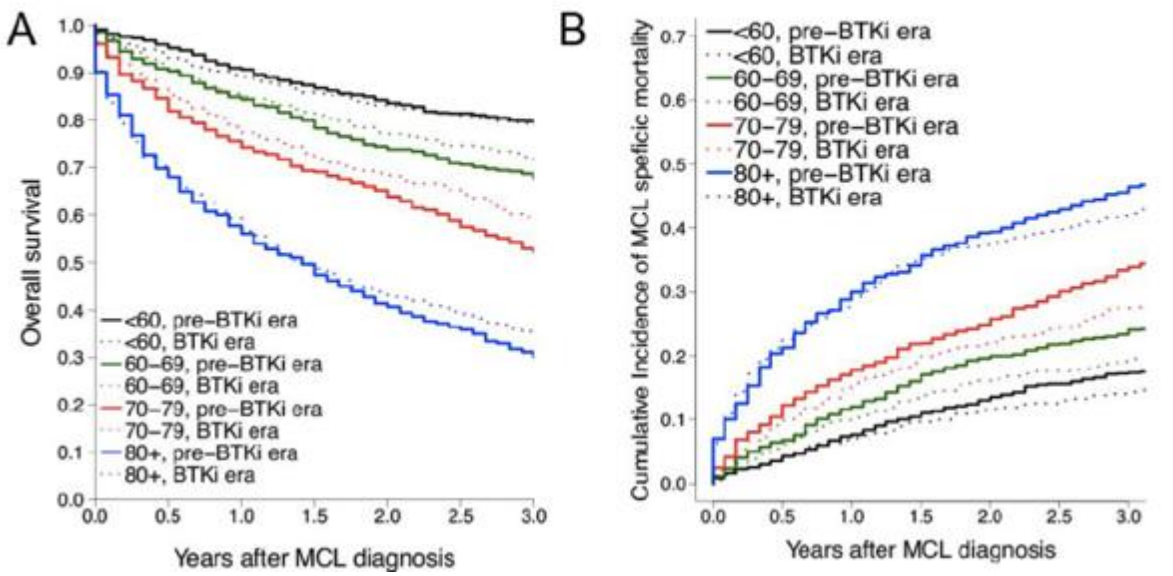
N Engl J Med 2013.
DOI: 10.1056/NEJMoa1306220

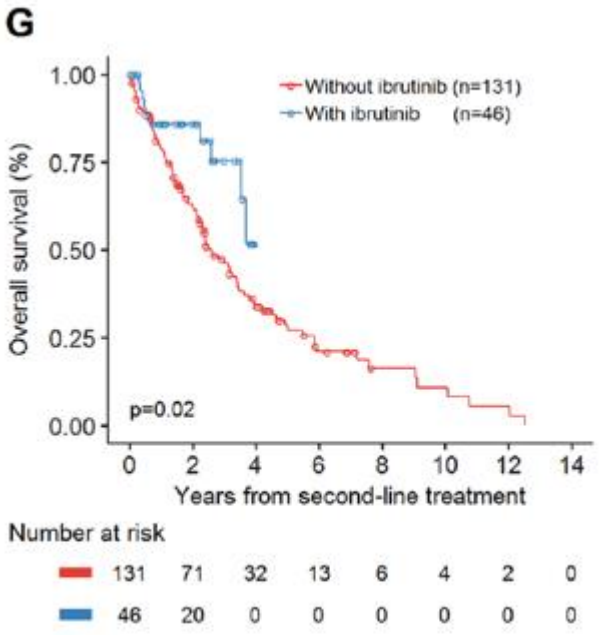


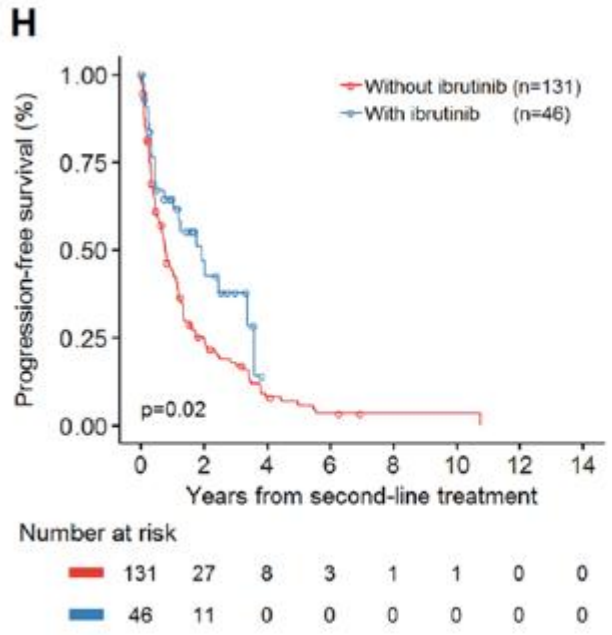


Ibrutinib and **survival** in MCL

Survival of Mantle Cell Lymphoma in the Era of Bruton Tyrosine Kin
Population-Based Analysis. Number: 182. Presenter: Mengyang Di



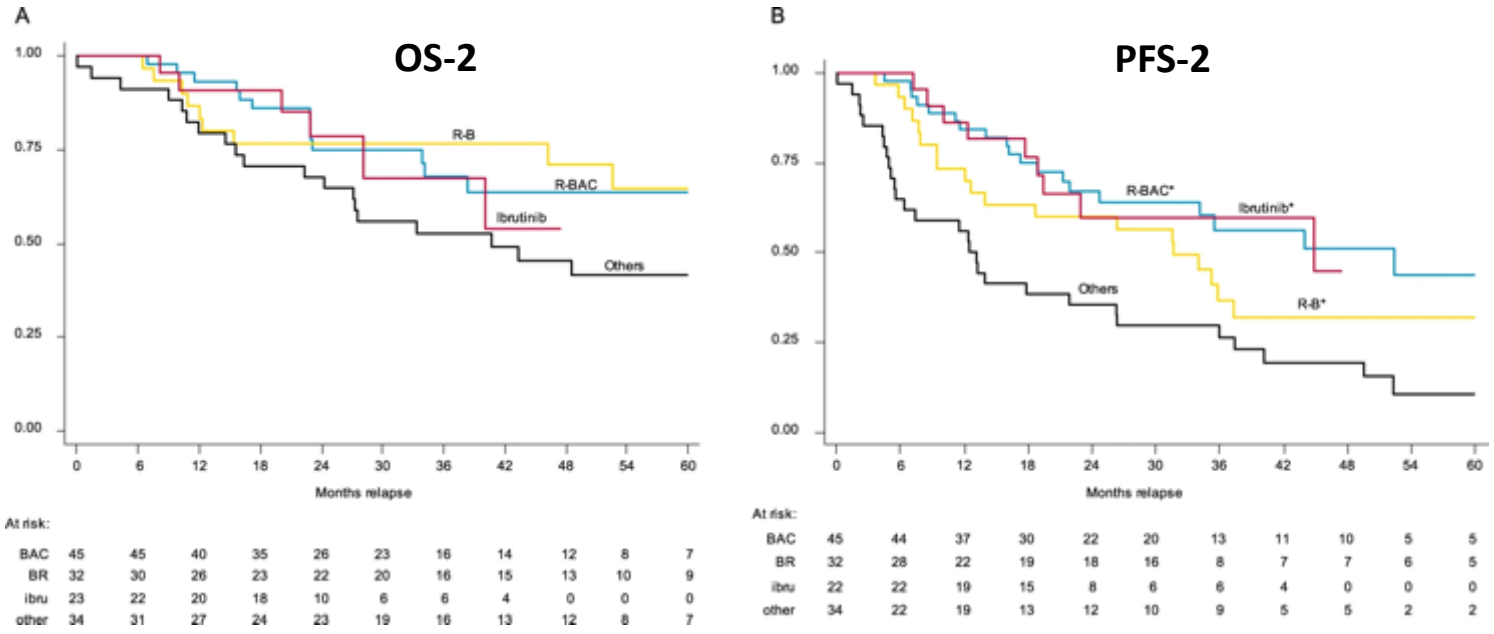




Kumar et al. *Blood Cancer Journal* (2019)9:50
https://doi.org/10.1038/s41408-019-0209-5

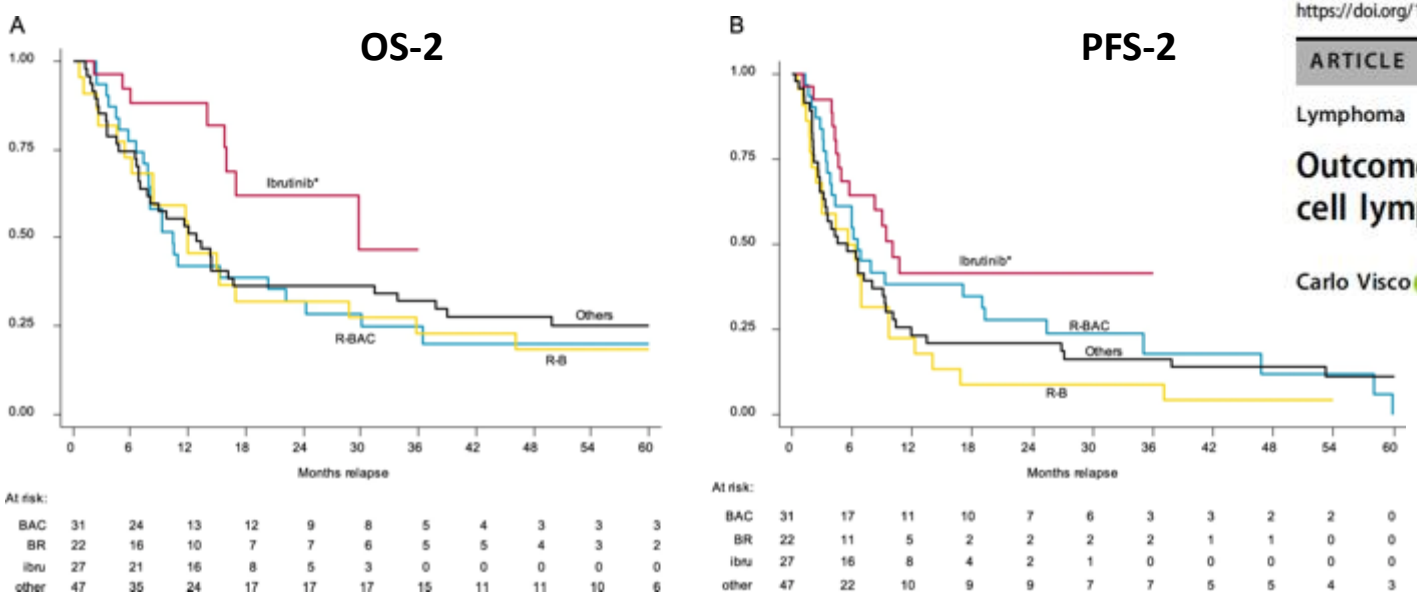
POST-ATLANTA 2021
Novità dal Meeting della Società Americana di Ematologia

Survival curves for patients with late-POD.



Ibrutinib as best second line for both early and late POD patients

Survival curves for patients with early-POD.



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

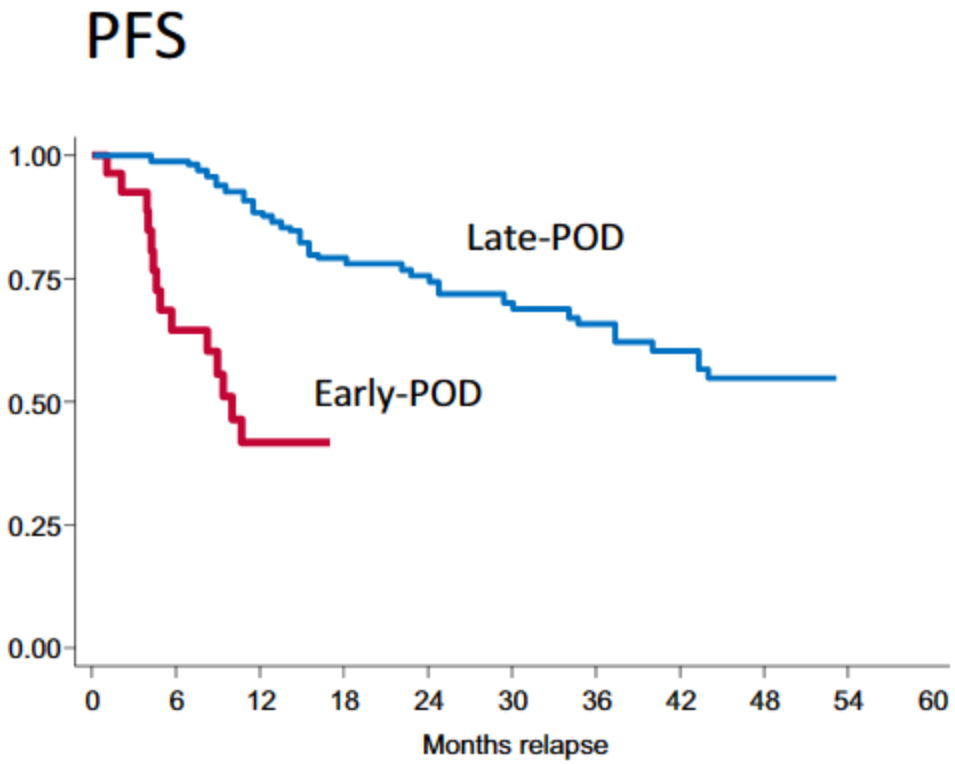
ARTICLE

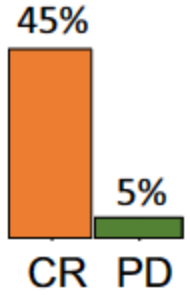
Lymphoma

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

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

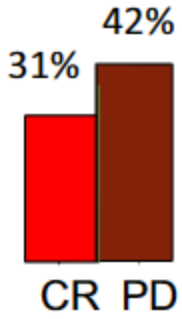
Ibrutinib at first relapse: late versus early POD





Late-POD

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

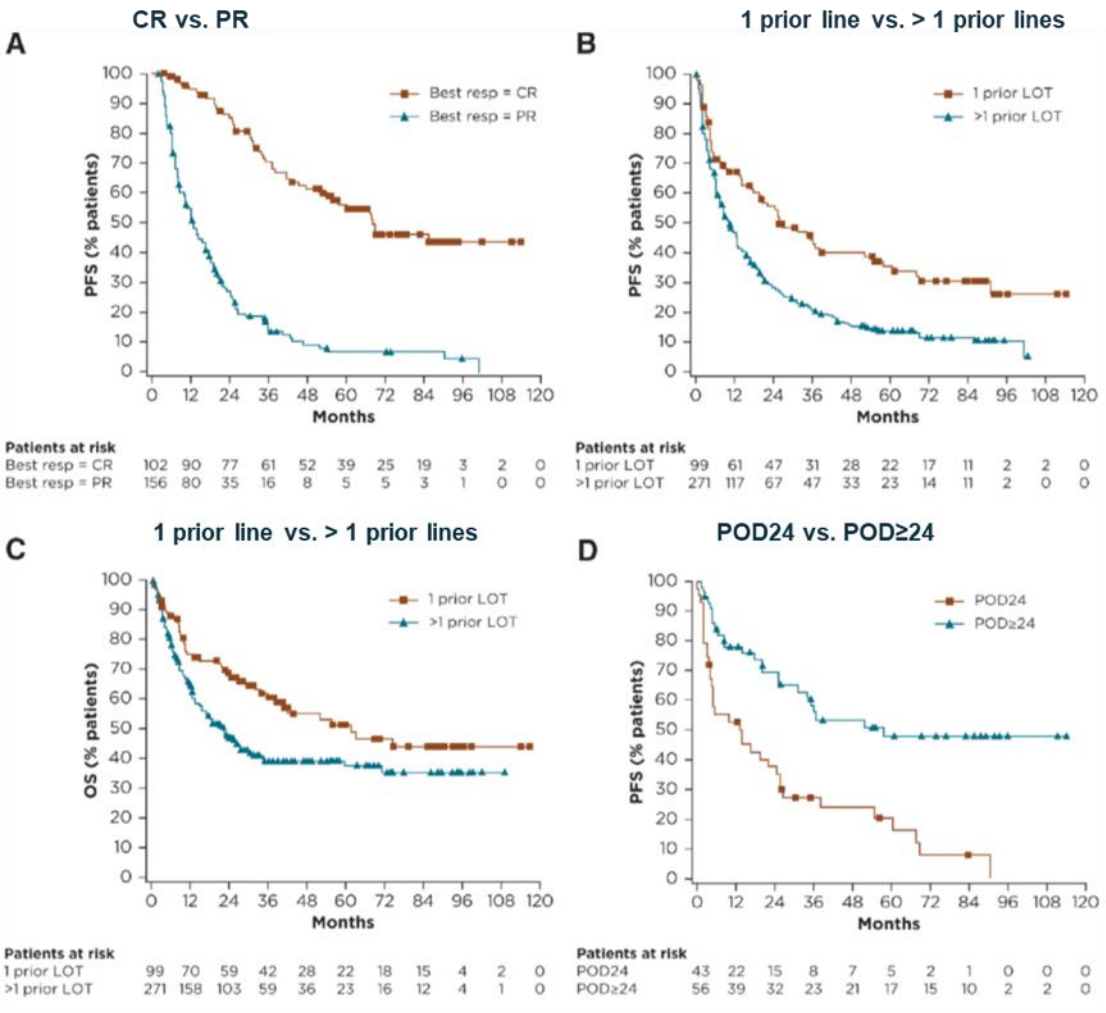


Early-POD

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

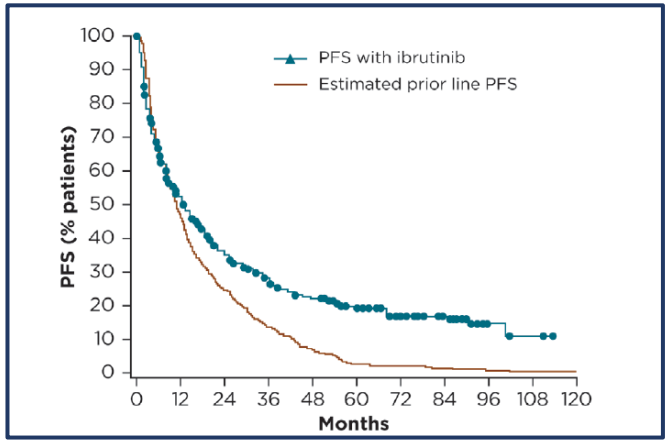
Visco, BJH 2023

Ibrutinib in RR-MCL: PFS and OS by status after first line of therapy



- Pooled analysis of ibrutinib treatment in **R/R MCL (3 trials; 370 pts)** @ FU of ~10 years [PCYC-1104, SPARK, RAY]
- Single-agent ibrutinib mitigates the historical trend of successive decline in PFS with each line of CIT regardless of age and prior LOT
- Patients achieving PFS > prior regimen:
  - **low-risk sMIPI**
  - **non-bulky disease**
  - **non-blastoid histology**
  - **wild-type TP53**

