Linfoma del Manto
Rol de los iBTK en primera línea:
NO

MIGUEL A PAVLOVSKY
Médico y Director Científico en FUNDALEU

High-Risk Mantle Cell Lymphoma: Definition, Current Challenges, and Management

Jain et al, J Clin Oncol 2020;38:4302-4317

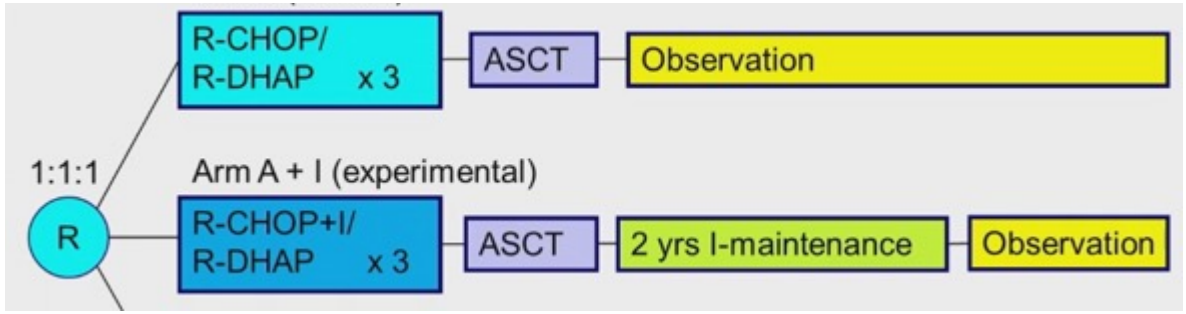
LCM de alto riesgo:
- Formas blastoides
- Ki67 ≥ 30%
- TP53 mutado
- MIPI de alto riesgo

Guías GELTAMO 2022

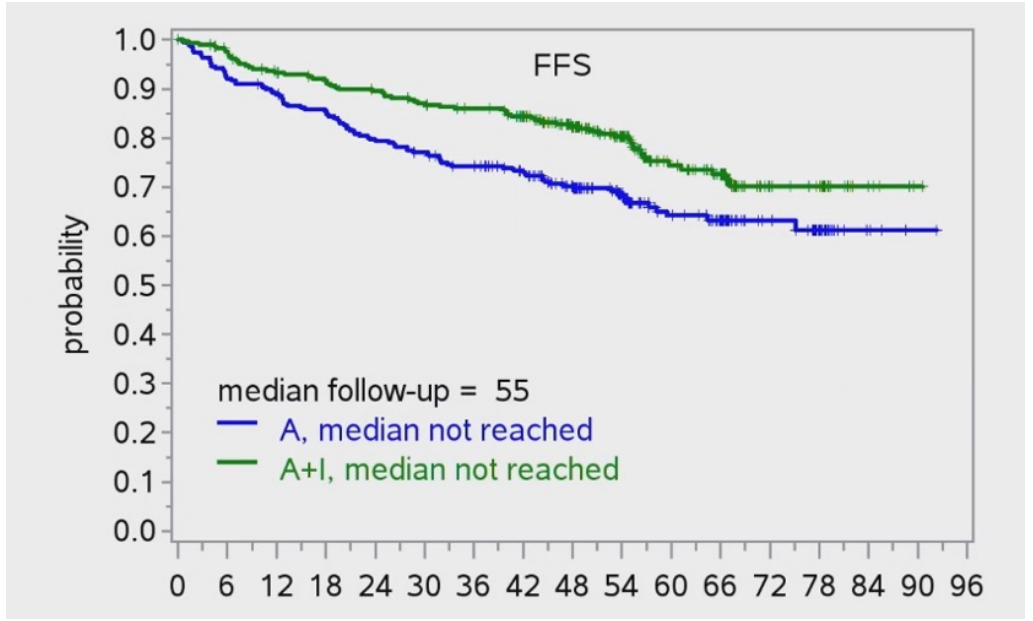
TABLE 3. Groups of Risk Factors That May Influence Outcome in Newly Diagnosed and Previously Treated Patients With MCL

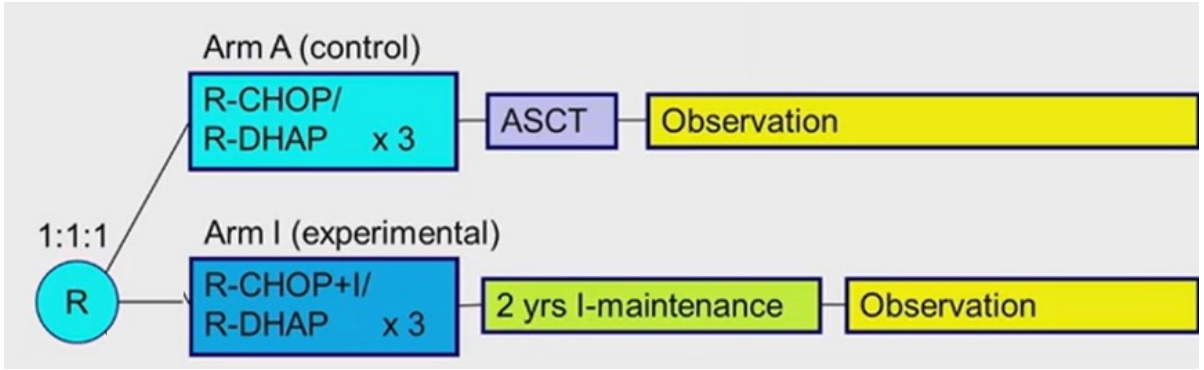
Clinical Course	Newly Diagnosed MCL	Previously Treated Relapsed or Refractory MCL[a]
Ultra-high risk	De novo blastoid/pleomorphic histology	Blastoid/pleomorphic histology (transformed from classic histology)
	Ki-67 ≥ 30%/50% in involved tissues with blastoid/pleomorphic histology[b]	
	TP53 mutated with other high-risk gene mutations (*KMT2D, NSD2, CCND1, NOTCH1, CDKN2A, NOTCH2, SMARCA4*)	Refractory to ≥ 3 prior lines of standard therapies (including BTK Inhibitor)
	CNS involvement	Triple-resistant MCL (resistant to BTK inhibitor, venetoclax and anti-CD19 CAR-T)
High risk	Blastoid/pleomorphic histology	≤ 2 prior lines of standard therapies
	Ki-67 ≥ 30%/50% in involved tissues with classic histology[b]	
	TP53 mutated with high variant allele frequency (≥ 10%) or del(17p) by FISH	Progression within 24 months of first-line therapy
	Complex kartyyope	
	Simplified high-risk MIPI score (≥ 6.2)	Persisting MRD-positive disease after therapy[d]
	Bulky disease[c]	
Standard risk	Classic histology	No other features of high-risk disease
	Ki-67 < 30% in involved tissues	
	Presence of B symptoms	
	Bulky or nonbulky disease[c]	
	No other features of high-risk disease	
Generally smoldering or indolent	Classic histology	No other features of high-risk disease
	Ki-67 < 30% in involved tissues	
	Low-risk MIPI score	
	No B symptoms	
	Nonnodal leukemic MCL type	
	Low tumor burden	
	No other features of high-risk disease	