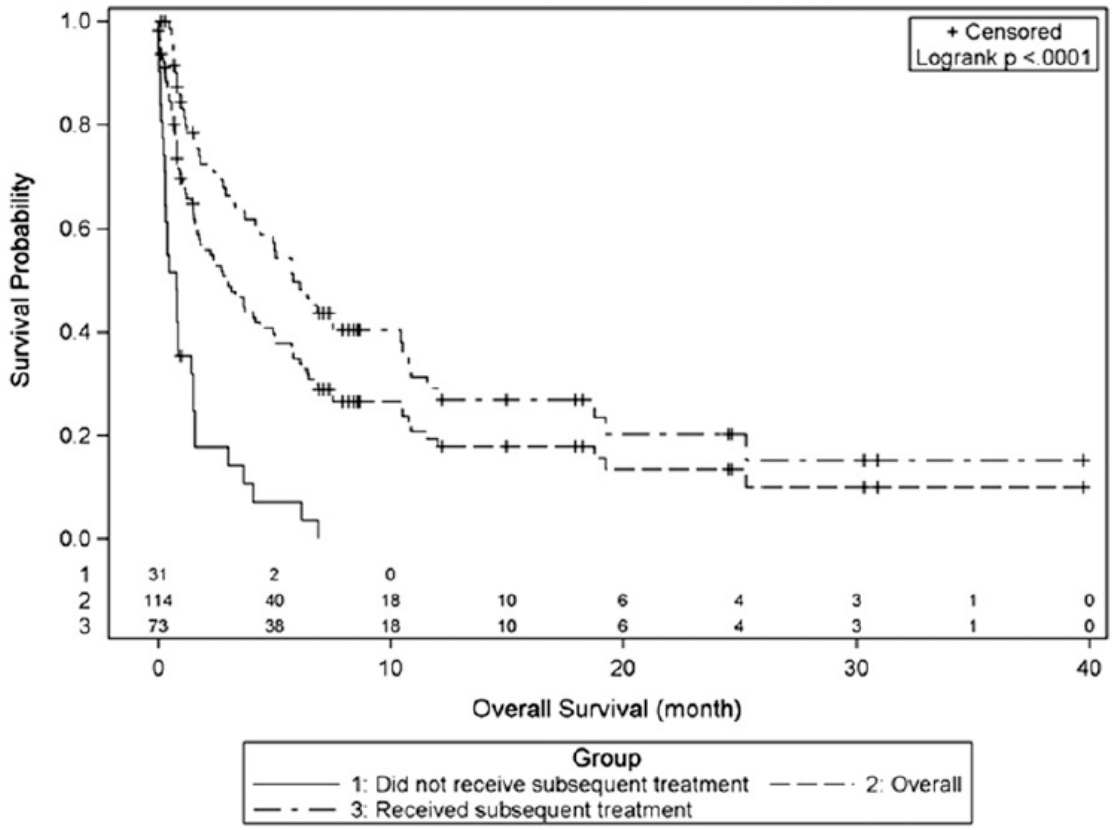
EUROPEAN mcl NETWORK



Dreyling M. et al. Hemasphere. 2022

Postibrutinib outcomes in patients with mantle cell lymphoma

Peter Martin,[1] Kami Maddocks,[2] John P. Leonard,[1] Jia Ruan,[1] Andre Goy,[3] Nina Wagner-Johnston,[4] Simon Rule,[5] Ranjana Advani,[6] David Iberri,[6] Tycel Phillips,[7] Stephen Spurgeon,[8] Eliana Kozin,[8] Katherine Noto,[1] Zhengming Chen,[9] Wojciech Jurczak,[10] Rebecca Auer,[11] Ewa Chmielowska,[12] Stephan Stilgenbauer,[13] Johannes Bloehdorn,[13] Craig Portell,[14] Michael E. Williams,[14] Martin Dreyling,[15] Paul M. Barr,[16] Selina Chen-Kiang,[17] Maurizio DiLiberto,[17] Richard R. Furman,[1] and Kristie A. Blum[2]



New time has come (2022…)

Martin P. et al. Blood 2016

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Non covalent BTK inhibitor (2024)
- Pirtobrutinib (after covalent BTK inhibitor)

Rielaborazione grafica dell'esperto -Courtesy of Prof. Maurizio Martelli

The NEW ENGLAND JOURNAL of MEDICINE April 1, 2020

ORIGINAL ARTICLE

KTE-X19 CAR T-Cell Therapy in Relapsed or Refractory Mantle-Cell Lymphoma

M. Wang, J. Munoz, A. Goy, F.L. Locke, C.A. Jacobson, B.T. Hill, J.M. Timmerman, H. Holmes, S. Jaglowski, I.W. Flinn, P.A. McSweeney, D.B. Miklos, J.M. Pagel, M.-J. Kersten, N. Milpied, H. Fung, M.S. Topp, R. Houot, A. Beitinjaneh, W. Peng, L. Zheng, J.M. Rossi, R.K. Jain, A.V. Rao, and P.M. Reagan

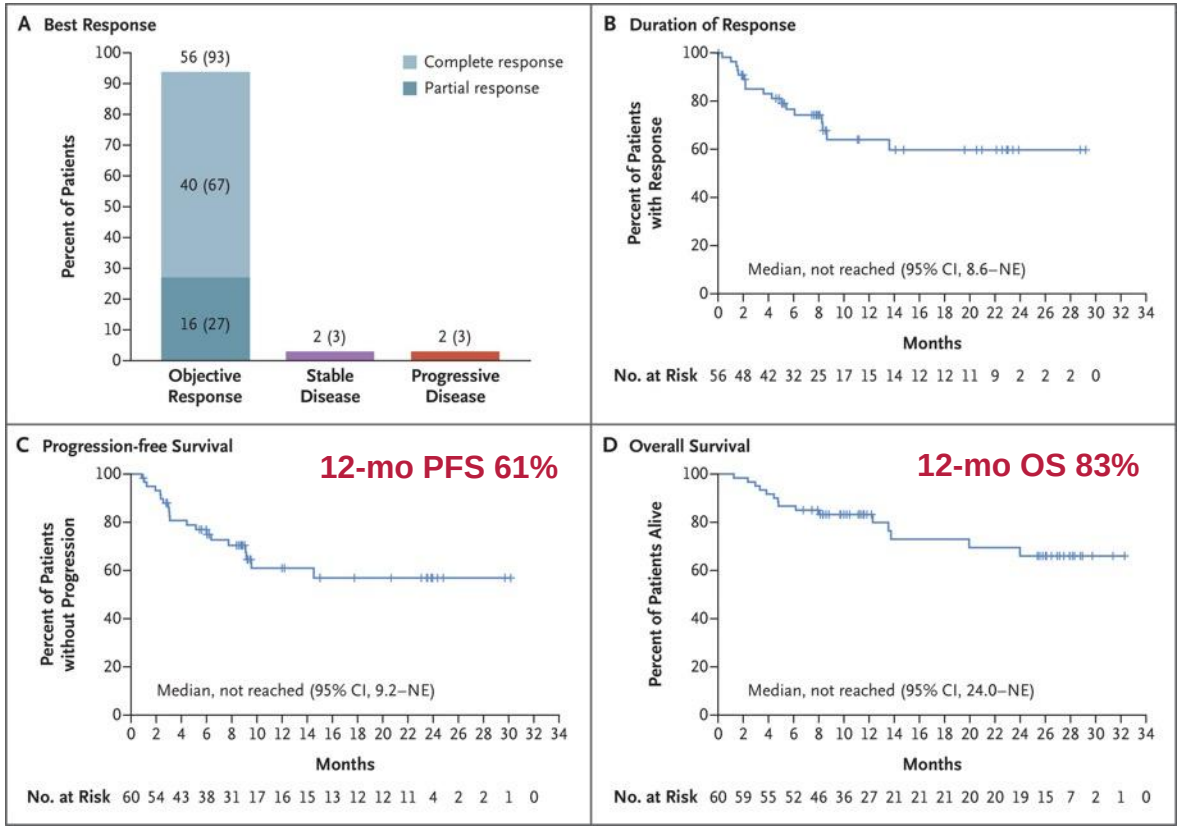


Table 3. Cytokine Release Syndrome and Neurologic Events among All 68 Treated Patients.*

Event	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
			number of patients (percent)			
Symptom of cytokine release syndrome						
Any	62 (91)	20 (29)	32 (47)	8 (12)	2 (3)	0
Pyrexia	62 (91)	15 (22)	40 (59)	7 (10)	0	0
Hypotension	35 (51)	4 (6)	16 (24)	14 (21)	1 (1)	0
Hypoxemia	23 (34)	1 (1)	10 (15)	8 (12)	4 (6)	0
Chills	21 (31)	12 (18)	9 (13)	0	0	0
Tachycardia	16 (24)	11 (16)	5 (7)	0	0	0
Headache	15 (22)	7 (10)	8 (12)	0	0	0
Alanine aminotransferase increased	10 (15)	5 (7)	1 (1)	3 (4)	1 (1)	0
Aspartate aminotransferase increased	9 (13)	4 (6)	0	5 (7)	0	0
Fatigue	9 (13)	6 (9)	2 (3)	1 (1)	0	0
Nausea	9 (13)	5 (7)	4 (6)	0	0	0
Neurologic event	43 (63)	13 (19)	9 (13)	15 (22)	6 (9)	0
Tremor	24 (35)	19 (28)	5 (7)	0	0	0
Encephalopathy	21 (31)	5 (7)	3 (4)	7 (10)	6 (9)	0
Confusional state	14 (21)	3 (4)	3 (4)	8 (12)	0	0
Aphasia	10 (15)	3 (4)	4 (6)	3 (4)	0	0

Journal of Clinical Oncology®

June 4, 2022

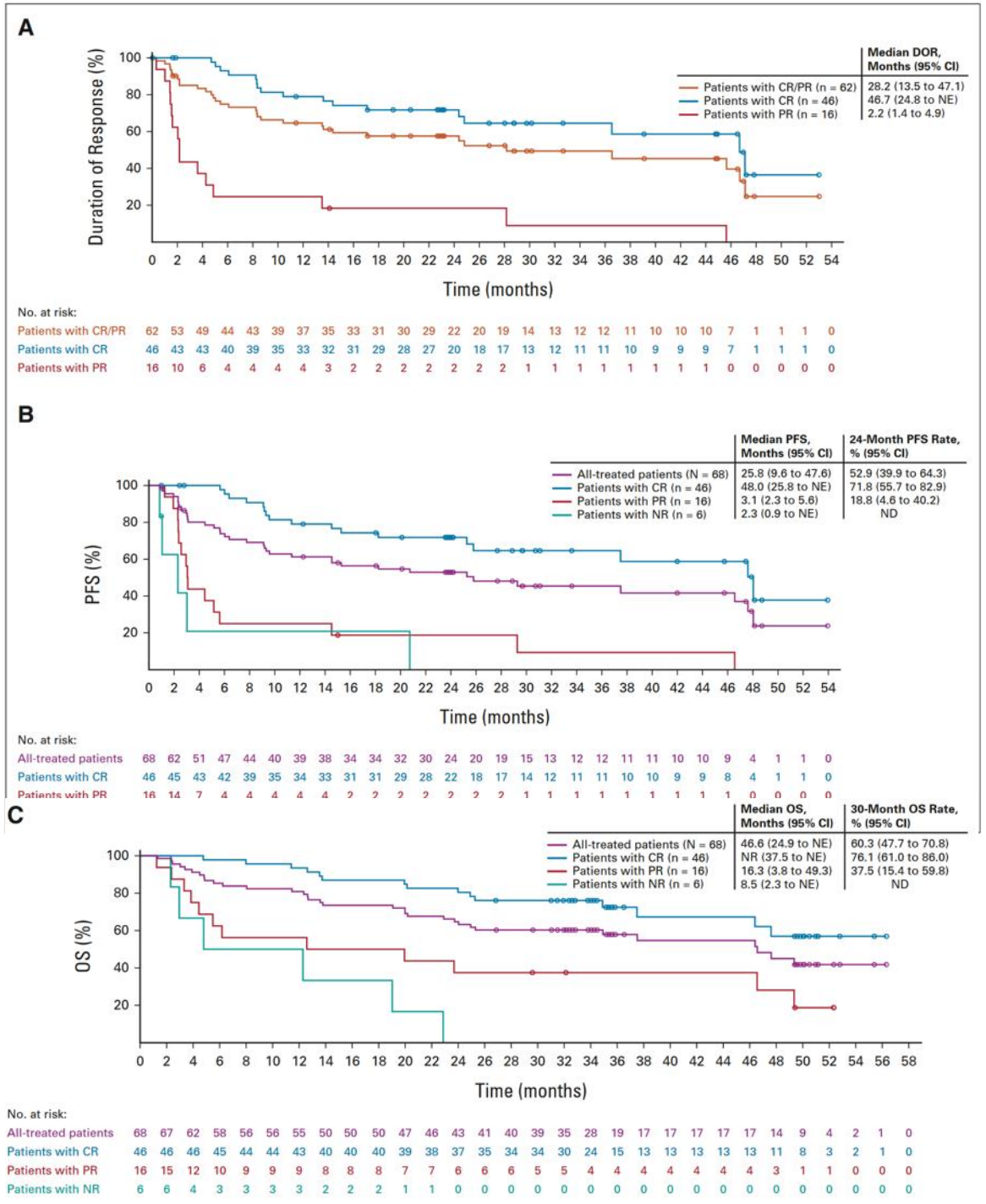
Three-Year Follow-Up of KTE-X19 in Patients With Relapsed/Refractory Mantle Cell Lymphoma, Including High-Risk Subgroups, in the ZUMA-2 Study

Michael Wang, MD[1]; Javier Munoz, MD, MS, MBA[2]; Andre Goy, MD, MS[3]; Frederick L. Locke, MD[4]; Caron A. Jacobson, MD, MMSc[5]; Brian T. Hill, MD, PhD[6]; John M. Timmerman, MD[7]; Houston Holmes, MD, MBA[8]; Samantha Jaglowski, MD[9]; Ian W. Flinn, MD, PhD[10]; Peter A. McSweeney, MB, ChB[11]; David B. Miklos, MD, PhD[12]; John M. Pagel, MD, PhD, DSc[13]; Marie José Kersten, MD, PhD[14]; Krimo Bouabdallah, MD[15]; Rashmi Khanal, MD[16]; Max S. Topp, MD[17]; Roch Houot, MD, PhD[18]; Amer Beitinjaneh, MD[19]; Weimin Peng, PhD[20]; Xiang Fang, PhD[20]; Rhine R. Shen, PhD[20]; Rubina Siddiqi, PhD[20]; Ioana Kloos, MD[20]; and Patrick M. Reagan, MD[21]

Patients with CR/PR mDOR 28.2 m (13.5 to 47.1)

All-treated patients mPFS 25.8 m (9.6 to 47.6)

All-treated patients mOS 46.6 m (24.9 to NE)



Journal of Clinical Oncology® February 08, 2023

original reports

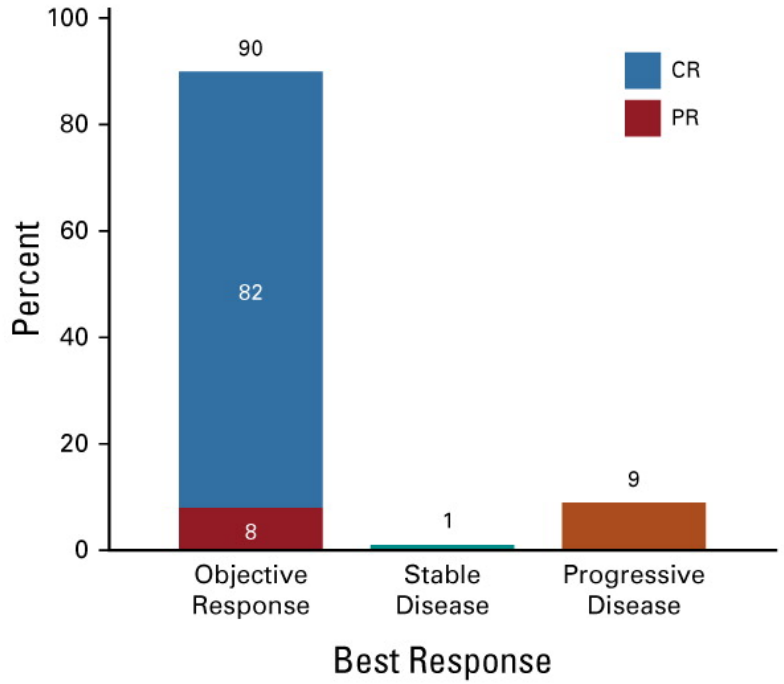
Brexucabtagene Autoleucel for Relapsed or Refractory Mantle Cell Lymphoma in Standard-of-Care Practice: Results From the US Lymphoma CAR T Consortium

Yucai Wang, MD, PhD[1]; Preetesh Jain, MBBS, MD, DM, PhD[2]; Frederick L. Locke, MD[3]; Matthew J. Maurer, DMSc[1]; Matthew J. Frank, MD, PhD[4]; Javier L. Munoz, MD, MS, MBA[5]; Saurabh Dahiya, MBBS[6]; Amer M. Beitinjaneh, MD[7]; Miriam T. Jacobs, MD[8]; Joseph P. Mcguirk, MD, PhD[9]; Julie M. Vose, MD[10]; Andre Goy, MD[11]; Charalambos Andreadis, MD, MSCE[12]; Brian T. Hill, MD, PhD[13]; Kathleen A. Dorritie, MD[14]; Olalekan O. Oluwole, MBBS, MPH[15]; Abhinav Deol, MD[16]; Jonas Paludo, MD[1]; Bijal Shah, MD[3]; Trent Wang, DO, MPH[7]; Rahul Banerjee, MD[12]; David B. Miklos, MD[4]; Aaron P. Rapoport, MD[6]; Lazaros Lekakis, MD[7]; Armin Ghobadi, MD[8]; Sattva S. Neelapu, MD[2]; Yi Lin, MD, PhD[1]; Michael L. Wang, MD[2]; and Michael D. Jain, MD, PhD[3]