Resultados

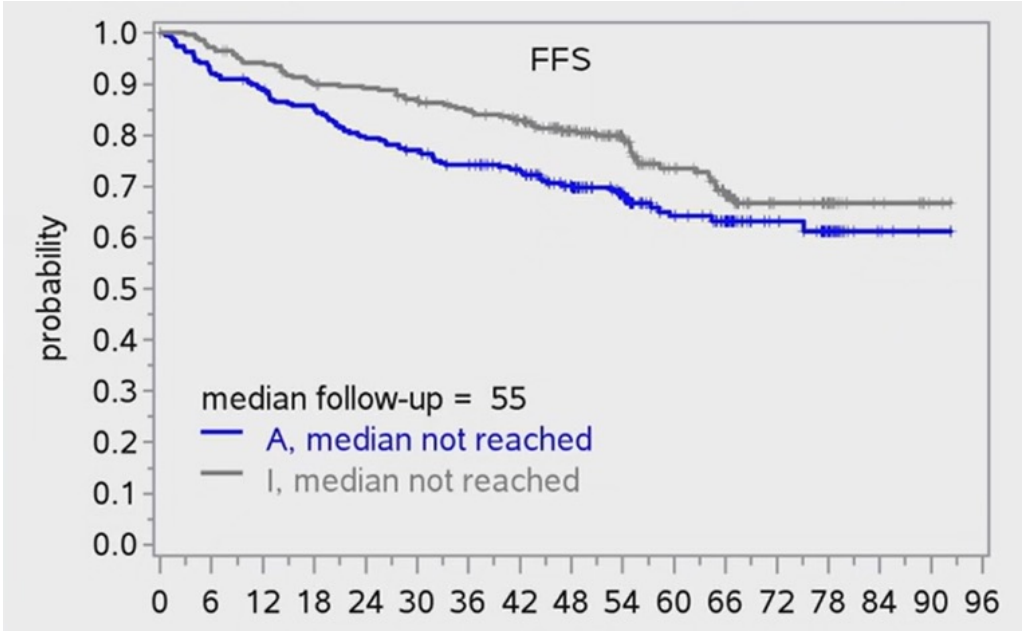


FFS a 4 años: A: 70 % A+ I:82% p= 0,0026

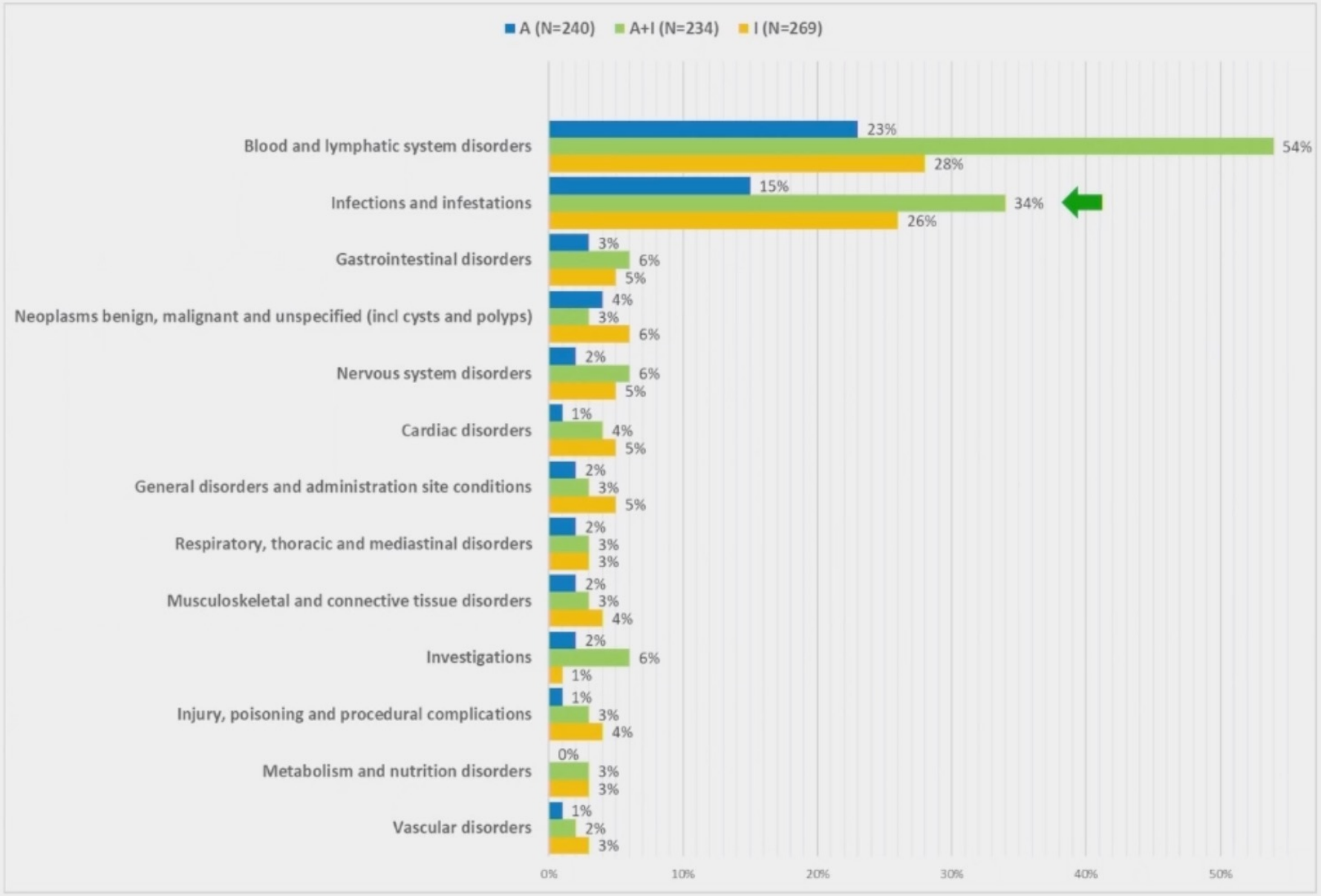




FFS a 4 años: A: 70 % I:81% p= 0,98



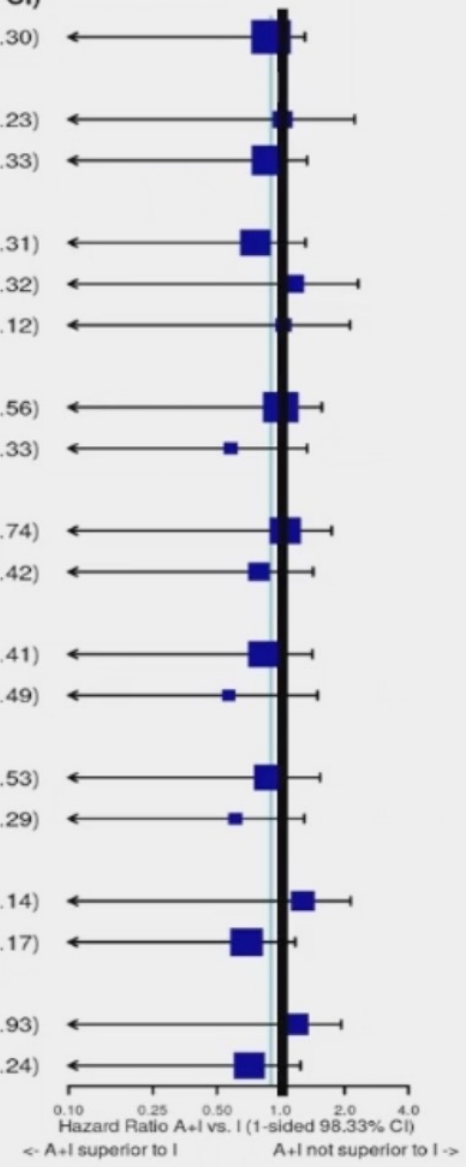
TRIANGLE: Grade ≥3 AEs (maintenance/follow-up)



Dreyling M et al. ASH 2024.

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

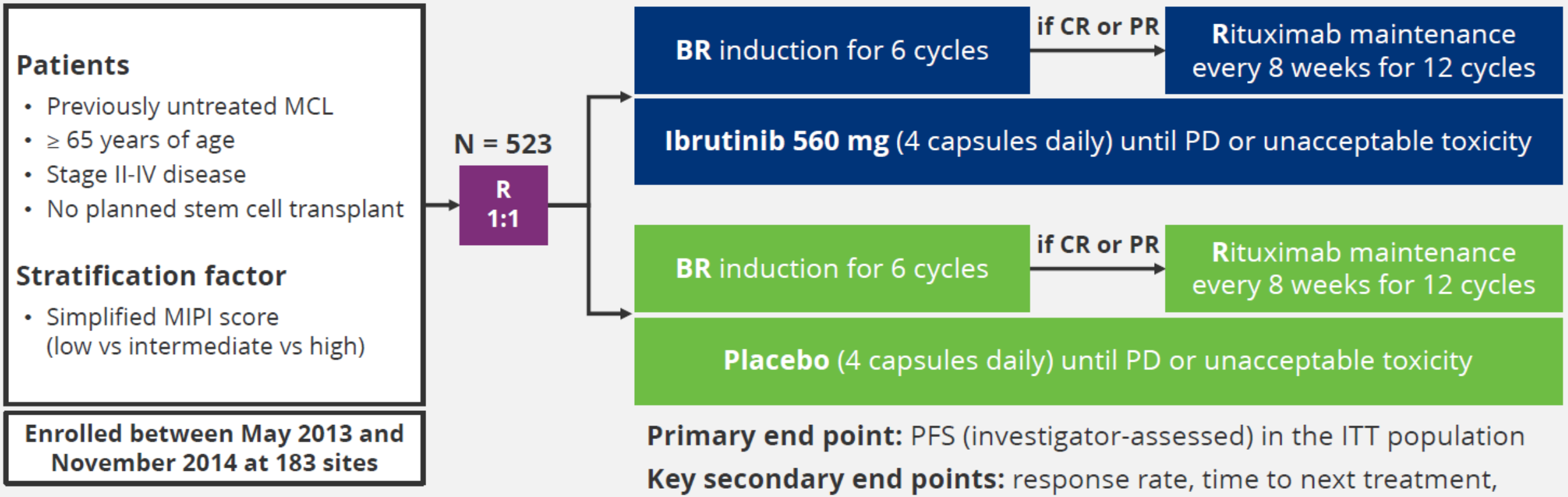
Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	582	134	0.90 (0 - 1.30)
Sex (p=0.71)			
Female	138	30	1.02 (0 - 2.23)
Male	444	104	0.88 (0 - 1.33)
MIPI			
Low	336	62	0.76 (0 - 1.31)
Intermediate (p=0.33)	157	37	1.15 (0 - 2.32)
High (p=0.56)	89	35	1.03 (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