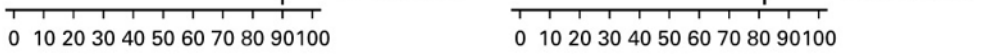
LK: 189 patients
CART: 168 patients

RWE

A



Subgroup	ORR (95% CI)	CR Rate (95% CI)
All (n = 168)	90 (84 to 94)	82 (75 to 88)
Blastoid/pleomorphic		
No (n = 100)	90 (82 to 95)	82 (73 to 89)
Yes (n = 68)	90 (80 to 96)	82 (71 to 91)
TP53 aberration		
No (n = 65)	91 (81 to 97)	88 (77 to 95)
Yes (n = 61)	89 (78 to 95)	72 (59 to 83)
Complex karyotype		
No (n = 80)	86 (77 to 93)	81 (71 to 89)
Yes (n = 31)	87 (70 to 96)	74 (55 to 88)
Ki-67 proliferation index		
< 30% (n = 34)	91 (76 to 98)	91 (76 to 98)
30%-49% (n = 32)	97 (84 to 100)	84 (67 to 95)
≥ 50% (n = 86)	88 (80 to 94)	78 (68 to 86)
Simplified MIPI risk group		
Low risk (n = 55)	95 (85 to 99)	91 (80 to 97)
Intermediate risk (n = 87)	90 (81 to 95)	82 (72 to 89)
High risk (n = 26)	81 (61 to 93)	65 (44 to 83)
POD24		
No (n = 81)	94 (86 to 98)	89 (80 to 95)
Yes (n = 87)	86 (77 to 93)	76 (65 to 84)
CNS involvement		
No (n = 152)	91 (85 to 95)	83 (76 to 89)
Yes (n = 16)	81 (54 to 96)	75 (48 to 93)
BTKi history		
BTKi-naïve (n = 24)	96 (79 to 100)	88 (68 to 97)
BTKi-exposed (n = 144)	89 (83 to 94)	81 (74 to 87)
BTKi-refractory (n = 128)	89 (82 to 94)	80 (73 to 87)
BTKi intolerance (n = 10)	80 (44 to 97)	80 (44 to 97)
BTKi-sensitive (n = 6)	100 (54 to 100)	100 (54 to 100)
ZUMA-2 eligibility		
Eligible (n = 39)	90 (76 to 97)	85 (69 to 94)
Ineligible (n = 129)	90 (83 to 95)	81 (74 to 88)
Ineligible because of BTKi- or anthracycline-/bendamustine-naïve (n = 26)	96 (80 to 100)	96 (80 to 100)
Ineligible because of disease status or comorbidities (n = 103)	88 (81 to 94)	78 (68 to 85)
Bridging therapy		
No (n = 54)	93 (82 to 98)	81 (69 to 91)
Yes (n = 114)	89 (81 to 94)	82 (74 to 89)



Wang Y. et al, J Clin Oncol 2023

Journal of Clinical Oncology® February 08, 2023

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" […] efficacy and toxicity of brexu-cel were consistent with those reported in the ZUMA-2 trial […]"

	CRS and ICANS Incidences			
Measurement	CRS	ICANS	CRS in ZUMA-2, %	Neurologic Events in ZUMA-2, %
Total, No. (%)	151 (90)	103 (61)	91	63
Maximum grade, No. (%)				
1-2	138 (82)	49 (29)	76	32
3-4	12 (7)	54 (32)	15	31
5	1 (1)			
Days to onset, median (range)	4 (0-13)	6 (1-18)	2 (1-13)	7
Days to maximum grade, median (range)	5 (0-30)	8 (1-18)	—	—
Duration in days, median (range)	5 (1-33)	6 (1-144+)[a]	11	12
Management of CRS and/or ICANS				
Tocilizumab	129 (77)[b]		In ZUMA-2, for CRS: 59%	In ZUMA-2, for neurologic event: 26%
Tocilizumab doses, No., median (range)	2 (1-4)			
Corticosteroids	116 (69)		In ZUMA-2, for CRS: 22%	In ZUMA-2, for neurologic event: 38%
Anakinra[c]	28 (17)			
Siltuximab[d]	5 (3)			

Other Adverse Events and Management of Interest

Adverse Event/Management	No. (%)	Adverse Event/Management	Day 30, No./n (%)	Day 90, No./n (%)
ICU admission	34 (20)	Hemoglobin < 8 g/dL	13/164 (8)	8/146 (5)
ICU days, median (range)	3 (1-12)	Platelet < 50,000/μL	70/164 (43)	16/146 (11)
Vasopressors	18 (11)	ANC < 1,000/μL	54/164 (33)	27/146 (18)
Mechanical ventilation	5 (3)	ANC < 500/μL	23/164 (14)	9/146 (6)
Dialysis[e]	4 (2)	Infections[f]	Days 0-30: 35/168 (21)	Days 31-90: 19/164 (12)

Abbreviations: ANC, absolute neutrophil count; CRS, cytokine release syndrome; ICANS, immune effector cell–associated neurotoxicity syndrome; ICU, intensive care unit.

[a]At day 90, 12 (8%) of 154 patients reported ongoing cognitive deficits of varying degrees.

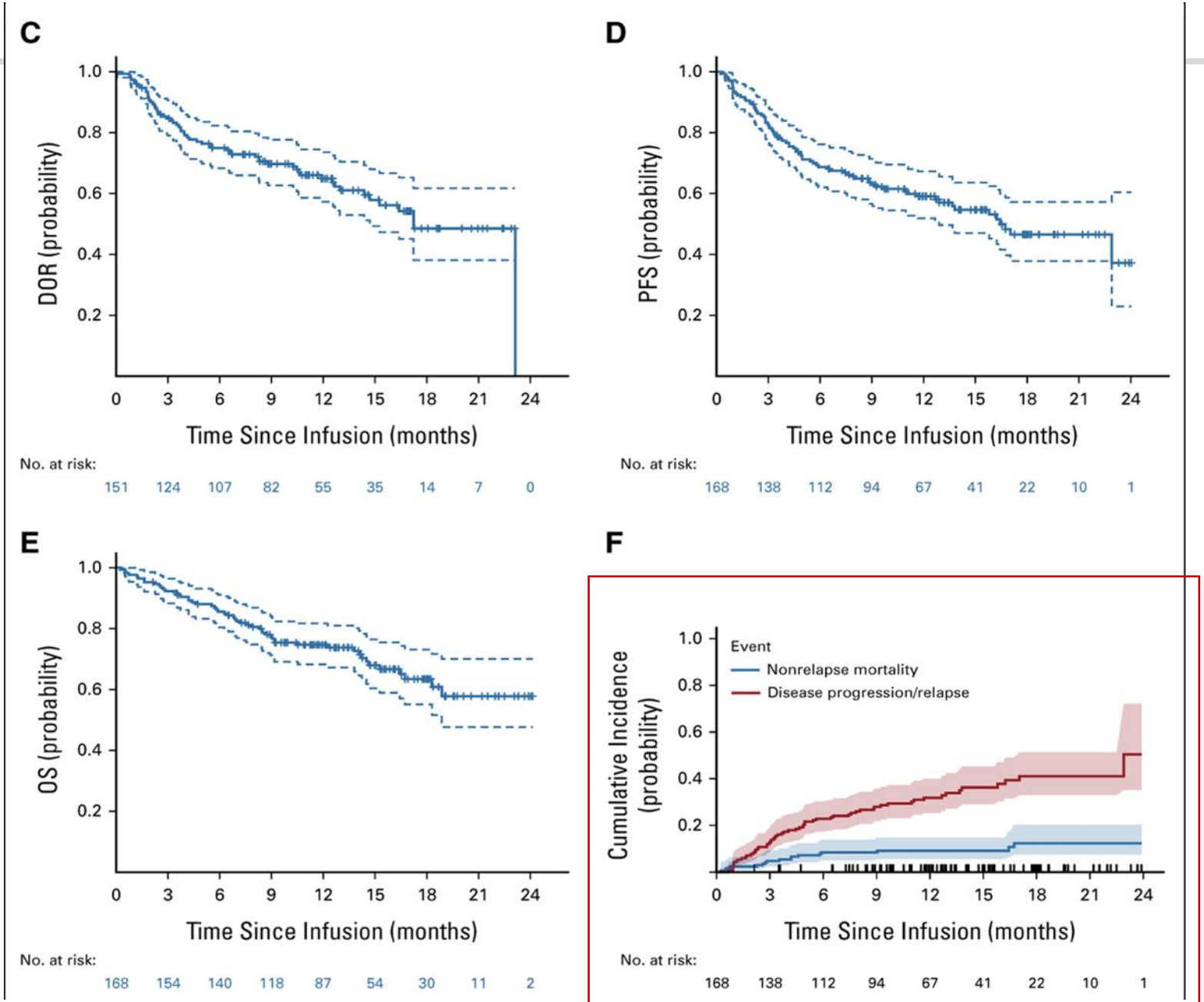
[b]Fifty-four of 71 patients (76%) with maximum grade 1 CRS received tocilizumab, of which 26 had maximum grade 1 ICANS and 28 had grade 2 or higher ICANS.

[c]Ankinra was used for CRS (n = 4), ICANS (n = 16), both CRS and ICANS (n = 6), possible macrophage activation syndrome (n = 1), or suspected hemophagocytic lymphohistiocytosis (n = 1). Tocilizumab and corticosteroids were used in all these patients.

[d]Siltuximab was used for CRS (n = 2, in the setting of tocilizumab shortage), ICANS (n = 2), or both (n = 1, in the setting of tocilizumab shortage).

[e]One patient was on dialysis at baseline. For the three patients who started dialysis after CAR T-cell infusion, one died of grade 5 CRS, one died of multiorgan failure, and one recovered renal function.

[f]Bacterial, fungal, or viral infections that required antimicrobial treatment. Prophylactic antimicrobial use without infection was not counted.



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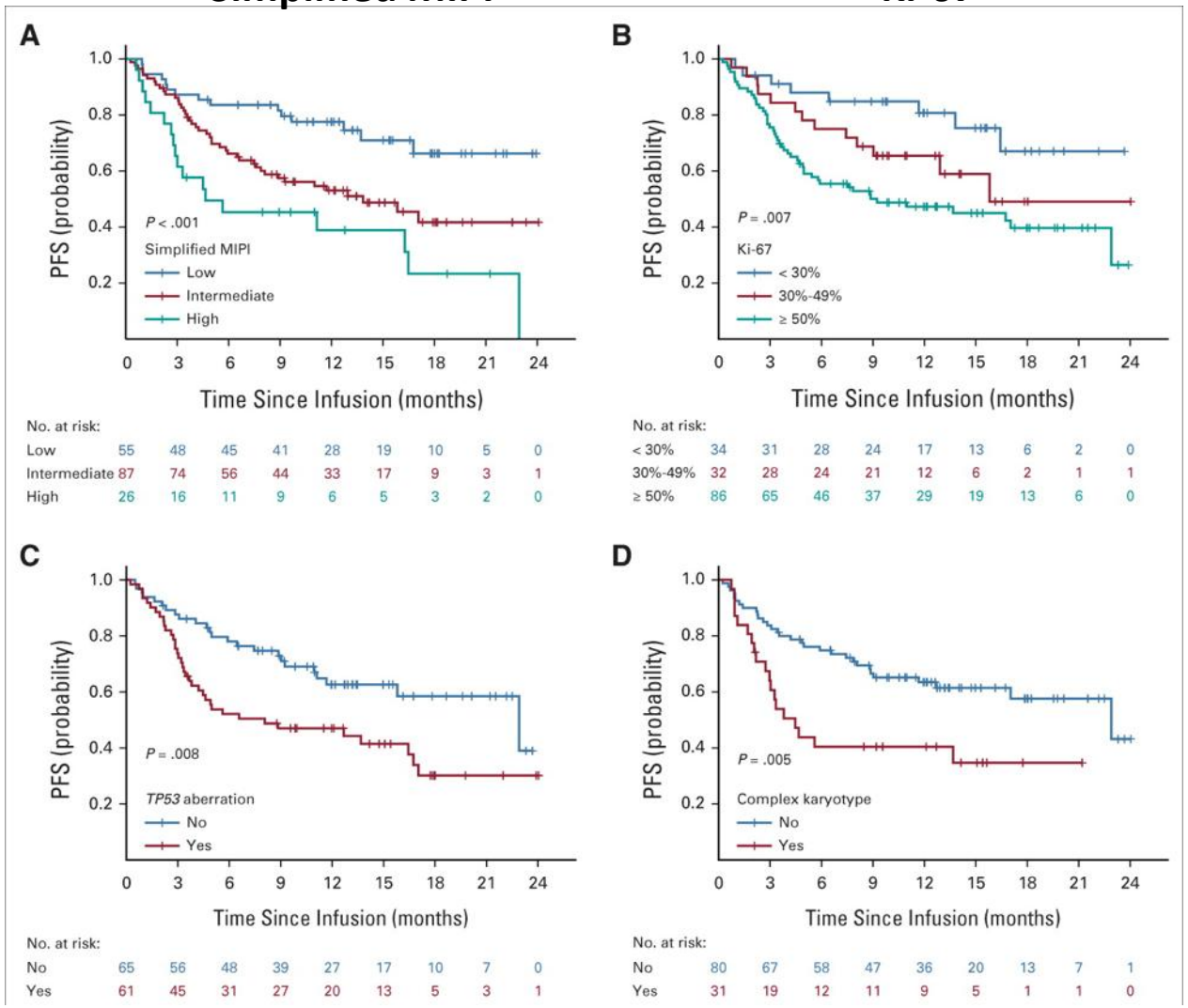
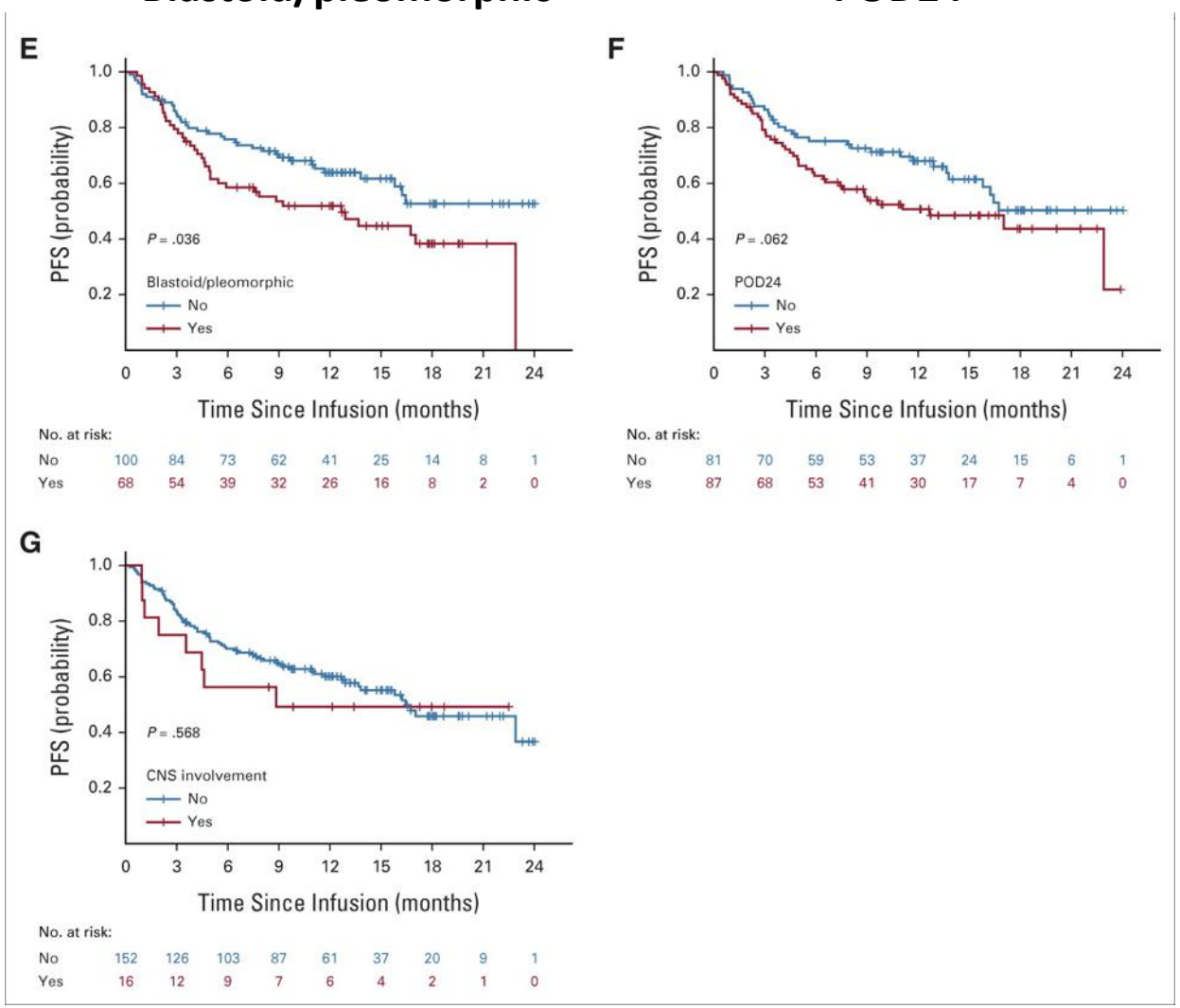
Simplified MIPI | **Ki-67** | **Blastoid/pleomorphic** | **POD24**





TP53 aberrations | **Complex Karyotype** | **CNS involvement**

Wang Y. et al, J Clin Oncol 2023

A systematic review and meta-analysis of nonrelapse mortality after CAR T cell therapy

David M. Cordas dos Santos[1,2,3,4,11], Tobias Tix[4,11], Roni Shouval[5,6], Anat Gafter-Gvili[7,8], Jean-Baptiste Alberge[1,2,3], Edward R. Scheffer Cliff[1,2,9], Sebastian Theurich[4,10], Michael von Bergwelt-Baildon[4,10], Irene M. Ghobrial[1,2,3], Marion Subklewe[4,10], Miguel-Angel Perales[5,6] & Kai Rejeski[4,5,6,10]

nature medicine
| Volume 30 | September 2024 |

A focus on toxicity…

Entity	Study	Author, ref.	Year	Treatment setting	Product	Cohort size	Number of deaths	Follow-up (months)	Reported NRM (%)	NRM point estimate (%)	Therapy line	Inclusion before/ after 2020
IL	ELARA	Dreyling et al.[33]	2024	Phase I–II	Tisa-Cel	97	5	29	N/R	5.15	Later	After
	ZUMA-5	Jacobson et al.[34]	2022A	Phase I–II	Axi-Cel	148	9	17.5	N/R	6.08	Later	After
LBCL	TRANSCEND NHL 001	Abramson et al.[35]	2020	Phase I–II	Liso-Cel	269	7	18.8	N/R	2.60	Later	Before
	BELINDA	Bishop et al.[36]	2022	Phase III	Tisa-Cel	155	9	40.3	N/R	5.80	Earlier	After
	ALYCANTE	Houot et al.[37]	2023	Phase I–II	Axi-Cel	62	7	12	N/R	11.29	Earlier	After
	TRANSFORM	Kamdar et al.[38]	2022	Phase III	Liso-Cel	92	5	6.2	N/R	5.43	Earlier	After
	JapicCTI-183914	Kato et al.[39]	2022	Phase I–II	Axi-Cel	16	0	13.4	N/R	0.00	Later	After
	ZUMA-12	Neelapu et al.[40]	2022	Phase I–II	Axi-Cel	40	2	15.9	N/R	5.00	Earlier	After
	ZUMA-1	Neelapu et al.[41]	2023	Phase I–II	Axi-Cel	101	13	63.1	N/R	12.87	Later	Before
	PILOT	Sehgal et al.[42]	2022	Phase I–II	Liso-Cel	61	4	13	N/R	6.56	Earlier	After
	ZUMA-7	Westin et al.[43]	2023	Phase III	Axi-Cel	170	23	47.2	N/R	13.53	Earlier	Before
MM	CRB-401	Lin et al.[44]	2023	Phase I–II	Ide-Cel	62	2	18.1	N/R	3.23	Later	Before
	CARTITUDE-1	Martin et al.[45]	2023	Phase I–II	Cilta-Cel	97	16	28	N/R	16.49	Later	Before
	CARTIFAN-1	Mi et al.[46]	2022	Phase I–II	Cilta-Cel	48	9	18	N/R	18.75	Later	After
	KarMMa	Munshi et al.[47]	2021	Phase I–II	Ide-Cel	128	9	13.3	N/R	7.03	Later	Before
	KarMMa-3	Rodriguez-Otero et al.[48]	2023	Phase III	Ide-Cel	225	18	18.6	N/R	8.00	Earlier	After
	CARTITUDE-4	San-Miguel et al.[49]	2023	Phase III	Cilta-Cel	176	24	15.9	N/R	13.64	Earlier	After
MCL	ZUMA-2	Wang et al.[50]	2023	Phase I–II	Brexu-Cel	68	5	35.6	N/R	7.35	Later	Before

N/R, not reported.