Linfoma del Manto:
Estudios fase III con iBTK en 1L en pacientes añosos

SHINE: A Randomized, Double-Blind, Phase 3 Study

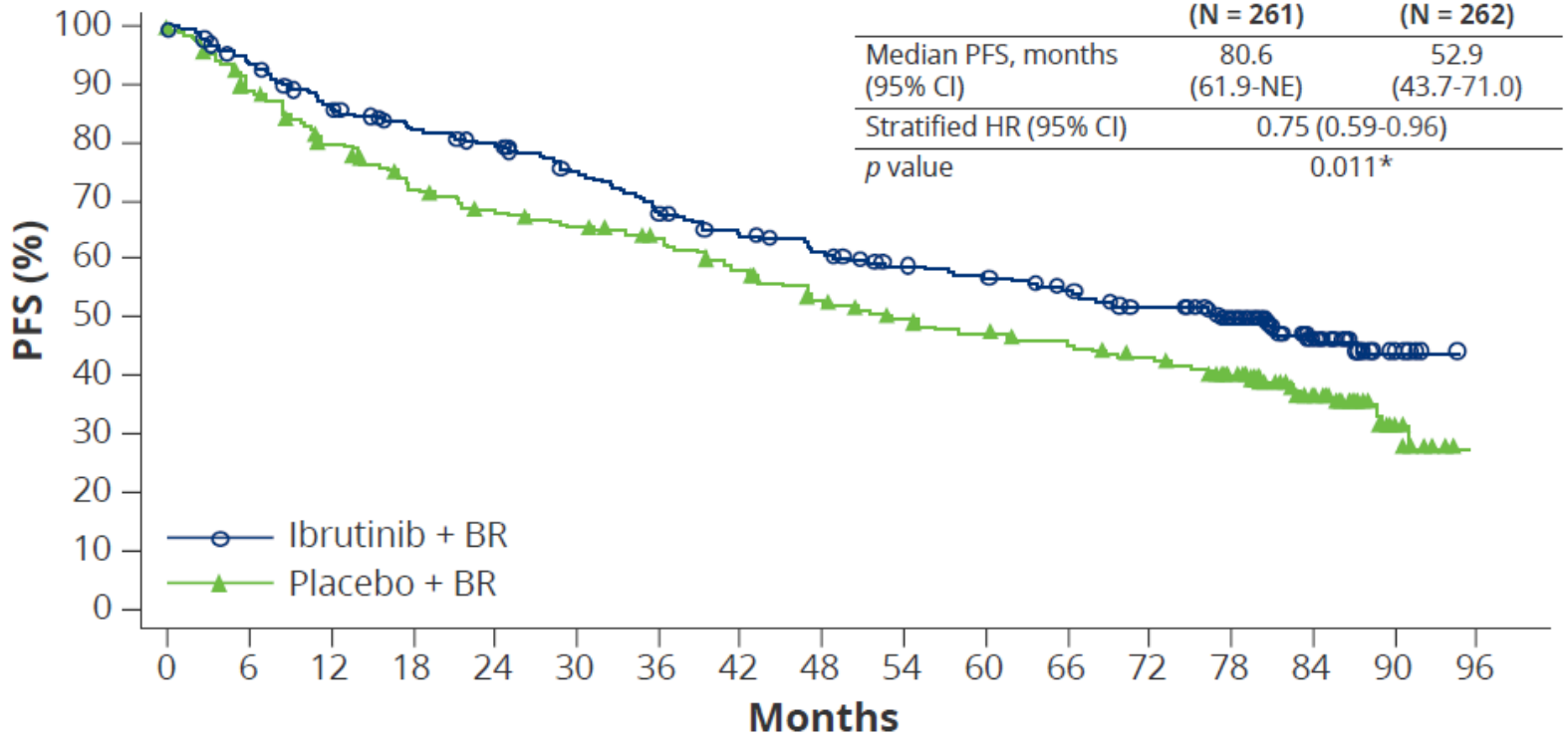


Primary end point: PFS (investigator-assessed) in the ITT population

Key secondary end points: response rate, time to next treatment, overall survival, safety

Induction: **B**endamustine 90 mg/m2 Days 1 and 2, **R**ituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.
CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.

Primary End Point of Improved PFS Was Met



	Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median PFS, months (95% CI)	80.6 (61.9-NE)	52.9 (43.7-71.0)
Stratified HR (95% CI)	0.75 (0.59-0.96)	
p value	0.011*	

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

Ibrutinib + BR and R maintenance achieved:

- **Significant improvement in median PFS by 2.3 years** (6.7 vs 4.4 years)
- **25% reduction** in risk of PD or death

CI, confidence interval; HR, hazard ratio; NE, not evaluable.
*Significance boundary for superiority was $p < 0.023$.

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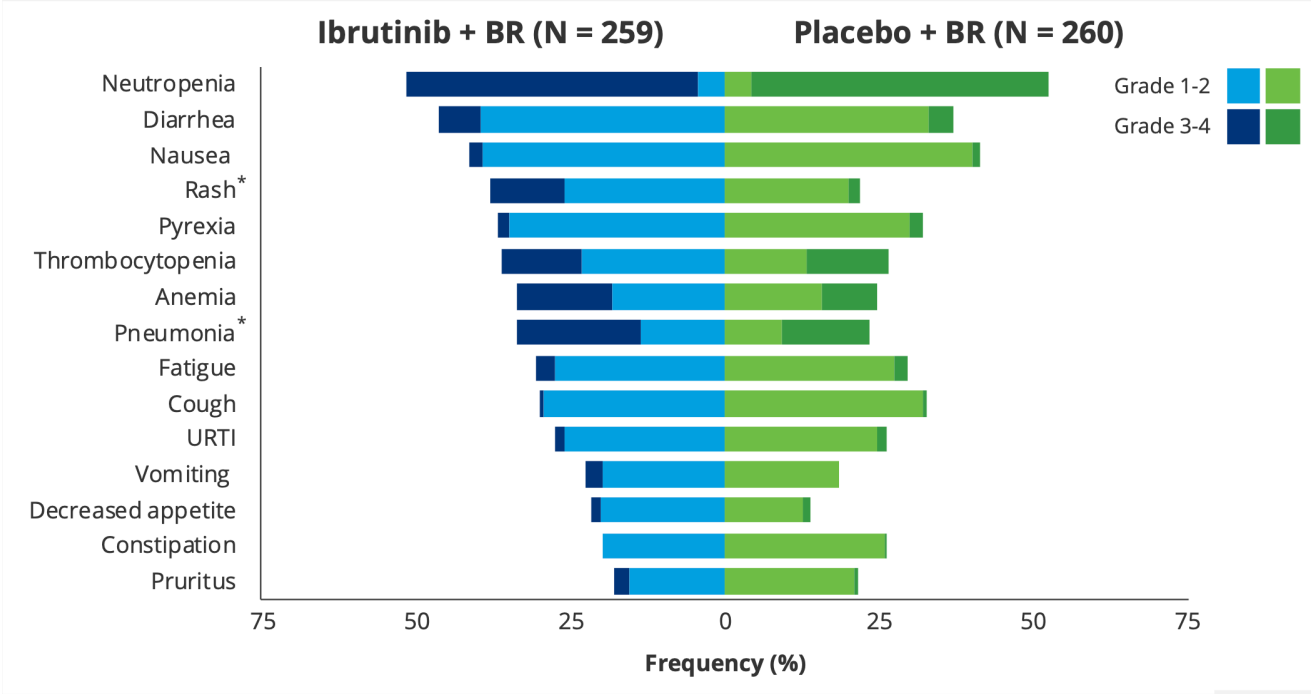
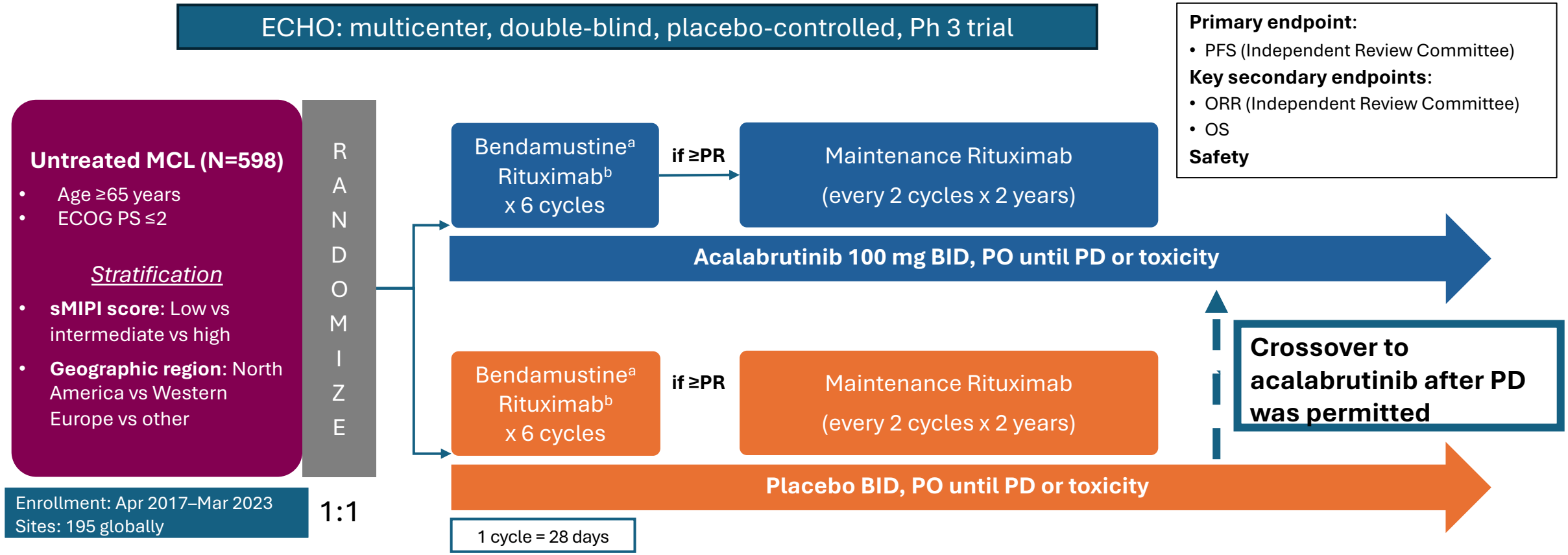
SHINE: AE

	Ibrutinib + BR (N = 259)		Placebo + BR (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Any bleeding*	42.9%	3.5%	21.5%	1.5%
Major bleeding	5.8%	–	4.2%	–
Atrial fibrillation*	13.9%	3.9%	6.5%	0.8%
Hypertension	13.5%	8.5%	11.2%	5.8%
Arthralgia	17.4%	1.2%	16.9%	0



Wang M et al. LBA, EHA 2022

Study Design for ECHO (NCT02972840)



[a]Bendamustine 90 mg/m^2 on days 1 and 2. [b]Rituximab 375 mg/m^2 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.

Impact of COVID-19

n (%)	COVID-19–related TEAEs	
	Acalabrutinib + BR (n=297)	Placebo + BR (n=297)
Any TEAE	121 (40.7)	88 (29.6)
Grade ≥3	60 (20.2)	50 (16.8)
Grade 5	28 (9.4)	20 (6.7)
SAEs	60 (20.2)	52 (17.5)
Grade ≥3	58 (19.5)	48 (16.2)
TEAE leading to acalabrutinib/ placebo discontinuation	31 (10.4)	19 (6.4)

* Prespecified Sensitivity Analysis

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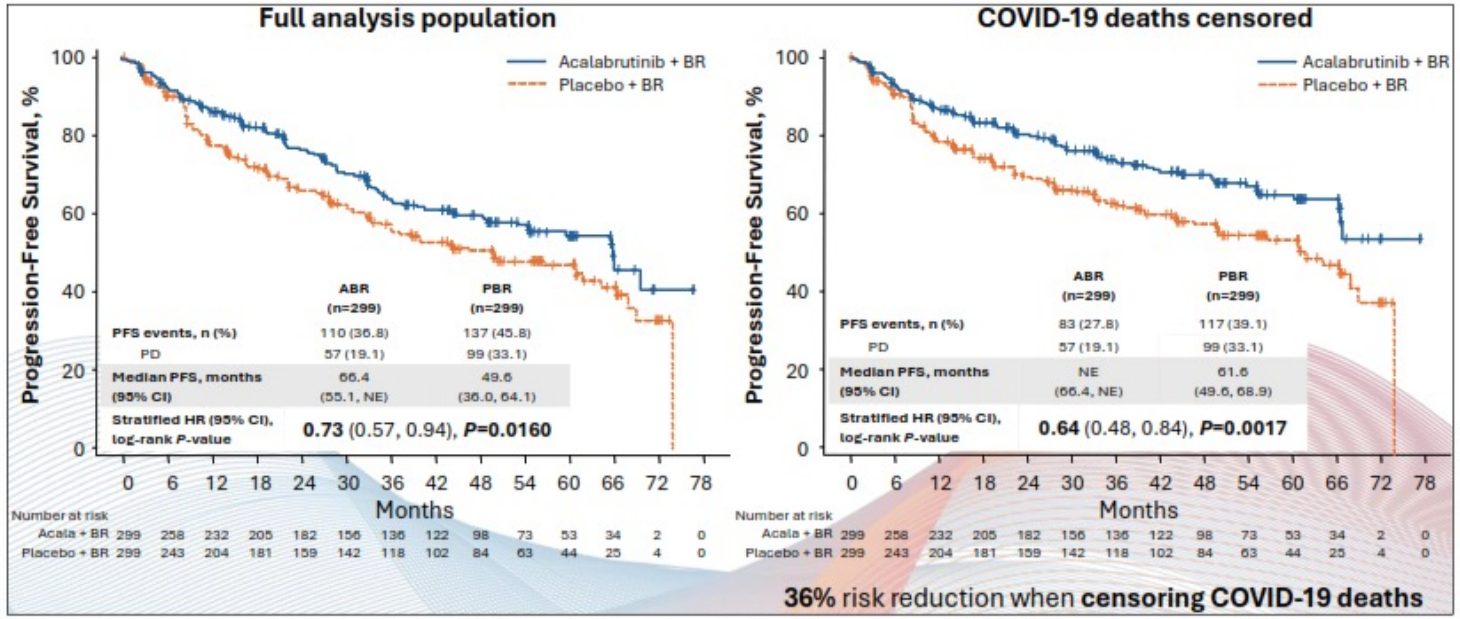
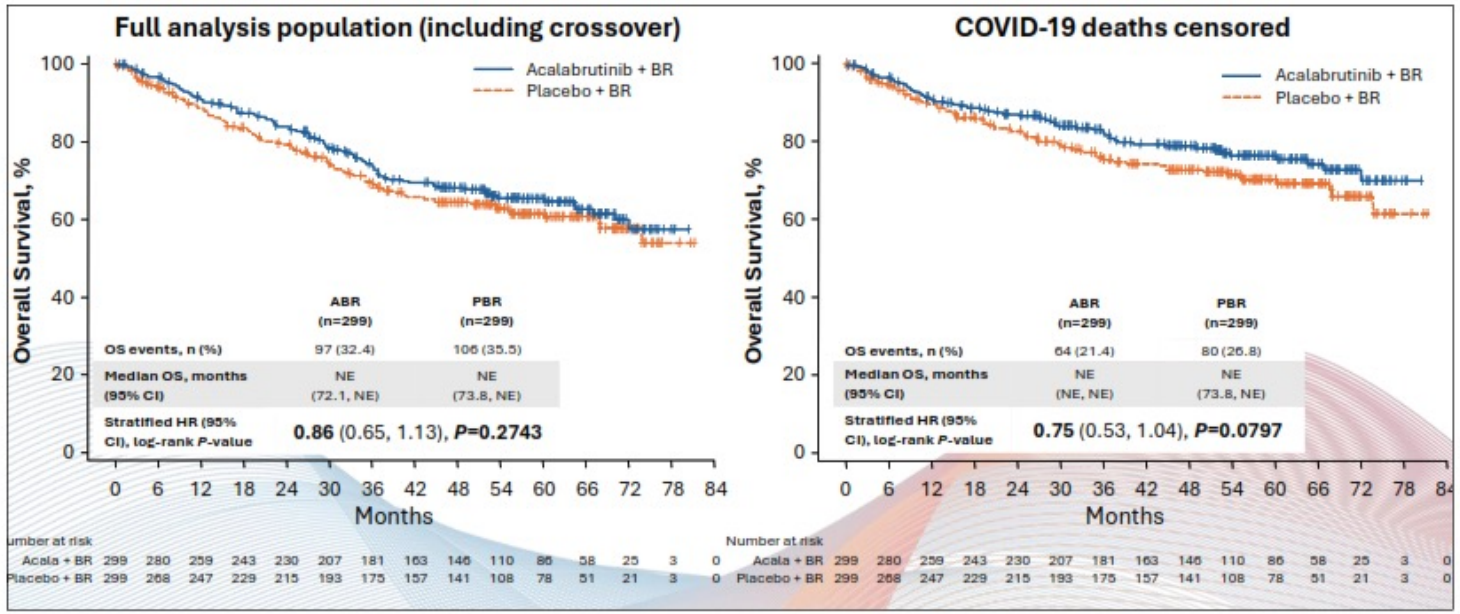
PFS*



OS*



Safety

Treatment emergent AEs

n (%)	Acalabrutinib + BR (n=297)	Placebo + BR (n=297)
Any TEAE	296 (99.7)	294 (99.0)
Grade ≥3	264 (88.9)	262 (88.2)
Grade 5	36 (12.1)	30 (10.1)
SAEs	205 (69.0)	184 (62.0)
Grade ≥3	191 (64.3)	166 (55.9)
TEAE related to acalabrutinib/ placebo	202 (68.0)	165 (55.6)
TEAE leading to acalabrutinib/ placebo discontinuation	127 (42.8)	92 (31.0)

AE of interest

	Acalabrutinib + BR (n=297)		Placebo + BR (n=297)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Event, n (%)				
Atrial fibrillation	18 (6.1)	11 (3.7)	13 (4.4)	5 (1.7)
Hypertension	36 (12.1)	16 (5.4)	47 (15.8)	25 (8.4)
Major bleeding[a]	7 (2.4)	6 (2.0)	16 (5.4)	10 (3.4)
Infections[b]	232 (78.1)	122 (41.1)	211 (71.0)	101 (34.0)
Second primary malignancies (excluding non-melanoma skin)[b]	29 (9.8)	16 (5.4)	32 (10.8)	20 (6.7)
Median treatment exposure	29 months		25 months	