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Entity	Author, ref.	Year	Cohort	Product	Cohort size	Number of deaths	Follow-up (months)	Reported NRM (%)	NRM point estimate (%)	Therapy line	Inclusion before/ after 2020
MCL	Chong et al.[71]	2024		Brexu-Cel	17	4	24.5	N/R	23.53	Later	After
	Iacoboni et al.[72]	2022		Brexu-Cel	33	5	10.1	N/R	15.15	Later	After
	Rejeski et al.[12]	2023		Brexu-Cel	54	4	15.4[b]	N/R	7.41	Later	After
	Wang et al.[73]	2023		Brexu-Cel	168	18	14.3	9.1	10.71	Later	After

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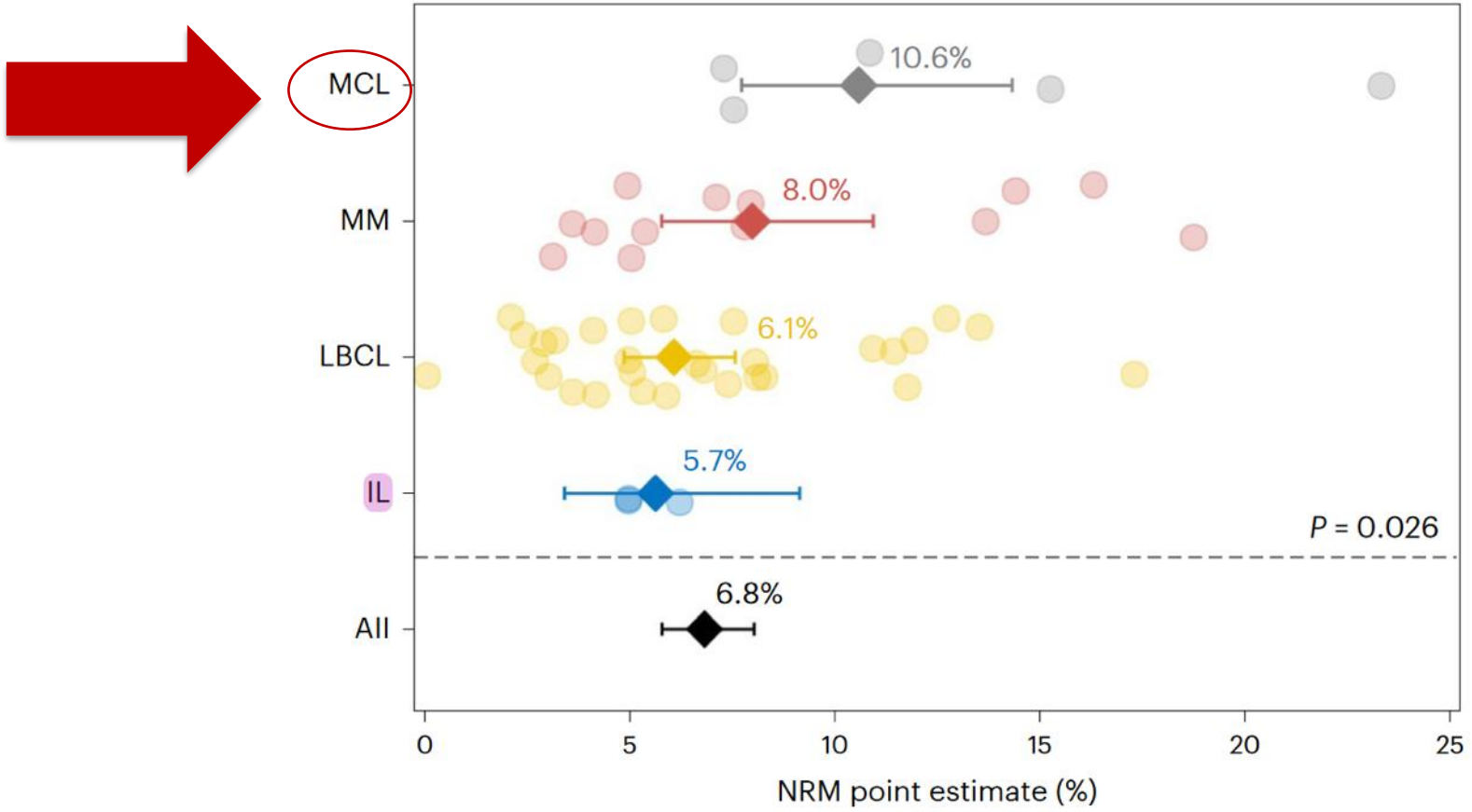

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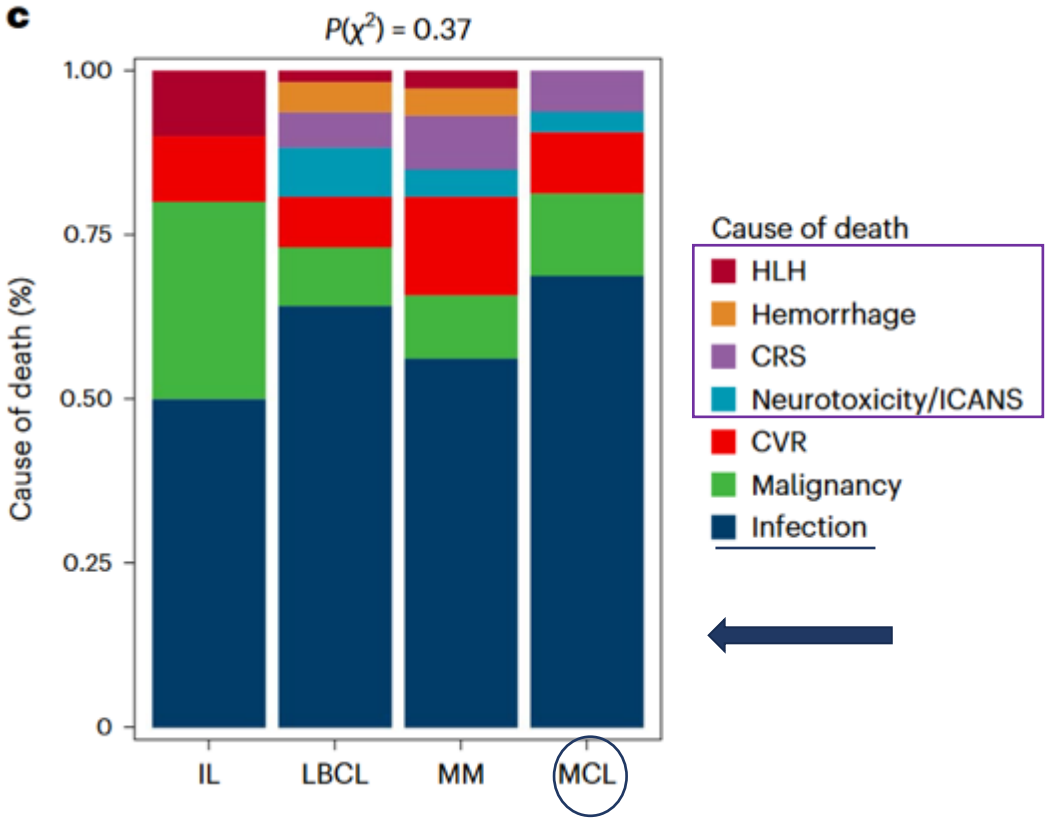
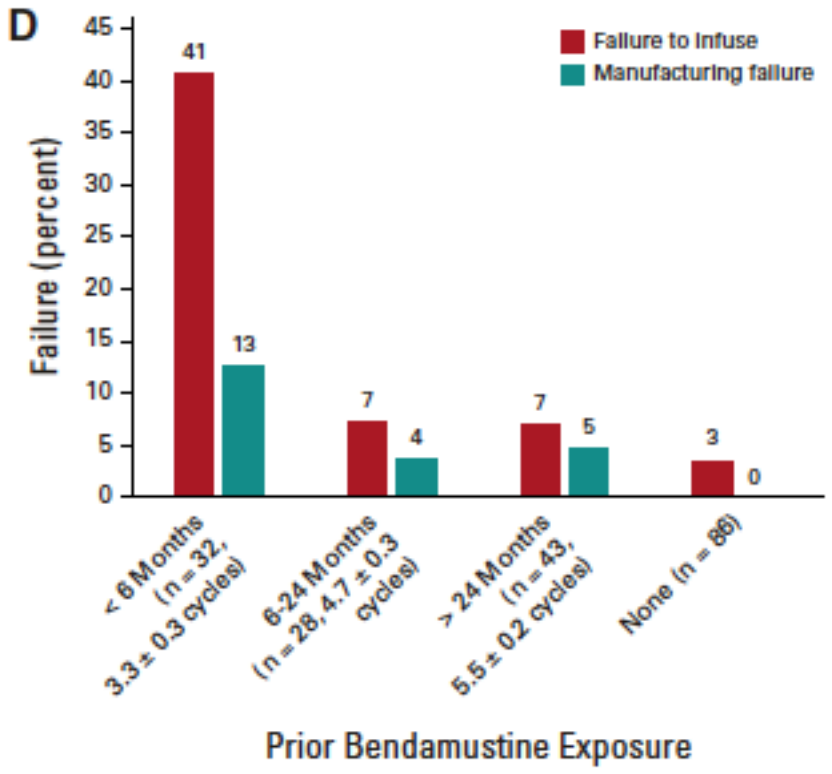
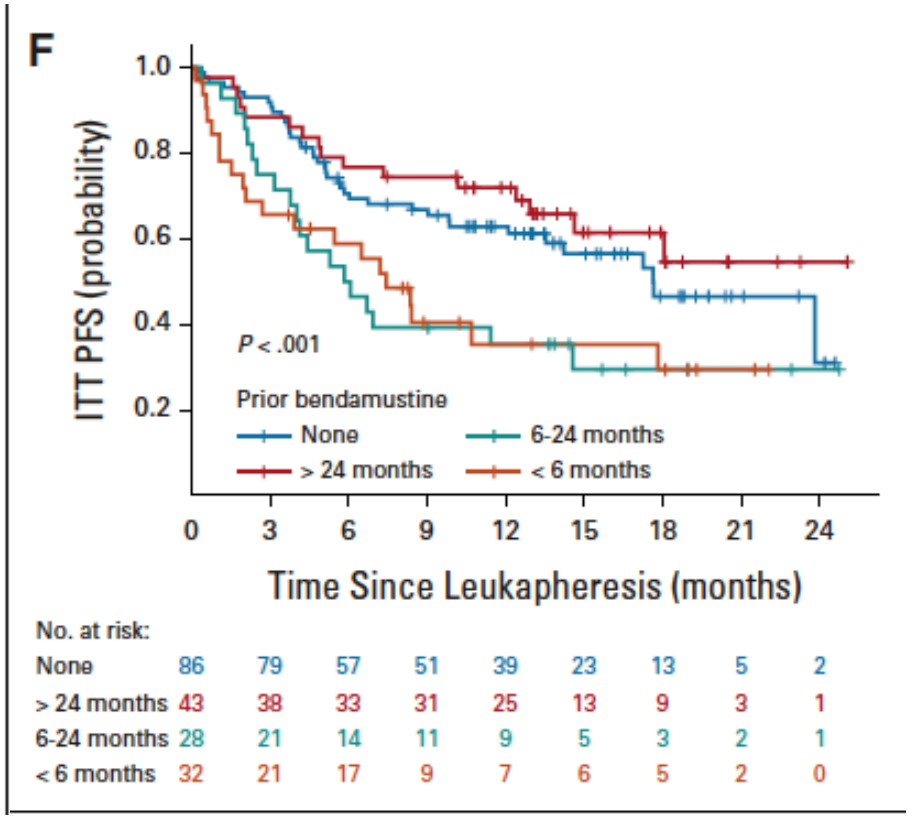


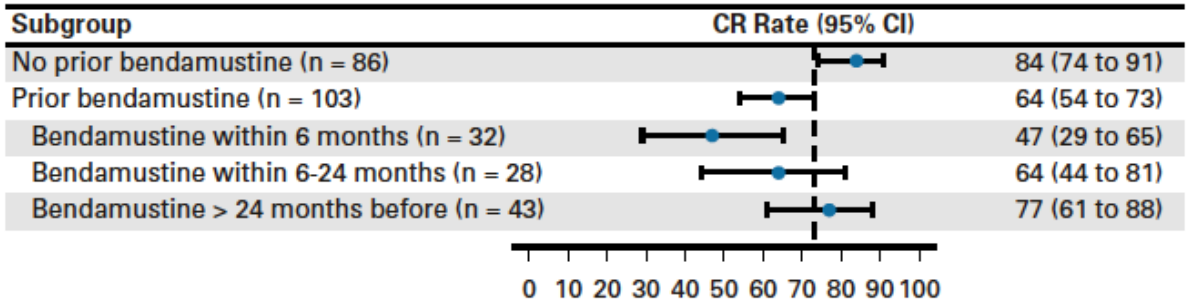
Brexu-cel in RWE: impact of prior **bendamustine** exposure





< 6 months

6 -24 months



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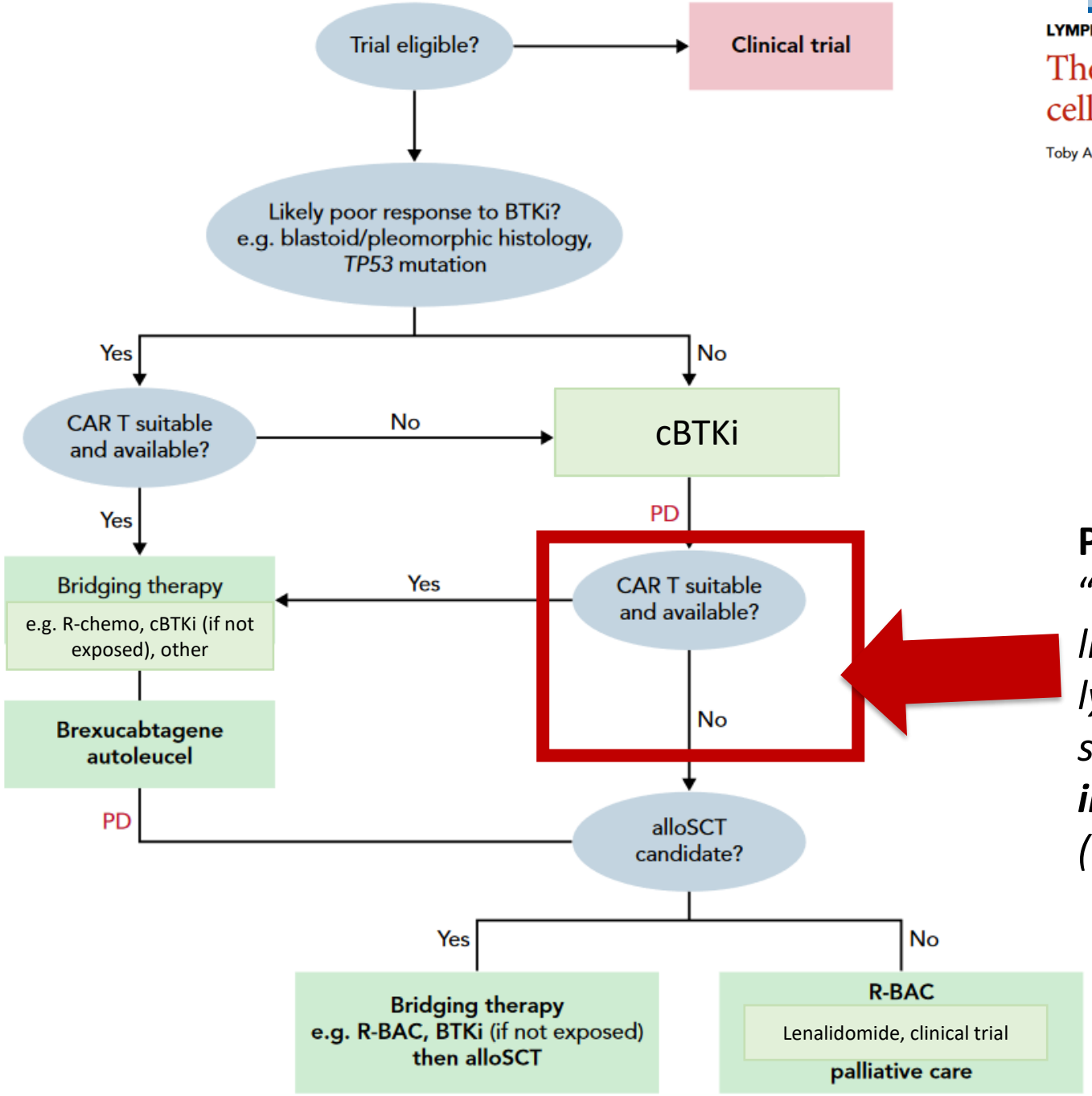


LYMPHOID NEOPLASIA

Therapeutic options for relapsed/refractory mantle cell lymphoma

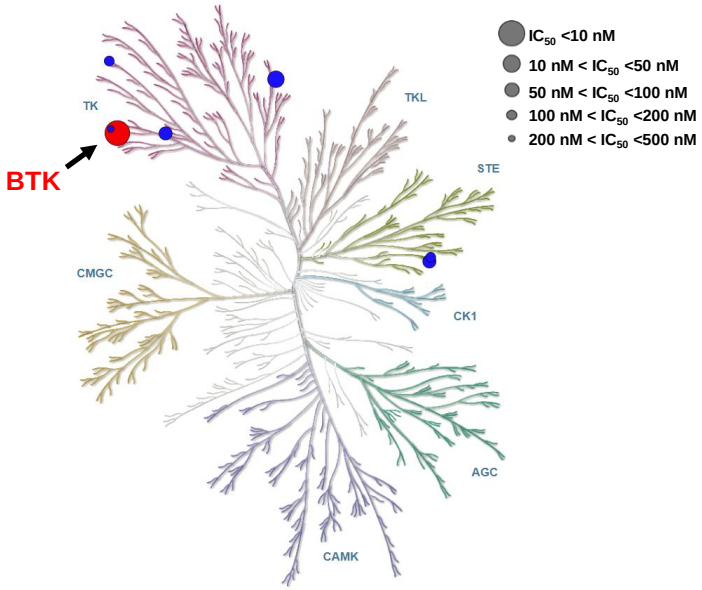
Toby A. Eyre,[1] Chan Y. Cheah,[2,3] and Michael L. Wang[4]

Pirtobrutinib è prescrivibile per il "*trattamento di pazienti adulti affetti da linfoma a cellule mantellari (mantle cell lymphoma, MCL) recidivante o refrattario che sono stati* ***precedentemente trattati con un inibitore della tirosin chinasi di Bruton*** *(Bruton's tyrosine kinase, BTK)*".