Deaths

n (%)	Acalabrutinib + BR (n=297)	Placebo + BR including crossover (N=297)
Total deaths	97 (32.7)	105 (35.4)
Due to disease progression	30 (10.1)	42 (14.1)
Due to TEAEs	36 (12.1)	32 (10.8)
Due to AEs >30 days after last dose of study drug	10 (3.4)	9 (3.0)
Other[a]	14 (4.7)	16 (5.4)
Unknown	7 (2.4)	6 (2.0)

Wang et al, LBA, EHA 2024

MAYO CLINIC

Multicenter Study of Mantle Cell Lymphoma Outcomes Following First-line Bendamustine-Rituximab and Second-line Bruton's Tyrosine Kinase Inhibitor Therapy

Yucai Wang[1], Melissa C. Larson[1], Steven R. Hwang[1], Anita Kumar[2], Ashlee Joseph[2], Brian T. Hill[3], Taylor R. Brooks[3], David A. Bond[4], Kami J. Maddocks[4], Alexey Danilov[5], Christine McCarthy[5], Jia Ruan[6], Imran A. Nizamuddin[7], Brad S. Kahl[7], Natalie S. Grover[8], Nazneen B. Khan[8], Evguenia Ouchveridze[9], Aung Tun[9], Philip Young[10], Craig A. Portell[10], Zoey I. Harris[11], Javier L. Munoz[11], Patrick M. Reagan[12], Georgios Pongas[13], Izidore S. Lossos[13], Christine E. Ryan[14], Reid W. Merryman[14], Firas Baidoun[15], Muhamad Alhaj Moustafa[15], Drew Gerber[16], Sabarish Ayyappan[17], Brian K. Link[17], I. Brian Greenwell[18], Lauren G. Banaszak[19], Priyanka A. Pophali[19], Anthony C. Stack[20], Marcus R. Messmer[20], Mayur S. Narkhede[21], Amitkumar Mehta[21], Preetesh Jain[22], Michael L. Wang[22], Tamara K. Moyo[23], Nilanjan Ghosh[23], Rahul S. Bhansali[24], Stefan K. Barta[24], Manali K. Kamdar[25], Jacob Anna[25], Alexander V. Stanisic[26], Reem Karmali[26], Laveniya Kugathasan[27], Diego Villa[27], Matthew J. Maurer[1], James R. Cerhan[1], Jonathon B. Cohen[15], Peter Martin[6]

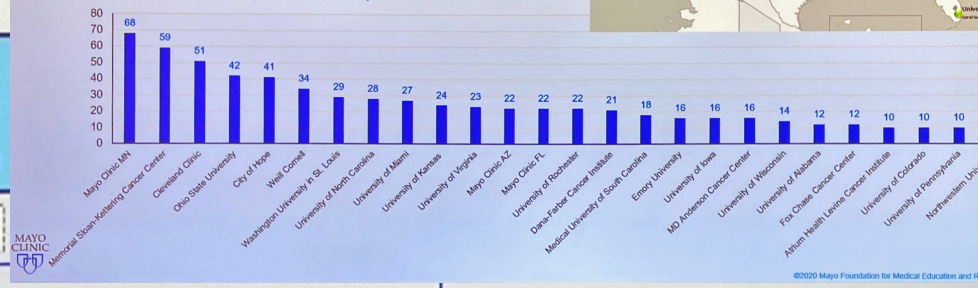
[1]Mayo Clinic, Rochester, MN; [2]Memorial Sloan-Kettering Cancer Center, New York, NY; [3]Cleveland clinic, Cleveland, OH; [4]Ohio state University, Columbus, OH; [5]City of Hope, Duarte, CA; [6]Weill Cornell Medicine, New York, NY; [7]Washington University in St. Louis, St, Louis, MO; [8]University of North Carolina, Chapel Hill, NC; [9]University of Kansas Medical Center, Kansas City, KS; [10]University of Virginia, Charlottesville, VA; [11]Mayo Clinic, Phoenix, AZ; [12]University of Rochester, Rochester, NY; [13]University of Miami, Miami, FL; [14]Dana Farber Cancer Institute, Boston, MA; [15]Mayo Clinic, Jacksonville, FL; [16]Emory university, Atlanta, GA; [17]University of Iowa, Iowa City, IO; [18]Medical University of South Carolina, Charleston, SC; [19]University of Wisconsin, Madison, WI; [20]Fox Chase Cancer Center, Philadelphia, PA; [21]University of Alabama, Birmingham, AL; [22]MD Anderson Cancer Center, Houston, TX; [23]Atrium Health Levine Cancer Institute, Charlotte, NC; [24]University of Pennsylvania, Philadelphia, PA; [25]University of Colorado, Aurora, CO; [26]Northwestern University, Chicago, IL; [27]BC Cancer Agency, Vancouver, Canada

ASH 2023
December 9, 2023

MAYO CLINIC

Consort Diagram

- LEO Consortium (PI: James R. Cerhan, Christopher R. Flowers)
- LEO MCL Working Group (Lead: Peter Martin, Jonathon B. Cohen)
- Statisticians (Melissa C. Larson, Matthew J. Maurer)
- Programmer (Brian F. Kabat)
- **All Investigators (26 centers)**



BR at 1L (N=651)
R maintenance n=269 (41%)
No R maintenance n=382 (59%)

Median follow-up 57.3 months (95% CI 54.0–63.2)

Alive and progression-free (n=265)
41%

Progression, relapse, or retreatment (n=294)
45%

Death without 2L (n=92)
14%

BTKi at 2L (n=220)
Ibrutinib n=109
Acalabrutinib n=82
Zanubrutinib n=29

Non-BTKi at 2L (n=74)

Median follow-up 38.5 months (95% CI 31.3–45.1)

Alive and progression-free (n=62)
28%

Progression, relapse, or retreatment (n=130)
59%

Death (n=28)
13%

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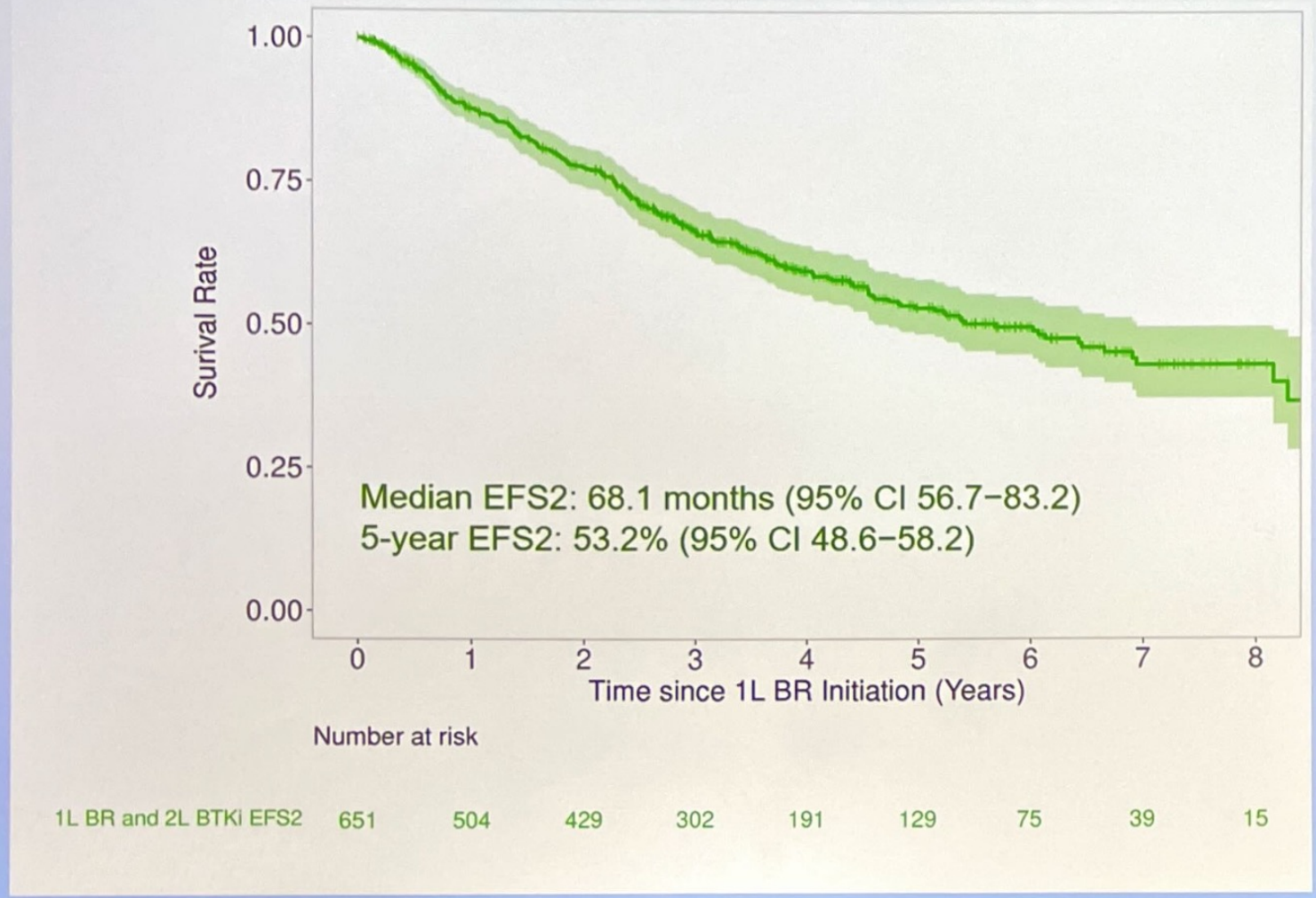
EFS2 after 1L BR and 2L BTKi



MAYO CLINIC

Summary of Data in the Context of SHINE

	This Retrospective Cohort	This Retrospective Cohort, Age ≥65	Ibrutinib Arm in SHINE	Placebo Arm in SHINE
Patient number	651	491	261	260
Age, median (range)	71 (35–91)	73 (65–91)	71 (65–86)	71 (65–87)
Age ≥65	491 (75%)	491 (100%)	261 (100%)	260 (100%)
ORR to BR (CR rate)	92% (79%)	92% (78%)	90% (66%)	89% (58%)
Rituximab maintenance	269 (41%)	207 (42%)	206 (79%)	210 (80%)
BTKi	At 2L: 220 (75% of 294; 34% of 651)	At 2L: 175 (78% of 224; 36% of 491)	At 1L: 261 (100%)	At 2L: 41 (39% of 106; 16% of 260)
Median EFS/PFS	EFS: 34.0 months (95% CI 31.0–39.3) EFS2: 68.1 months (95% CI 56.7–83.2)	EFS: 32.7 months (95% CI 29.0–36.2) EFS2: 62.6 months (95% CI 50.6–77.4)	PFS: 80.6 months (95% CI 61.9–NE)	PFS: 52.9 months (95% CI 43.7–71.0)
OS at 7 years	57.5%	54.4%	56.8%	55.0%

Ibrutinib-rituximab versus Immunochemotherapy in previously untreated mantle cell lymphoma

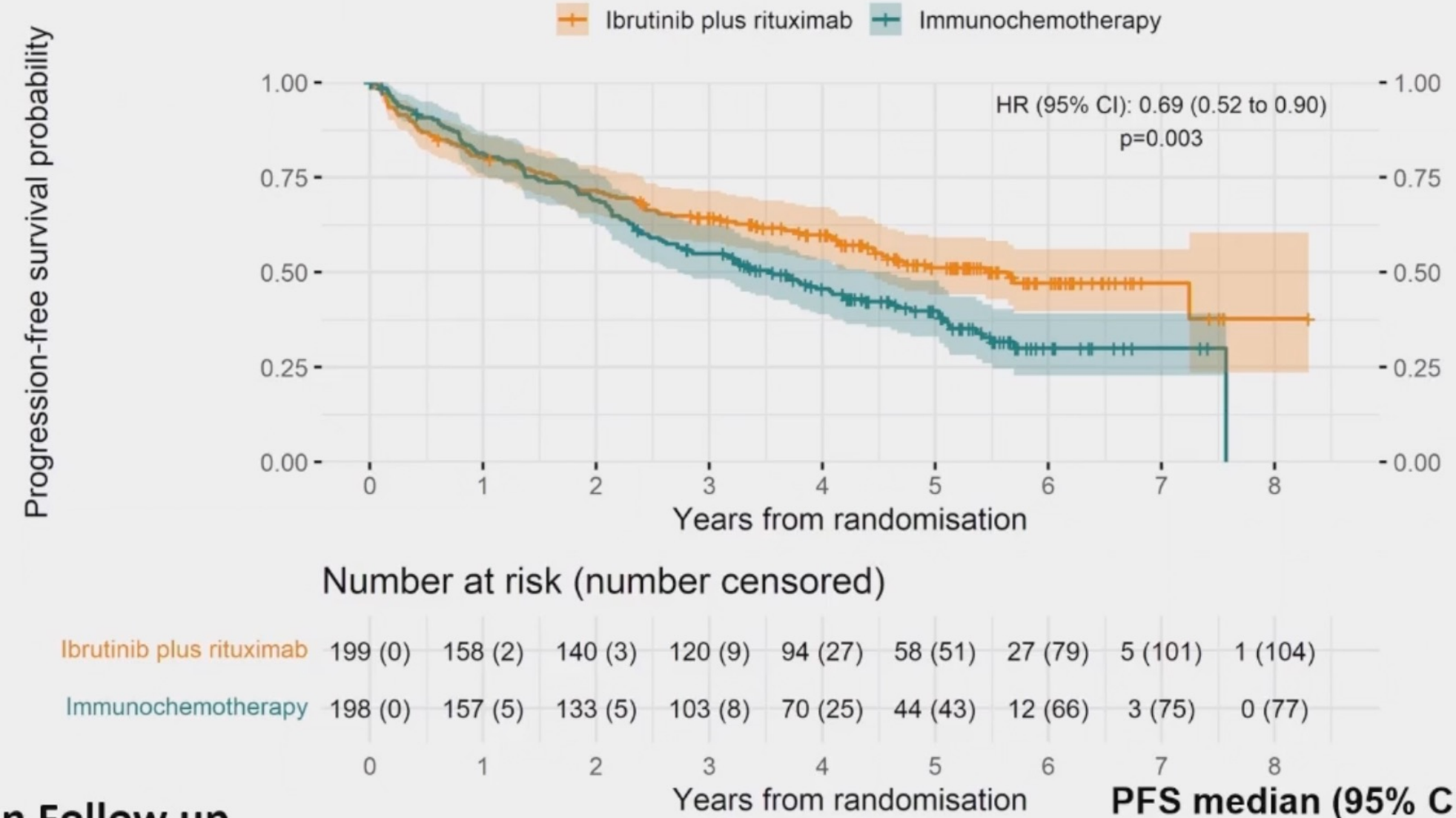
ENRICH

Dr David J Lewis [1], Prof Mats Jerkeman [2], Dr Lexy Sorrell [3], Prof David Wright [4], Prof Ingrid Glimelius [5], Dr Christian B Poulsen [6], Dr Annika Pasanen [7], Prof Andrew Rawstron [8], Dr Karin Wader [9], Dr Nick Morley [10], Dr Catherine Burton [8], Prof Andrew J Davies [11], Dr. Ingemar Lagerlöf [12], Dr Surita Dalal [8], Dr Ruth De Tute [8], Dr Chris McNamara [13], Mrs Nicola Crosbie [1], Mrs Helle Erbs Toldbod [14], Dr Jeanette Sanders [3], Prof Victoria Allgar [3], Dr Sree Aroori [3], Mr Mark Warner [3], Ms Claire Scully [3], Mr Brian Wainman [3], Dr Jacob Haber Christensen [15], Dr Jon Riise [16], Dr Kristina Sonnevi [17], Dr Mark J Bishton [18], Dr Toby A Eyre [19], Prof Simon Rule [20] on behalf of the ENRICH investigators

1 University Hospitals Plymouth NHS Trust, Plymouth, UK, PL6 8DH, 2 Lund University Hospital, 3University of Plymouth, 4University of Exeter, 5 Dept of Immunology, Genetics and Pathology, Uppsala University, 6 Zealand University Hospital Roskilde, 7 HUS Helsinki University Hospital, Helsinki, Finland, 8 Leeds Teaching Hospitals NHS Trust, 9 St Olav's Hospital HF, Trondheim, Norway, NO 700, 10 Sheffield Teaching Hospitals NHS Foundation Trust, 11 University of Southampton, 12 Linköping University Hospital, 13 University College London, 14 Aarhus University Hospital, 15 Odense Universitetshospital, 16 Oslo University Hospital,17 Karolinska University Hospital, 18 University of Nottingham, 19 Oxford University Hospitals NHS Trust, 20 AstraZeneca Mississaug