Modified from Eyre TA et al., Blood 2022

Pirtobrutinib is a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor

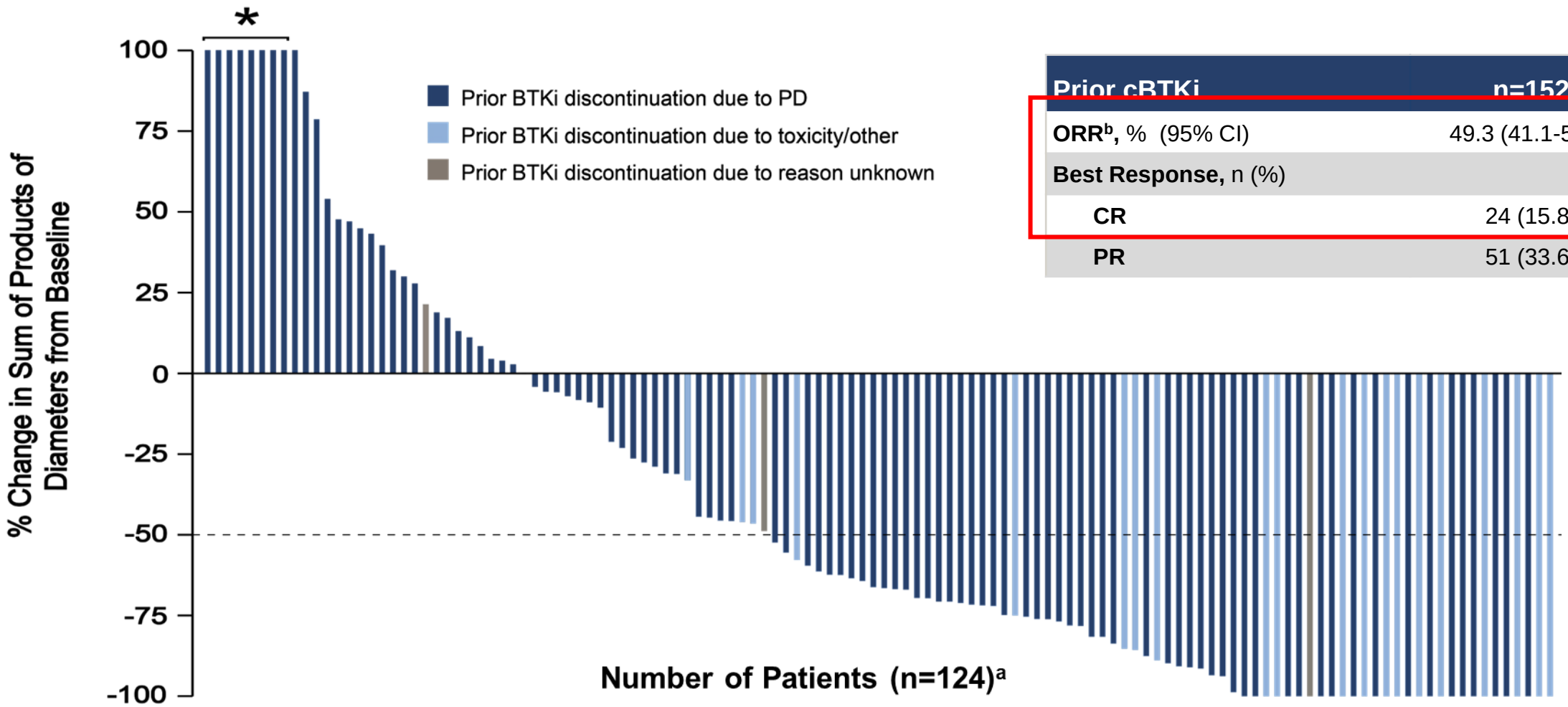
Highly selective for BTK[3,7]



- Inhibits both WT and C481-mutant BTK with equal low nM potency[8]
- Steady state plasma exposure corresponding to 96% BTK target inhibition and a half-life of about 20 hours[8]
- In contrast to cBTKi (A), pirtobrutinib (B) appears to stabilize BTK in a closed, inactive conformation, blocking access to upstream kinases and phosphorylation of Y551, thus inhibiting scaffolding interactions that support kinase-independent BTK signaling[8]

[3]Mato et al. *Lancet* 2021; 397: 892–901. [7]Brandhuber et al. *Clin Lymphoma Myeloma Leuk* 2018; 18(Suppl.1):S216. [8]Gomez et al. *Blood*.2023; 142(1):62-72.

Pirtobrutinib Efficacy in Patients with MCL who Received Prior cBTKi



Prior cBTKi	n=152
ORR[b], % (95% CI)	49.3 (41.1-57.6)
Best Response, n (%)	
CR	24 (15.8)
PR	51 (33.6)

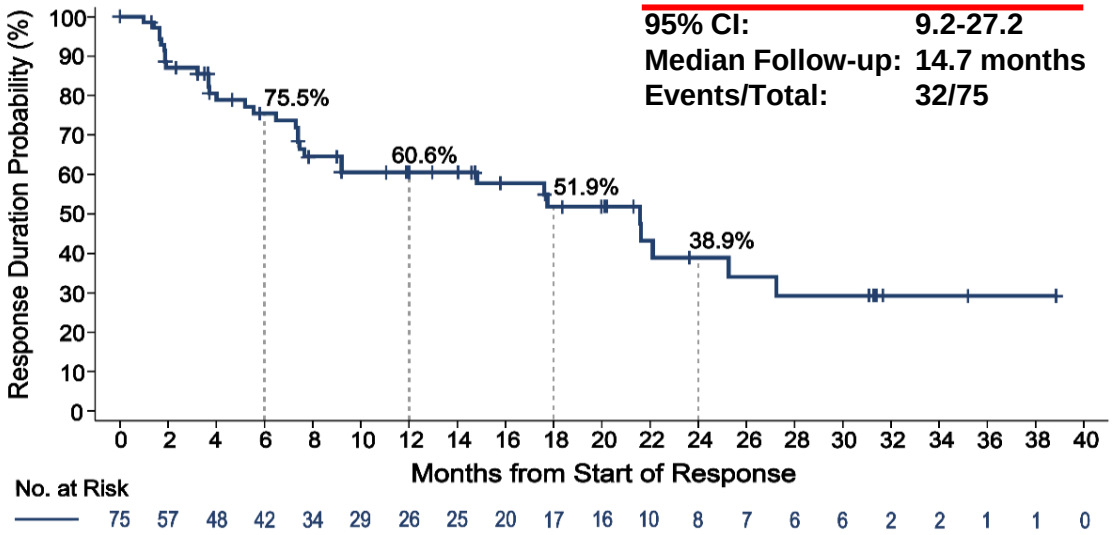
Median Time to First Response was 1.8 months (range: 0.8-13.8)

Data of patients with baseline and at least one evaluable post baseline tumor measurement. *Patients with >100% increase in SPD. [a]Data for 28/152 patients who received prior cBTKi are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [b]ORR is the number of patients with best response of CR or PR divided by the total number of patients; 13 patients with a best response of not evaluable (NE) are included in the denominator. Response status per Lugano 2014 criteria based on IRC assessment.

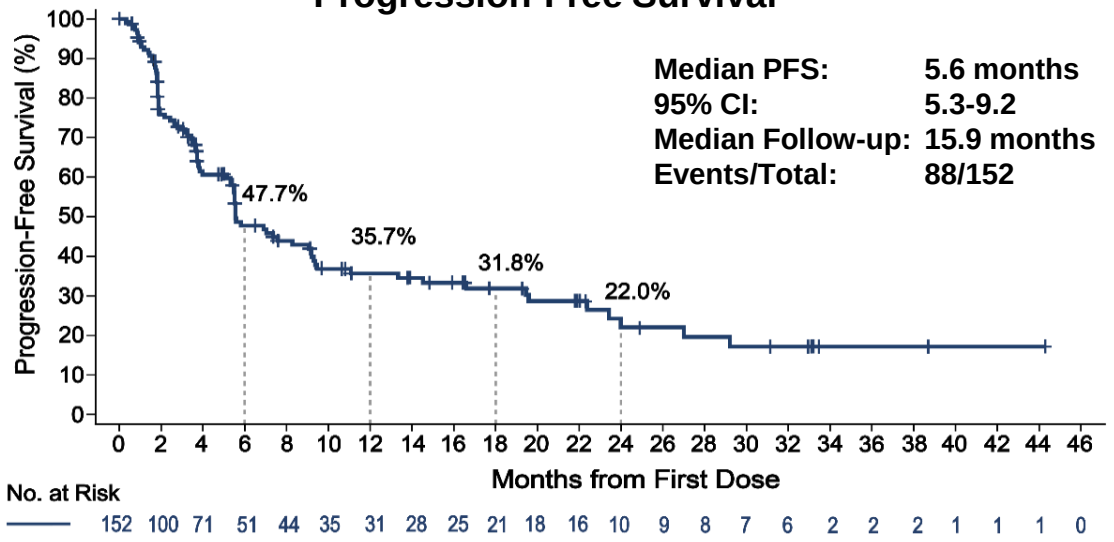
Cohen et al.; ASH 2023

Pirtobrutinib Outcomes in Prior cBTKi Patients with MCL

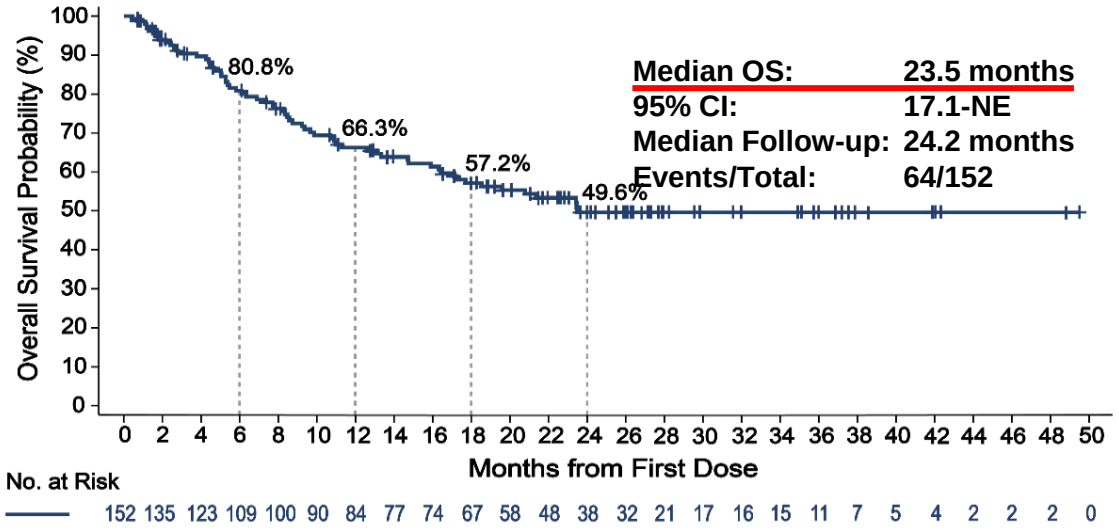
Duration of Response



Progression-Free Survival



Overall Survival



Cohen et al.; ASH 2023

Pirtobrutinib Safety Profile in MCL Patients

	Treatment-Emergent AEs in Patients with MCL (n=166)			
	All Cause AEs, (≥15%), %		Treatment-Related AEs, %	
Adverse Event	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	31.9	3.0	21.1	2.4
Diarrhea	22.3	0.0	12.7	0.0
Dyspnea	17.5	1.2	9.0	0.6
Anemia	16.9	7.8	7.2	2.4
Platelet Count Decreased	15.1	7.8	7.8	3.0
AEs of Interest[a]	**Any Grade**	**Grade ≥3**	**Any Grade**	**Grade ≥3**
Infections[b]	42.8	19.9	15.7	3.6
Bruising[c]	16.3	0.0	11.4	0.0
Rash[d]	14.5	0.6	9.0	0.0
Arthralgia	9.0	1.2	2.4	0.0
Hemorrhage[e]	10.2	2.4	4.2	0.6
Hypertension	4.2	0.6	1.8	0.0
Atrial Fibrillation/Flutter[f,g]	3.6	1.8	0.6	0.0

Median time on treatment was 5.5 months for the MCL cohort

Discontinuations due to TRAEs occurred in 3% (n=5) of patients with MCL

Dose reductions due to TRAEs occurred in 5% (n=8) of patients with MCL

[a]AEs of interest are those that were previously associated with covalent BTK inhibitors. [b]Aggregate of all preferred terms including infection and COVID-19. [c]Aggregate of contusion, bone contusion, ecchymosis, and increased tendency to bruise. [d]Aggregate of all preferred terms including rash. [e]Aggregate of all preferred terms including hemorrhage or hematoma. [f]Aggregate of atrial fibrillation and atrial flutter. [g]Of 6 total atrial fibrillation and atrial flutter TEAEs, 3 occurred in patients with a prior medical history of atrial fibrillation. In the MCL cohort, treatment-related AEs leading to discontinuation included weight decrease/alopecia/fatigue (1), neutropenia (1), platelet count decreased (1), pneumonitis (1), and cholecystitis (1).

Cohen et al.; ASH 2023

Lenalidomide versus investigator's choice in relapsed or refractory mantle cell lymphoma (MCL-002; SPRINT): a phase 2, randomised, multicentre trial

Marek Trněný, Thierry Lamy, Jan Walewski, David Belada, Jiri Mayer, John Radford, Wojciech Jurczak, Franck Morschhauser, Julia Alexeeva, Simon Rule, Boris Afanasyev, Kamil Kaplanov, Antoine Thyss, Alexej Kuzmin, Sergey Voloshin, Kazimierz Kuliczkowski, Agnieszka Giza, Noel Milpied, Caterina Stelitano, Reinhard Marks, Lorenz Trümper, Tsvetan Biyukov, Meera Patturajan, Marie-Laure Casadebaig Bravo, Luca Arcaini, on behalf of the SPRINT trial investigators and in collaboration with the European Mantle Cell Lymphoma Network

THE LANCET Oncology
Volume 17, Issue 3, March 2016, Pages 319-331

FURTHER OPTIONS:
LENALIDOMIDE (L648)

	Central review		
	Lenalidomide group (n=170)	Investigator's choice group (n=84)	p value
Median progression-free survival, months (95% CI)*	8·7 (5·5–12·1)	5·2 (3·7–6·9)	0·004
Response data			
Proportion of patients who achieved an objective response (n [%, 95% CI])	68 (40%, 33–48)	9 (11%, 5–19)	<0·001
Complete response and unconfirmed complete response	8 (5%)	0	0·043
Partial response	60 (35%)	9 (11%)	..
Stable disease	50 (29%)	44 (52%)	..
Progressive disease	34 (20%)	26 (31%)	..
Response not done or missing†	18 (11%)	5 (6%)	..

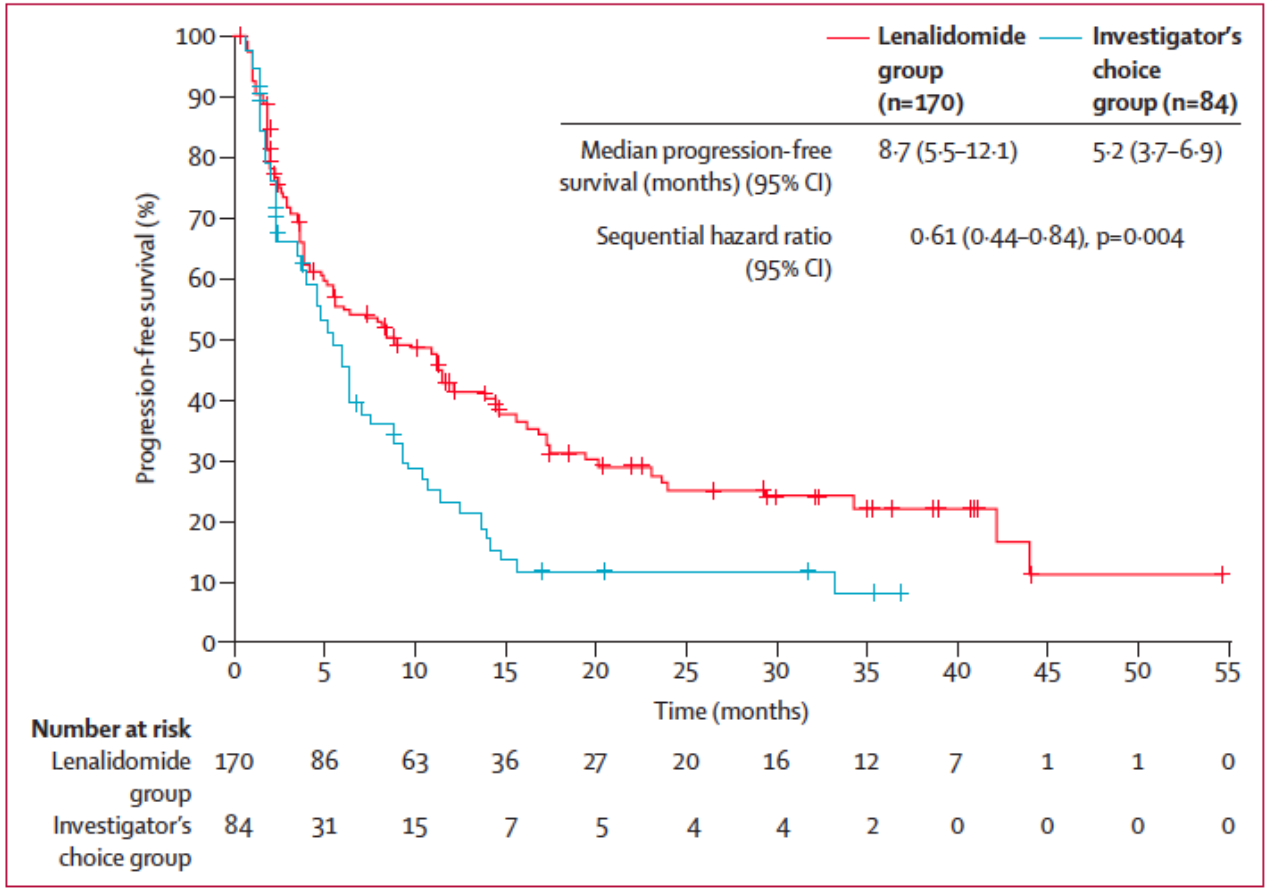


Figure 2: **Progression-free survival with lenalidomide compared with investigator's choice in relapsed or refractory mantle cell lymphoma (central review)**

FURTHER OPTIONS:

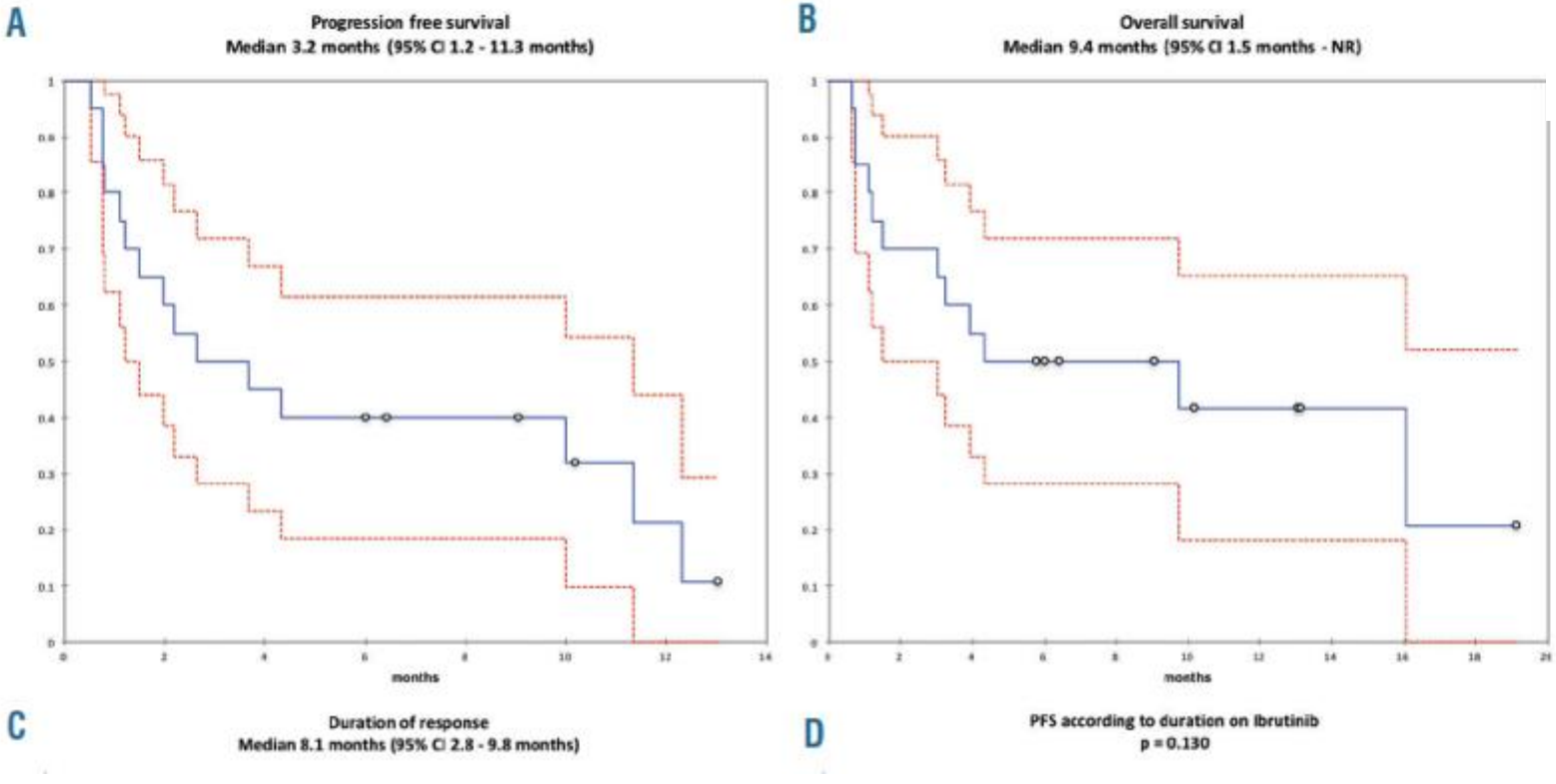
VENETOCLAX (NPP)

LETTERS TO THE EDITOR

haematologica 2019; 104:e68

Efficacy of venetoclax monotherapy in patients with relapsed, refractory mantle cell lymphoma after Bruton tyrosine kinase inhibitor therapy

Toby A. Eyre,[1] Harriet S. Walter,[2] Sunil Iyengar,[3] George Follows,[4] Matthew Cross,[5] Christopher P. Fox,[5] Andrew Hodson,[6] Josh Coats,[7] Santosh Narat,[8] Nick Morley,[6] Martin J.S. Dyer[2] and Graham P. Collins[1]

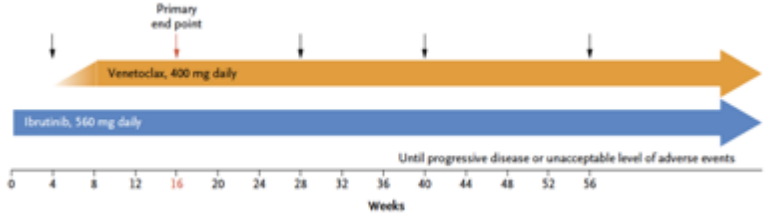


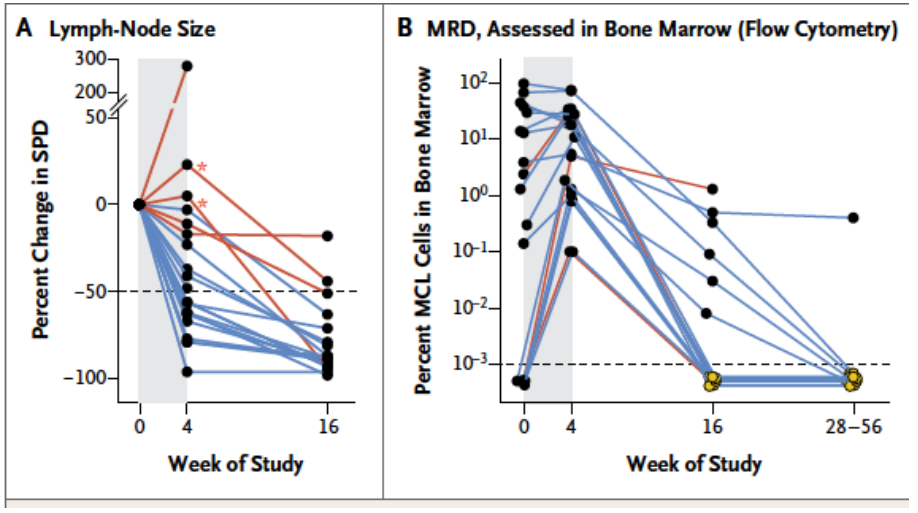
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma

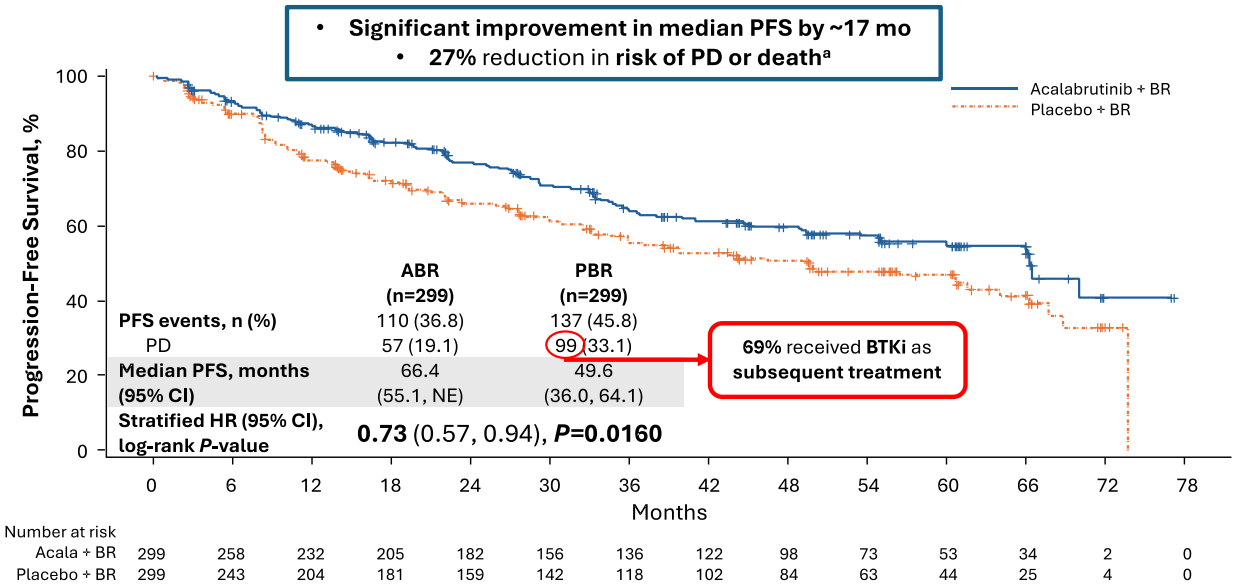
Constantine S. Tam, M.B., B.S., M.D., Mary Ann Anderson, M.B., B.S., Ph.D., Christiane Pott, M.D., Ph.D., Rishu Agarwal, M.B., B.S., Sasanka Handunnetti, M.B., B.S., Rodney J. Hicks, M.B., B.S., Kate Burbury, M.B., B.S., Gillian Turner, B.N., M.I.P.H., Juliana Di Iulio, Ph.D., Mathias Bressel, M.Sc., David Westerman, M.B., B.S., Stephen Lade, M.B., B.S., Martin Dreyling, M.D., Sarah-Jane Dawson, M.B., B.S., Ph.D., Mark A. Dawson, M.B., B.S., Ph.D., John F. Seymour, M.B., B.S., Ph.D., and Andrew W. Roberts, M.B., B.S., Ph.D.

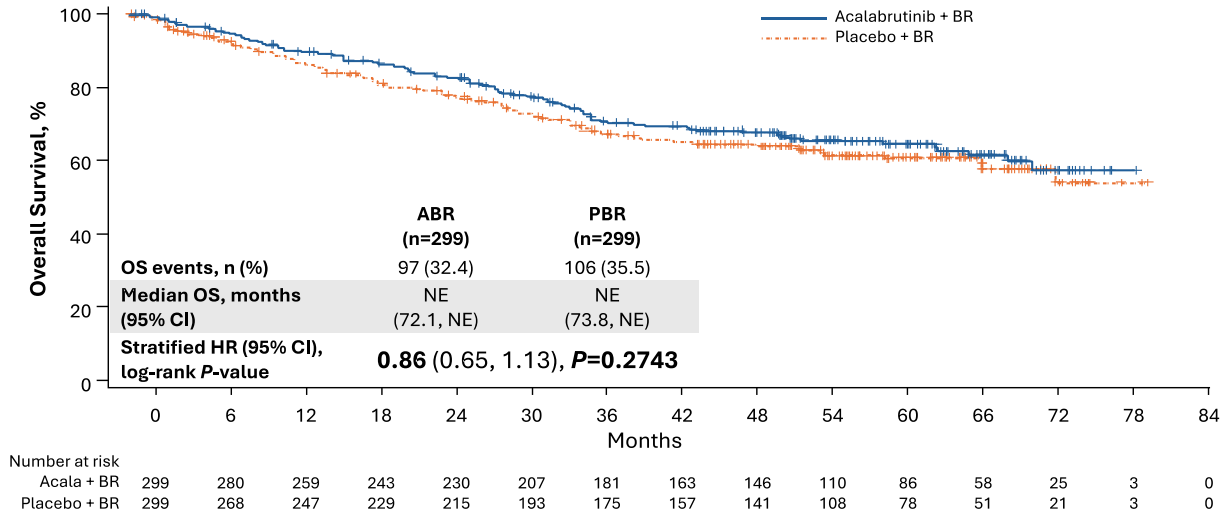





COMING SOON

Coming soon: chemo-containing **triplets** -> Acala-BR (ECHO first-line)



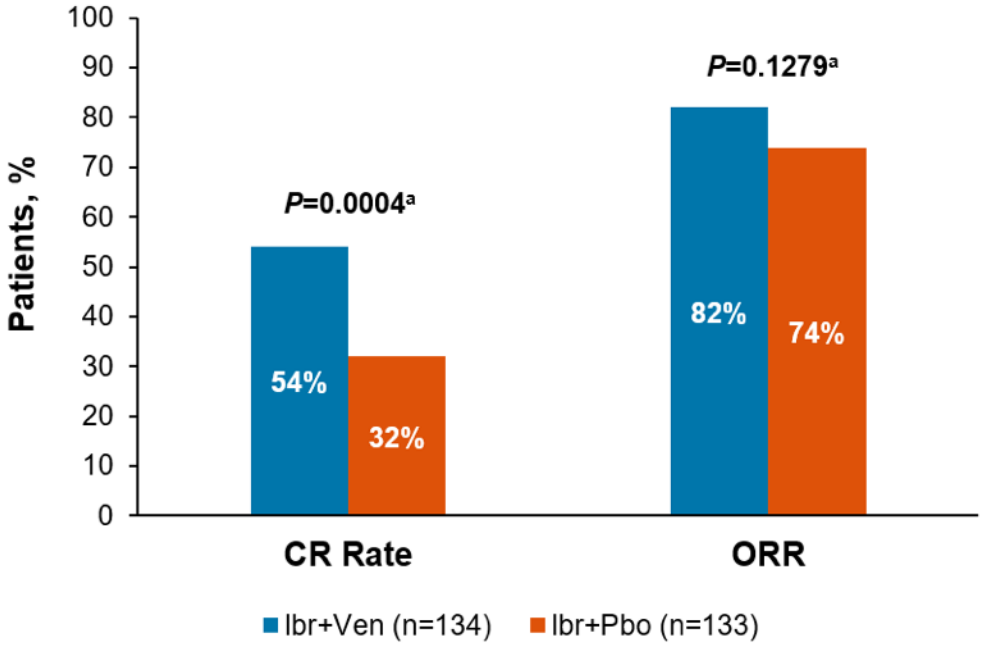


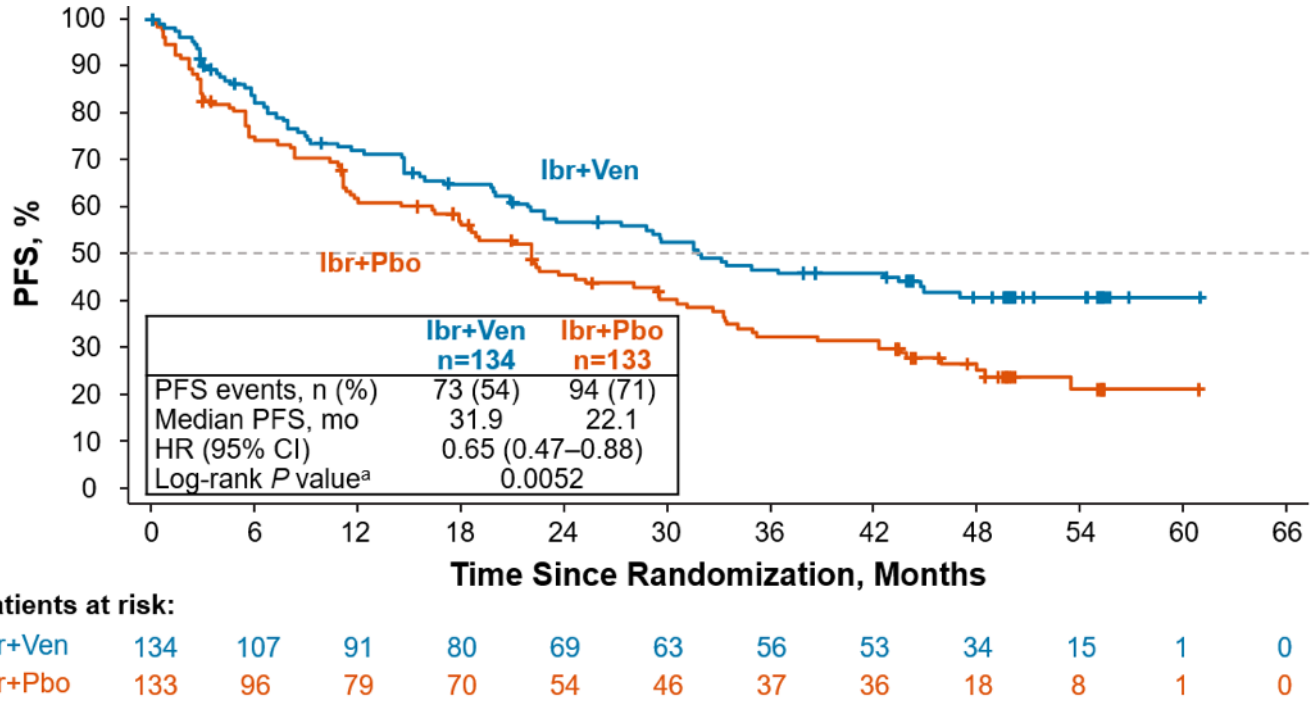
Median follow-up of 45 months.

ABR, acalabrutinib + bendamustine + rituximab; BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PBR, placebo + bendamustine + rituximab.