Progression-free survival

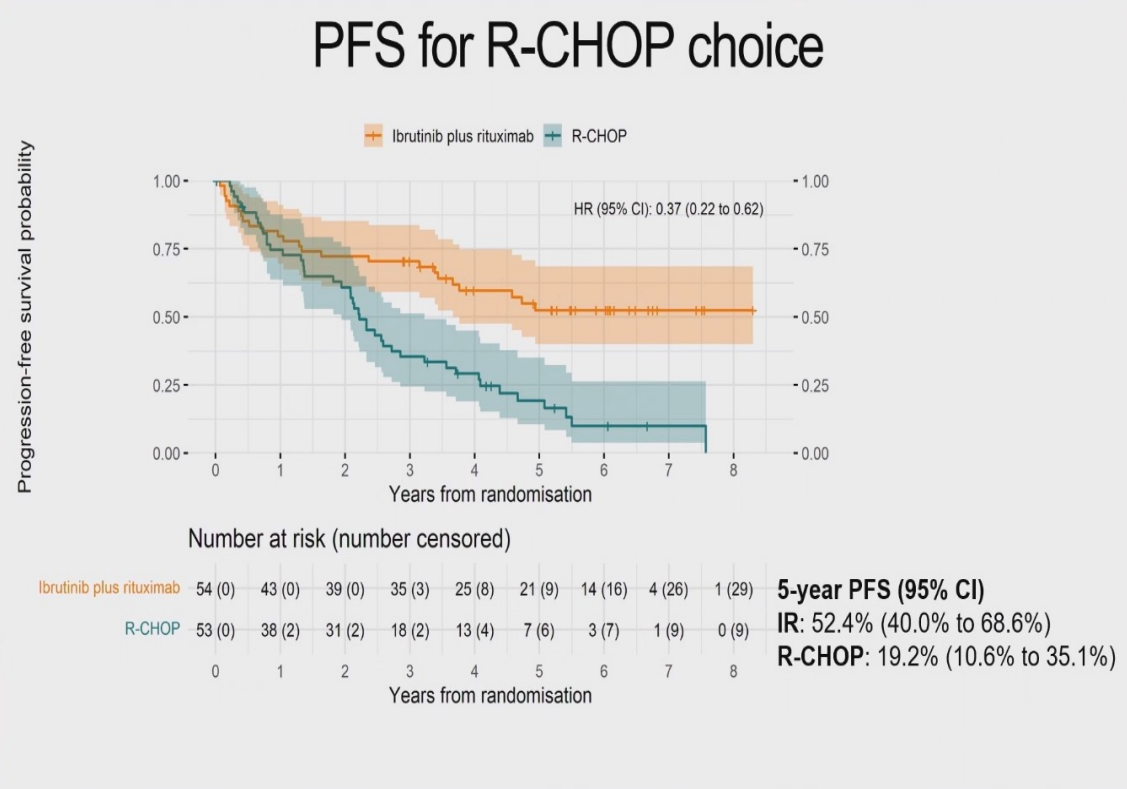
ENRICH

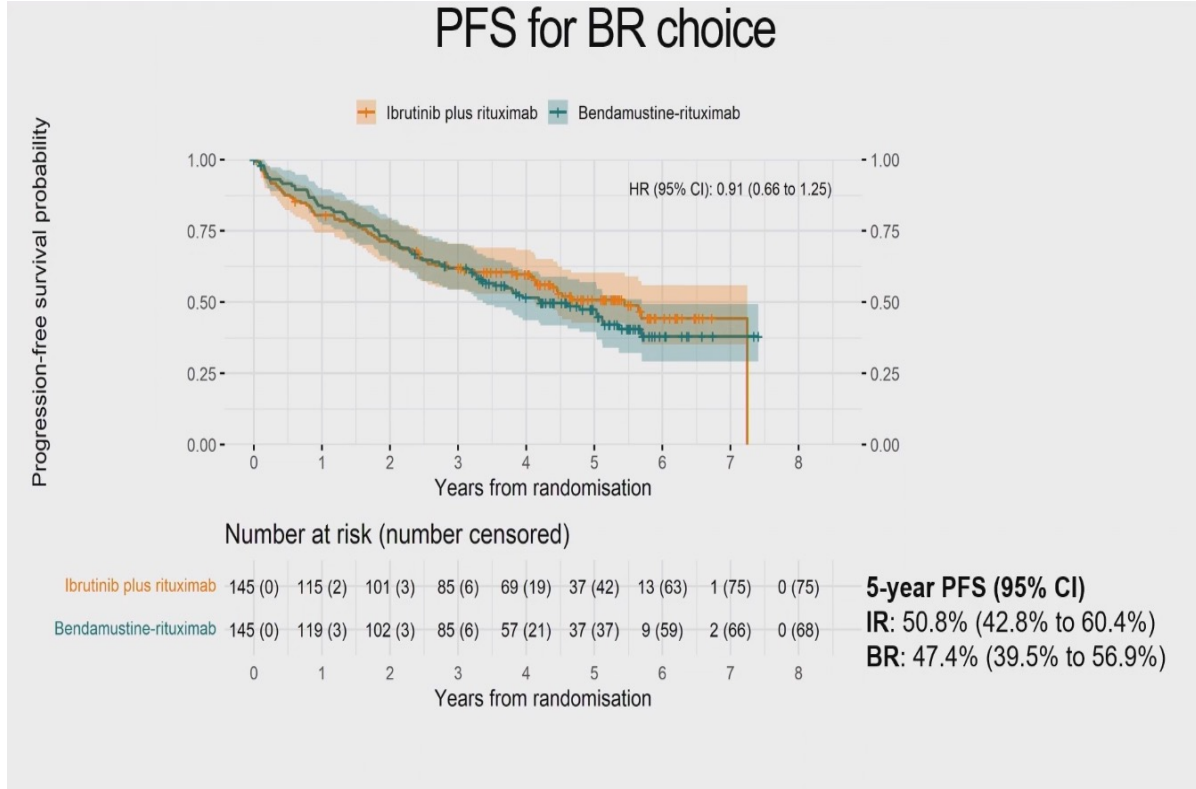


Median Follow up
47.9 months

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

Resultados





	IR (n eventos /n° ptes)	R- QMT (n eventos /n° ptes)	HR (IC95%)
R- CHOP	24/54	44/53	0,37(0,32-0,62)
R- Bendamustina	70/145	77/145	0,91(0,66-1,25)

Lewis D et al. ASH 2024

Three FDA-approved BTK inhibitors in MCL

	Ibrutinib	Acalabrutinib	Zanubrutinib
Approval Date	November 13, 2013	October 31, 2017	November 14, 2019
Approval Type	Accelerated	Accelerated	Accelerated
Indication	At least one prior therapy	At least one prior therapy	At least one prior therapy
Dose	560 mg QD	100 mg BID	160 mg BID or 320 QD
Pill Size	Tabs: 140 mg, 280 mg, 420 mg, 560 mg	Caps: 100 mg	Caps: 80 mg
Cost	$13,546.11/28 days	$14,692.32/30 days	$13,513.64/30 days

Costo anual iBTK USD 167.000 / 1 millon USD x 6 años !!!

- In April 2023 the Bruton's tyrosine kinase inhibitor, ibrutinib (Imbruvica) has been voluntarily withdrawn from the United States market as a treatment option for patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy, and for the treatment of patients with marginal zone lymphoma (MZL) who require systemic therapy and have received at least 1 prior anti-CD20-based therapy.[1]
- The withdrawal decision was made by The Janssen Pharmaceutical Companies of Johnson & Johnson in collaboration with Pharmacyclics, an AbbVie Company, following a consultation with the FDA regarding procedural guidance on accelerated approvals. The decision has no impact on other indications for ibrutinib.

TRIANGLE ES CON IBRUTINIB !!!!

The NEW ENGLAND JOURNAL of MEDICINE

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*

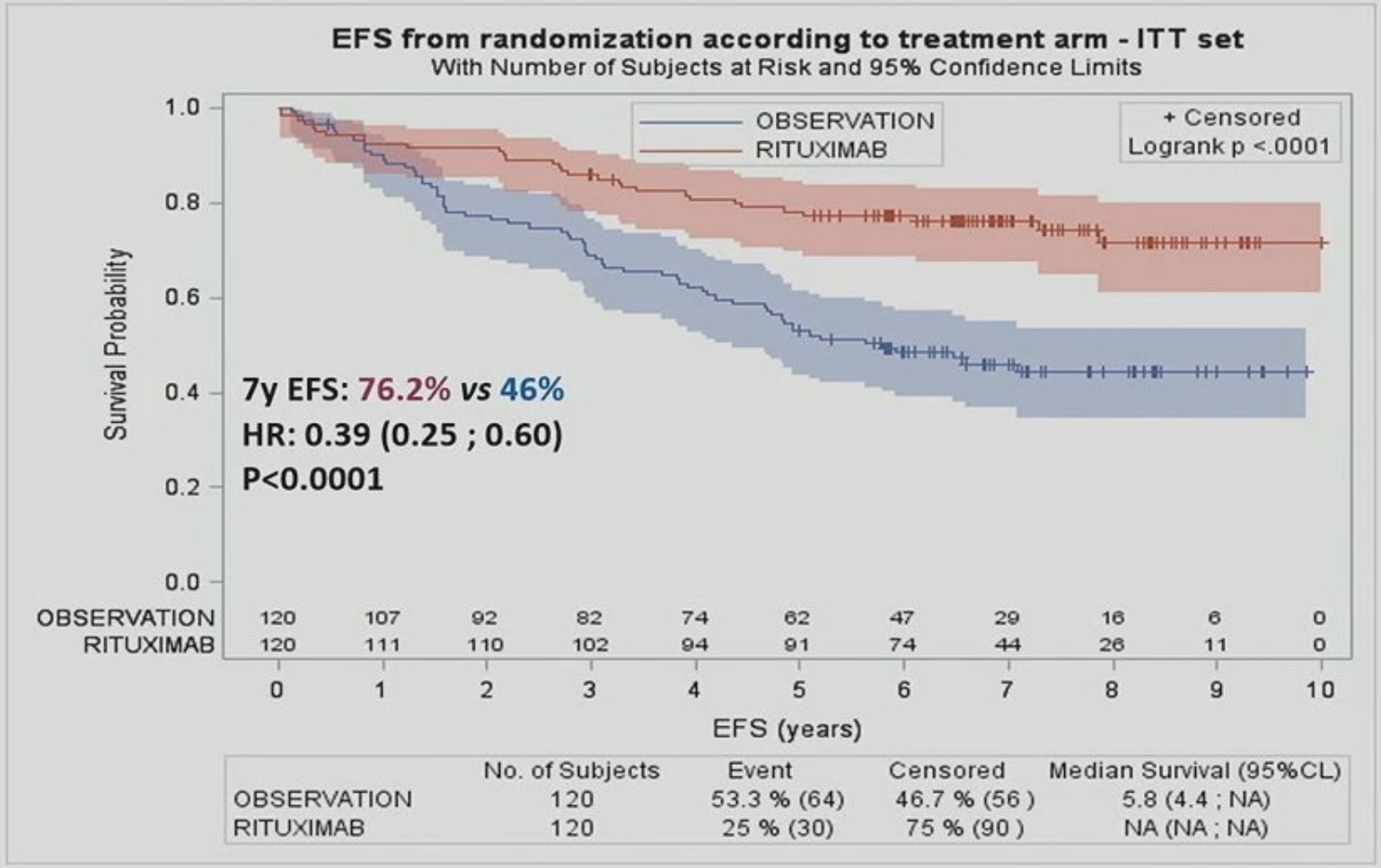
CONCLUSIONS

Rituximab maintenance therapy after transplantation prolonged event-free survival, progression-free survival, and overall survival among patients with mantle-cell lymphoma who were younger than 66 years of age at diagnosis. (Funded by Roche and Amgen; LyMa ClinicalTrials.gov number, NCT00921414.)