Wang M et al., EHA 2024

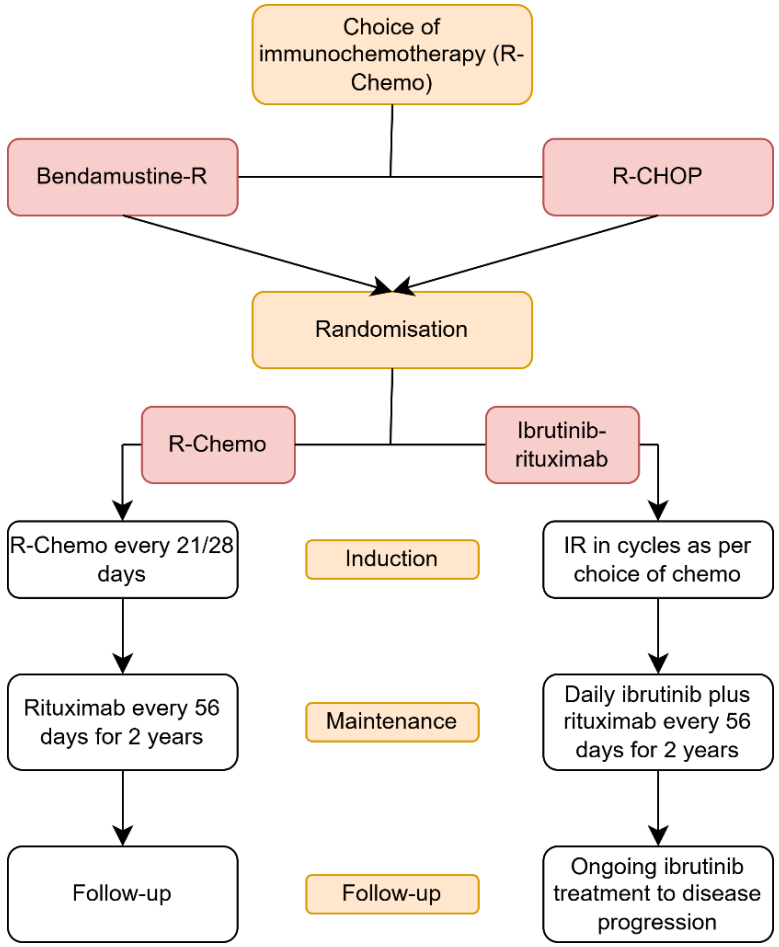
Coming soon: chemo-free **doublets** -> IV (SYMPATICO R/R)

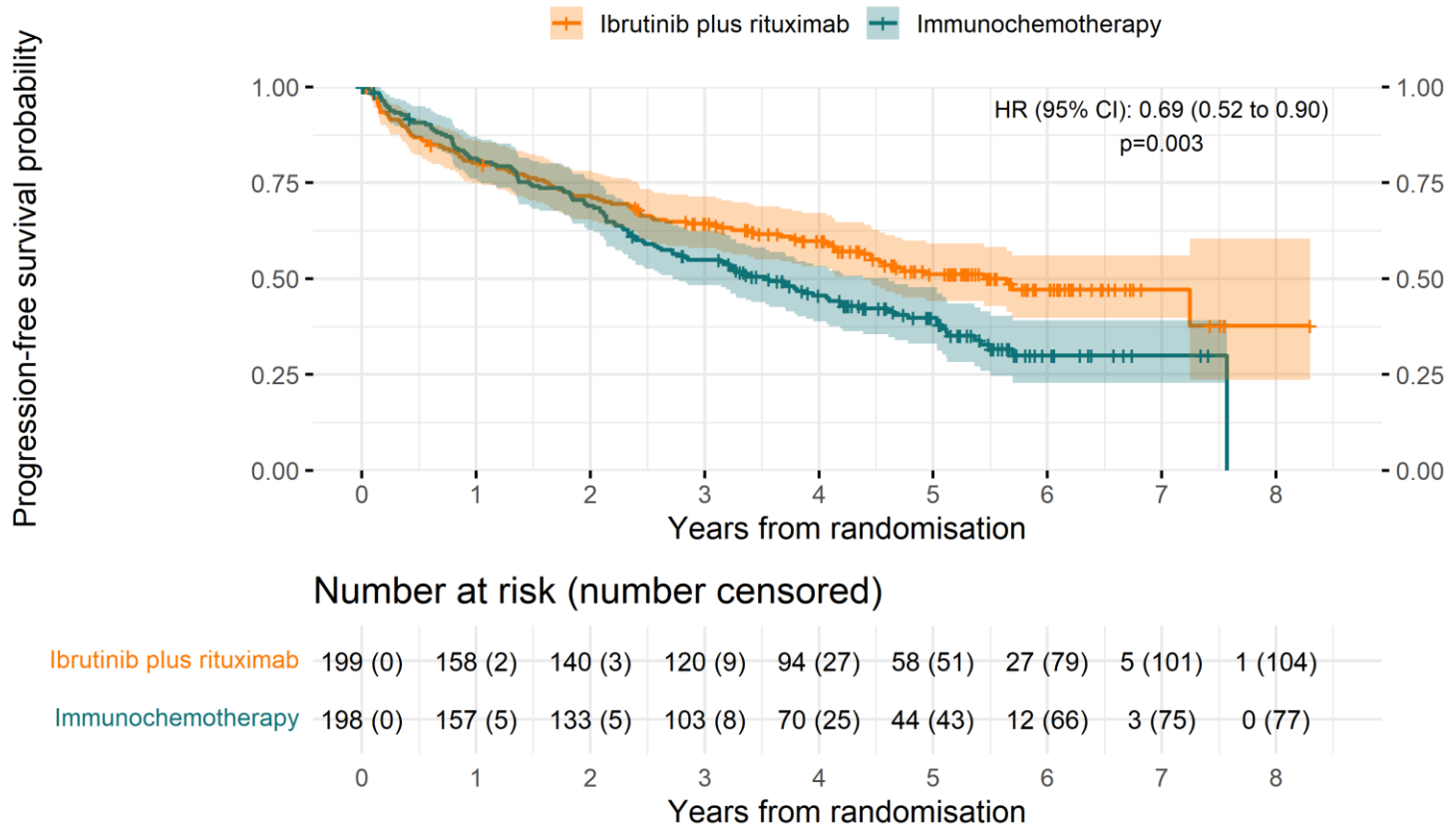




Wang M et al., ASH 2023

Coming soon: chemo-free **doublets** -> IR (first-line)





Median Follow up 47.9 months

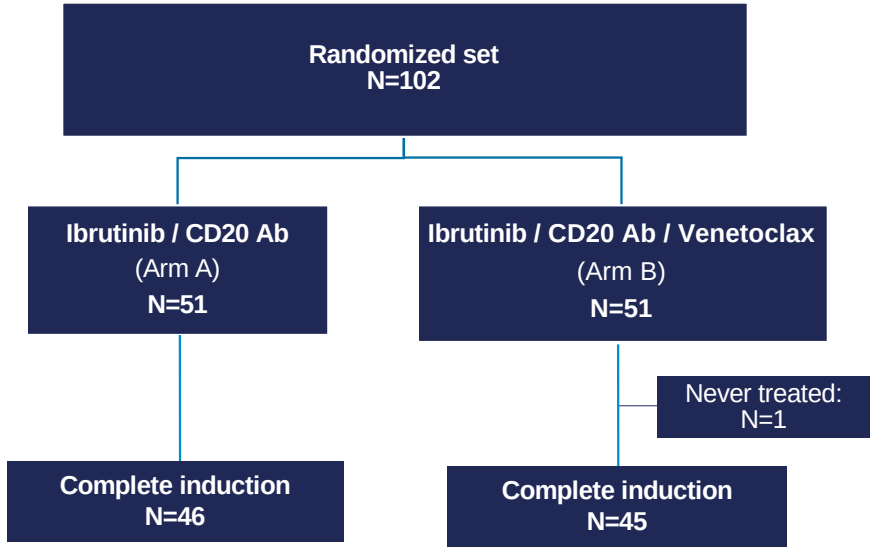
PFS median (95% CI)
IR: 65.3 mo (52.7 to not evaluable)
R-chemo: 42.4 mo (32.7 to 55.3)

Lewis DJ et al., ASH 2024

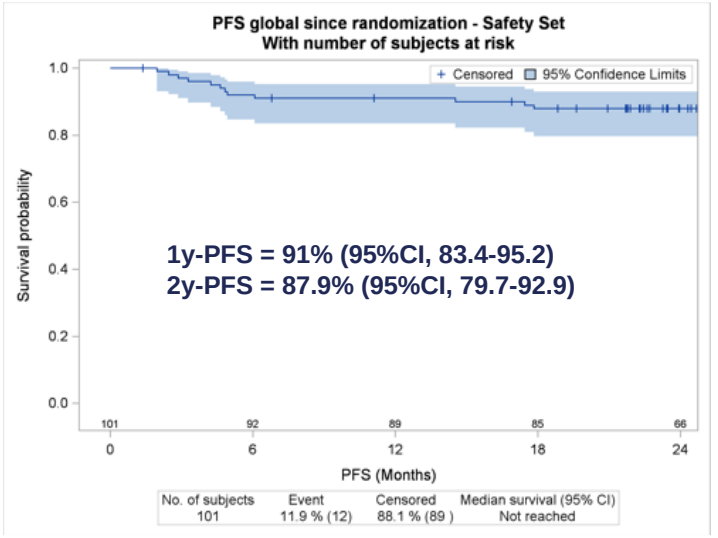
Coming soon: chemo-free **triplets** -> IVR (OASIS II first-line)

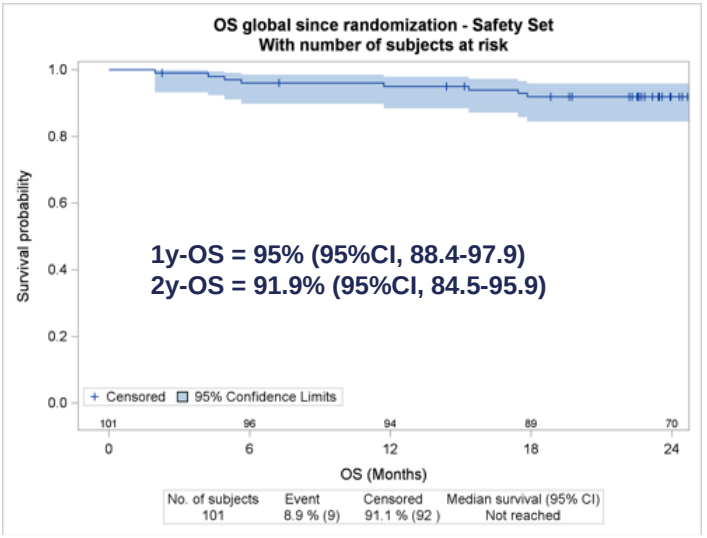
Follow-up duration:

- Export date: 10NOV23: 13.5m (95%CI, 12.6 - 14.4)
- Export date: 21OCT24: 27m (95%CI, 25.6 - 27.7)



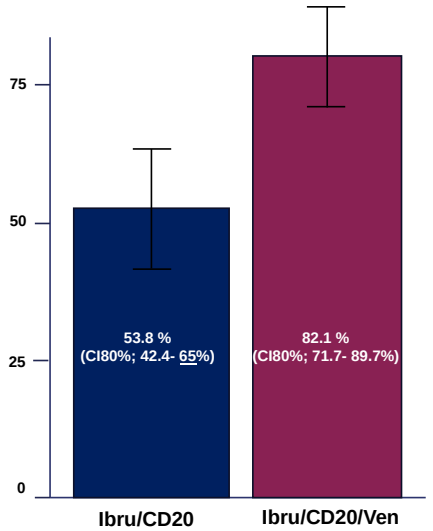
From January to December 2022, 102 patients were included and randomized





MRD Negativity at End of Induction (Primary Efficacy Endpoint) (n=39)

- **MRD negativity rate assessed by ddPCR at the end of induction (after C6)**
- **N=39 in each arms**



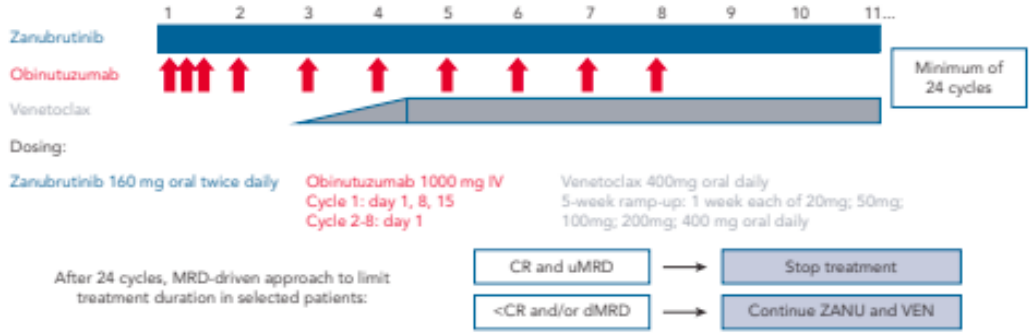
Le Gouill S et al., ASH 2024

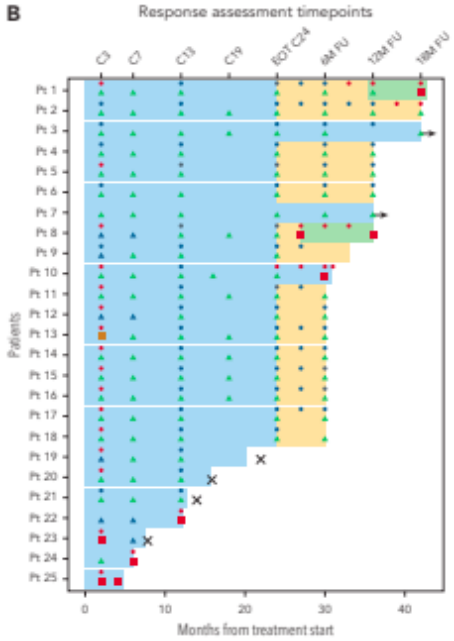
Coming soon: chemo-free **triplets in HR patients** -> BOVen (first-line)

CLINICAL TRIALS AND OBSERVATIONS

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

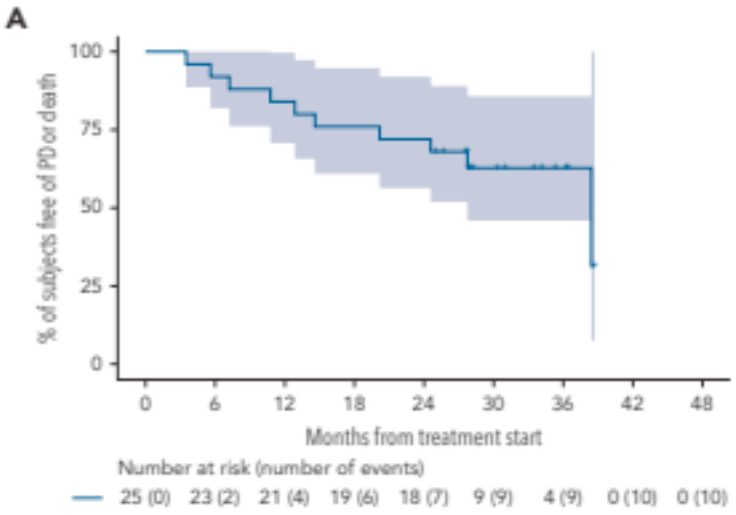
blood® 30 JANUARY 2025 | VOLUME 145, NUMBER 5

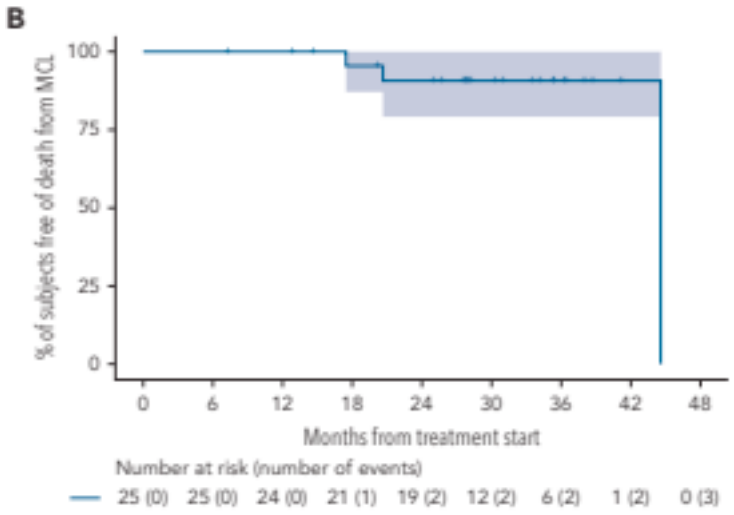


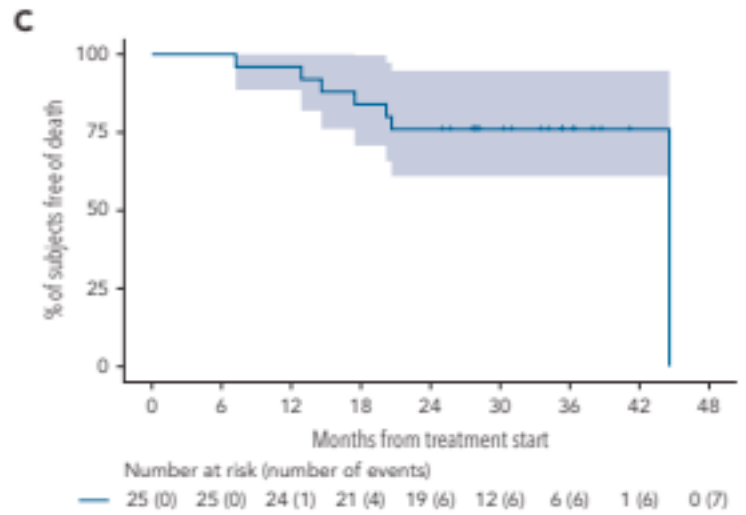


A 3-pronged attack on *TP53*-mutated MCL

Christine E. Ryan and Ann S. LaCasce | Dana-Farber Cancer Institute

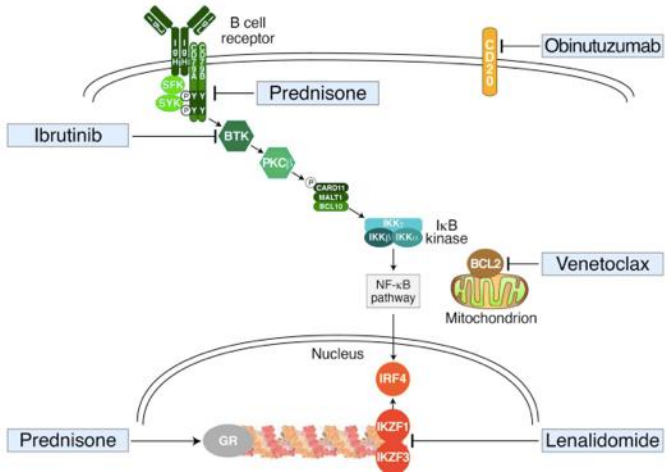


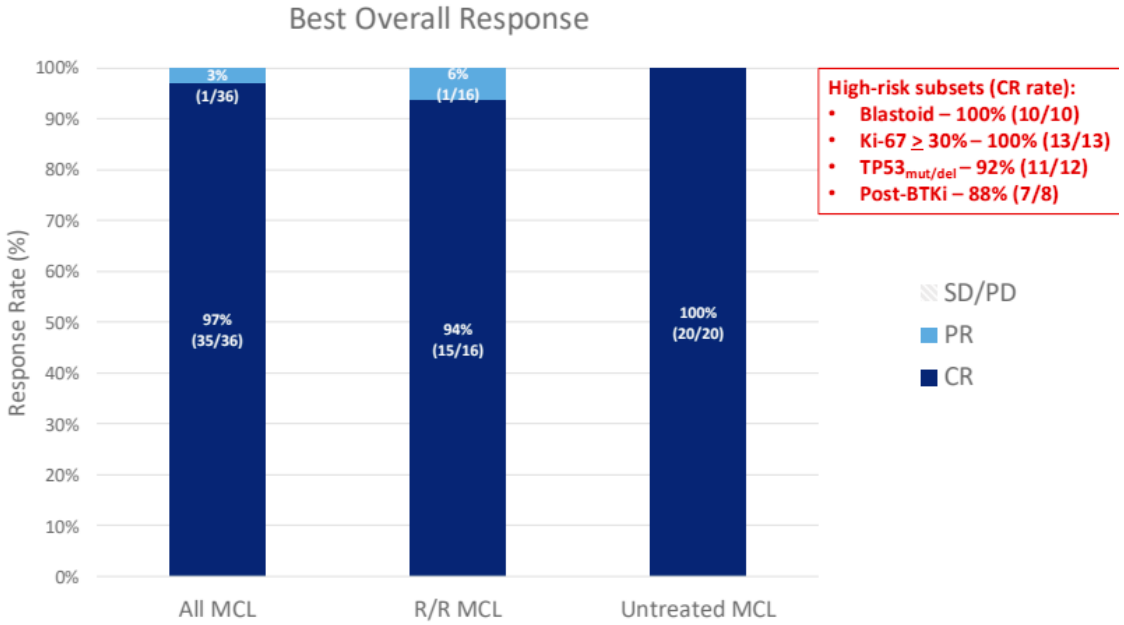




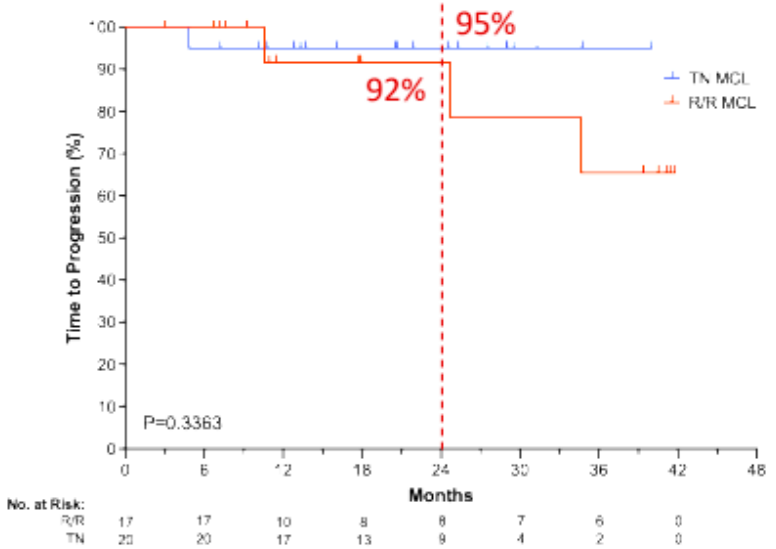
Kumar A et al., Blood 2025

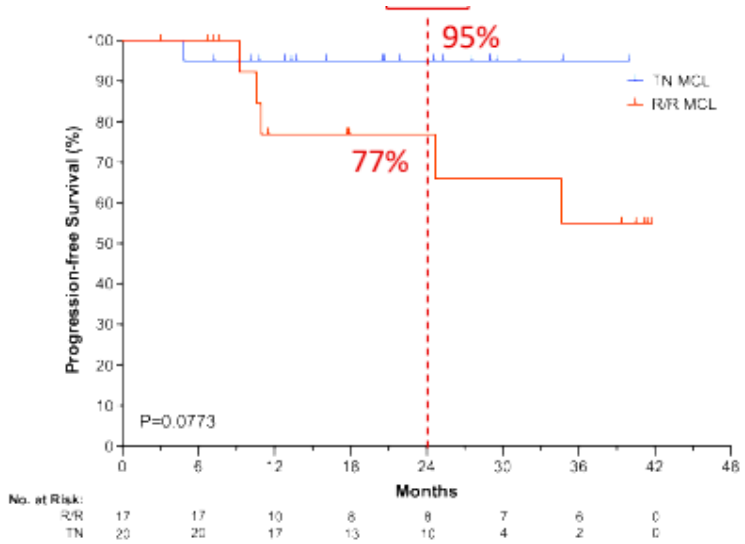
Coming soon: chemo-free **quintuplets** -> ViPOR (R/R & first-line)





High-risk subsets (CR rate):
- **Blastoid – 100% (10/10)**
- **Ki-67 ≥ 30% – 100% (13/13)**
- **TP53$_{mut/del}$ – 92% (11/12)**
- **Post-BTKi – 88% (7/8)**





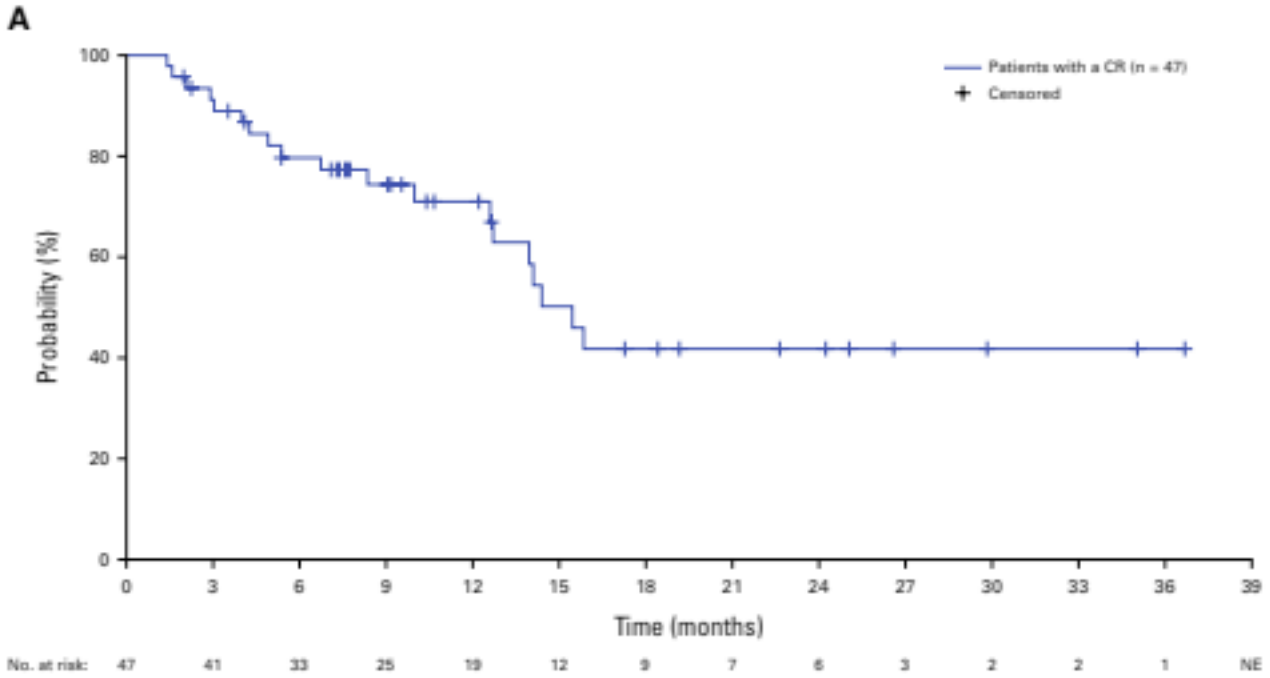
Median (range) follow-up = 27.6 (3.1-57.5) mo.

Melani C et al., ASH 2024

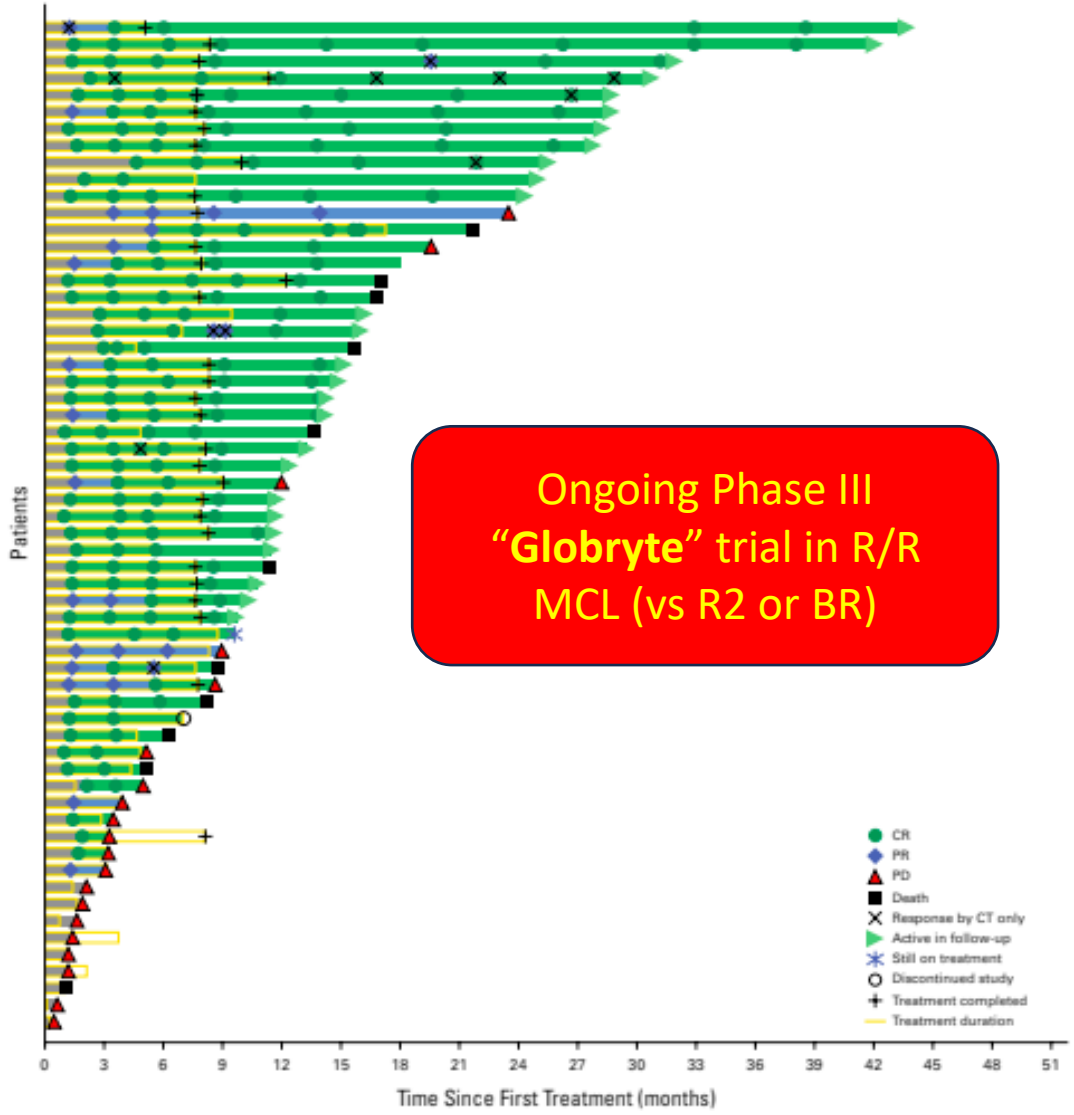
Coming soon: **Glofitamab** in R/R MCL (NP 30179)

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

Tycel Jovelle Phillips, MD[1,2]; Carmelo Carlo-Stella, MD[3]; Franck Morschhauser, MD, PhD[4]; Emmanuel Bachy, MD, PhD[5]; Michael Crump, MD, FRCPC[6]; Marek Trněný, MD[7]; Nancy L. Bartlett, MD[8]; Jan Zaucha, MD, PhD[9]; Tomasz Wrobel, PhD[10]; Fritz Offner, MD, PhD[11]; Kathryn Humphrey, BSc[12]; James Relf, MD[12]; Audrey Filézac de L'Etang, PhD[12]; David J. Carlile, PhD[12]; Ben Byrne, MSc[12]; Naseer Qayum, MBChB, DPhil[12]; Linda Lundberg, PhD[13]; and Michael Dickinson, MBBS, DMedSc[14]



Duration of CR



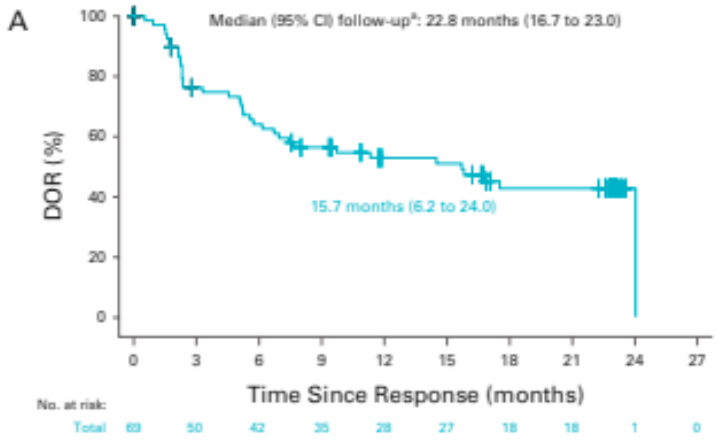
Ongoing Phase III "**Globryte**" trial in R/R MCL (vs R2 or BR)

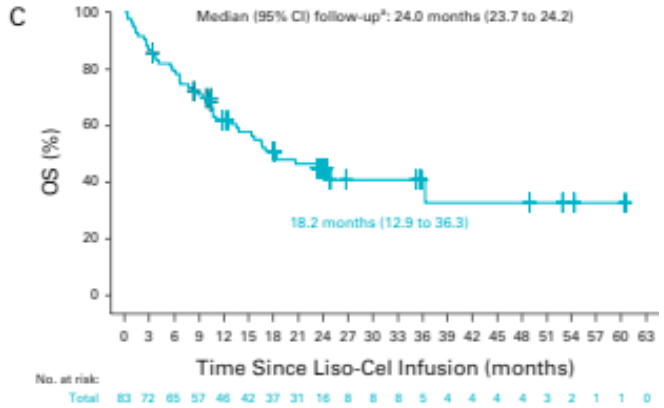
Phillips TJ et al., JCO 2024

Coming soon: **Liso-cel** in R/R MCL (TRANSCEND NHL 001)

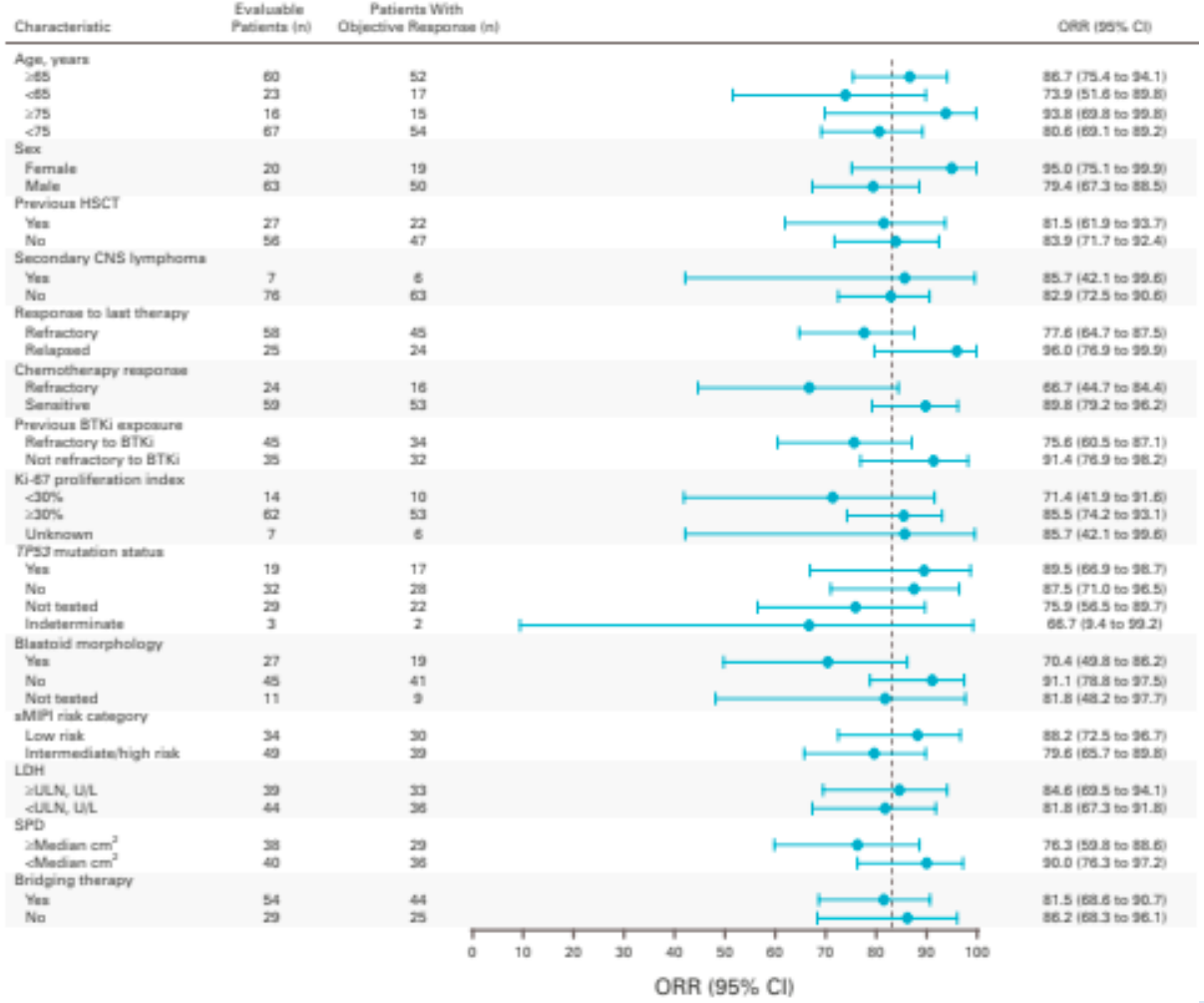
Lisocabtagene Maraleucel in Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis of the Mantle Cell Lymphoma Cohort From TRANSCEND NHL 001, a Phase I Multicenter Seamless Design Study

Michael Wang, MD[1]; Tanya Siddiqi, MD, MBBS[2]; Leo I. Gordon, MD[3]; Manali Kamdar, MD, MBBS[4]; Matthew Lunning, DO[5]; Alexandre V. Hirayama, MD[6]; Jeremy S. Abramson, MD, MMSc[7]; Jon Arnason, MD[8]; Nilanjan Ghosh, MD, PhD[9]; Amitkumar Mehta, MD[10]; Charalambos Andreadis, MD, MS[11]; Scott R. Solomon, MD[12]; Ana Kostic, MD[13]; Christine Dehner, BSc[13]; Ricardo Espinola, MD[14]; Lily Peng, MS[13]; Ken Ogasawara, PhD, MPH[15]; Amy Chattin, PhD[12]; Laurie Eliason, MPH[16]; and M. Lia Palomba, MD[16]





J Clin Oncol 42:1146-1157



Relevance *(J.W. Friedberg)*

Liso-cel represents a novel treatment option for patients with MCL refractory to Bruton tyrosine kinase inhibition, including patients with CNS involvement. Given the favorable toxicity profile, future studies should evaluate this treatment earlier in the disease course.*

Wang M et al., JCO 2023

MCL treatment algorithm (2025): **Conclusions and Take-home messages - 1**

The therapeutic landscape is rapidly evolving

First line YOUNGER patients:

- Intensified protocols containing R-Ara-C + ASCT remain the standard altought the integration of ibrutinib with the omission of ASCT has to be considered (off-label/648; HR patients)
- Maintenance in first-line MCL is crucial (rituximab + ibrutinib)

First line ELDERLY patients:

- BR + R maintenance is the standard therapy for the majority of patients, however:
- R-BAC500 is an effective, limited duration alternative for FIT patients
- FIT and HR patients should be considered for a TRIANGLE-like schedule

MCL treatment algorithm (2025): **Conclusions and Take-home messages - 2**

RELAPSED/REFRACTORY patients:

- Ibrutinib is the standard of care in controlling the disease in 2nd line for most patients
- Relapse after ibrutinib still represent an unmet clinical need but salvage options are increasing
- Those patients should be early considered for CAR-T (balancing foreseeable efficacy and toxicities)
- For patients not candidate to CAR-T pirtobrutinib represents a novel, safe and valuable option

CHALLENGES

- High risk features (*TP53*, Ki67, blastoid, MIPI, POD24) maintain a dismal prognostic role in the CAR-T era
- A risk-tailored approach should be implemented (anticipation of novel treatment strategies? MRD?)
- Several, effective, novel non-chemotherapeutic combinations are coming
- Bispecific antibodies (safe, effective) will soon have a major role
- Is there a role for allogeneic stem cell transplantation in this evolving scenario?

DBMSS
Dipartimento di Biotecnologie Molecolari e Scienze per la Salute

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

Thank you !

FONDAZIONE ITALIANA LINFOMI

EUROPEAN mCL NETWORK

UNIVERSITÀ DI TORINO