LYMA trial (NCT00921414)

Median FU for living patients:

- **from inclusion: 7.5 y (95% CI 7.4-7.7)**
- **from randomization: 7 y (95% CI 6.8-7.2)**



Nature of first Event	Observation, N=64/120 (53%)	Rituximab N=30/120 (25%)
Relapse	51 (80%)	19 (63%)
Death w/o relapse	9 (14%)	6 (20%)
Serious infections	4 (6%)	4 (13%)
Life threatening allergy to R	0	1 (4%)

ASCO, Abstract 7508, June 6th 2023.

Caso Clínico: Linfoma del Manto

Hombre 65 años FIT, ECOG 1. 3 meses de baja de peso (síntomas B)
Biopsia ganglionar: Linfoma del **Manto clásico (no blastoide, ni pleomórfico).**
Ki67 20%. NGS: sin mutación de TP53
MIPI intermedio riesgo standard

Triangle en LATAM: No indicaría iBTK a todos los pacientes

RCHOP/RDHAP o RDHAOX x 4 >> TAMO
>> Mantenimiento con Rituximab x tres años (EFS a 7 años 76%)

Conclusiones

- iBTK de primera línea solo haría por tiempo finito para pacientes aptos que presenten enfermedad de alto riesgo.
- Para LATAM el TAMO es la opción de consolidación más económica (NO TRIANGLE)
- En pacientes NO candidatos a TAMO (SHINE y ECHO) el uso de iBTK continuo, NO muestras una superioridad en la sobrevida global
- Favorecería para añosos CIT seguido por mantenimiento con antiCD20 y iBTK en recaída 2L (**secuenciación)**
- iBTK sin quimio tiempos finito es hoy una ocpion (ENRICH)

- Se incrementan los costos y toxicidad al emplear iBTK de primera línea sin demostrar claro beneficio en SG.
- Aumento de toxicidad EA y financiera

Back - up

Other ongoing trials that could change the first-line therapy in MCL

Young patients

ECOG-ACRIN EA4151

CIT (investigator choice): patients in CR and **MRD-** randomized to
- -ASCT followed to MR
- -MR alone

≥65y

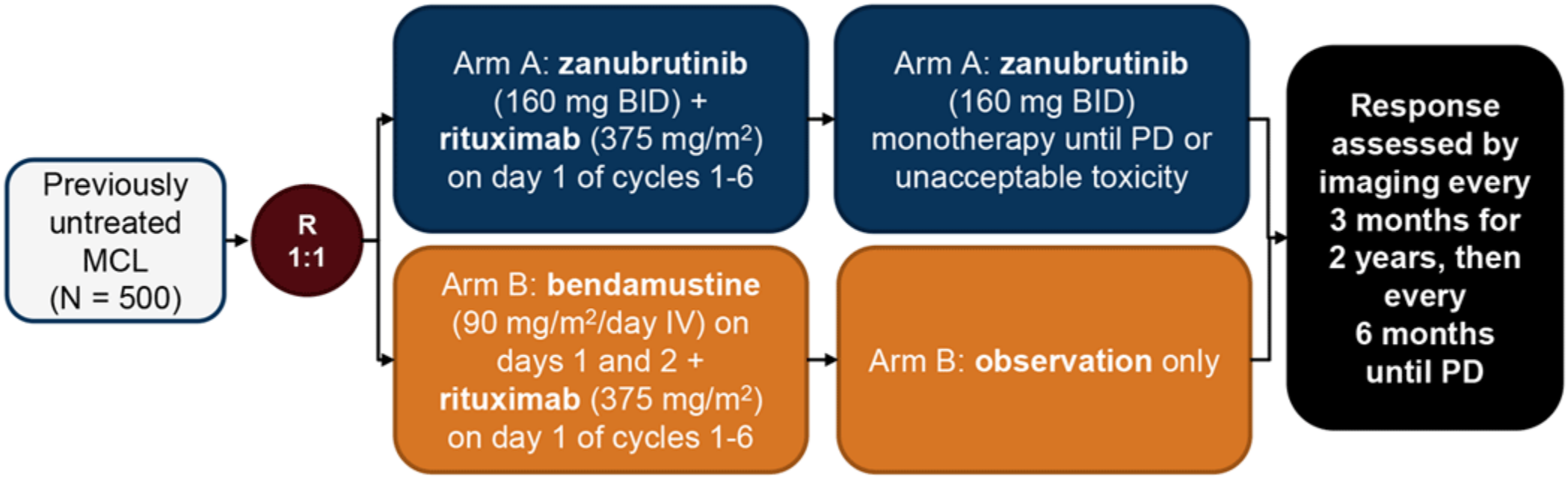
ENRICH

R-CHOP or R-benda, maintenance R
vs
R-ibrutinib, maintenance R-ibru

MANGROVE

R-zanubrutinib
vs
R-bendamustine

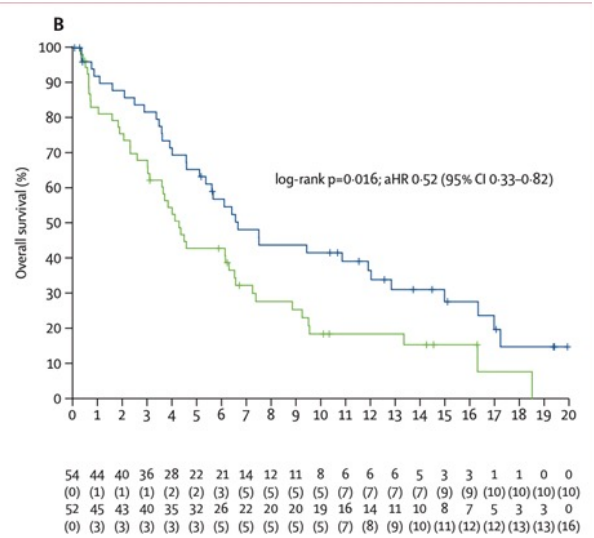
Mangrove Will Assess Zanubrutinib/Rituximab vs BR in Previously Untreated MCL[1]

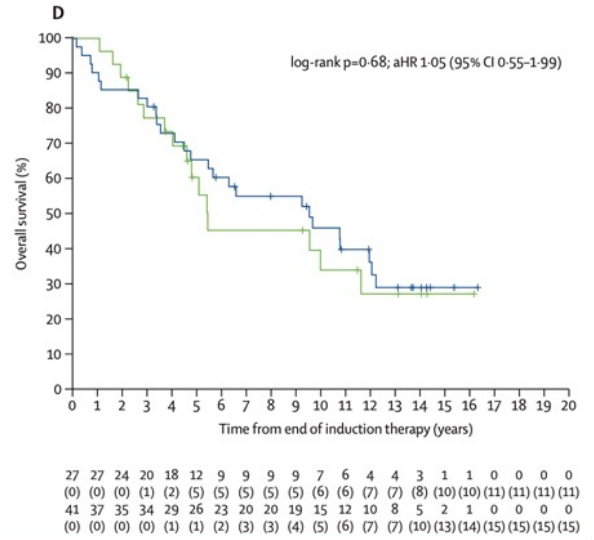


1. Dreyling M et al. *Future Oncol*. 2021;17:255-262.

Long-term survival of patients with mantle cell lymphoma after autologous haematopoietic stem-cell transplantation in first remission: a post-hoc analysis of an open-label, multicentre, randomised, phase 3 trial

Anna-Katharina Zoellner, Michael Unterhalt, Stephan Stilgenbauer, Kai Hübel, Catherine Thieblemont, Bernd Metzner, Max Topp, Lorenz Truemper, Christian Schmidt, Kamal Bouabdallah, Jürgen Krauter, Georg Lenz, Jan Dürig, Vibeke Vergote, Kerstin Schäfer-Eckart, Marc André, Hanneke C Kluin-Nelemans, Achiel van Hoof, Wolfram Klapper, Wolfgang Hiddemann, Martin Dreyling, Eva Hoster*, on behalf of the European Mantle Cell Lymphoma Network*





- Between Sept 30, 1996, and July 1, 2004, 269 patients were randomly assigned to receive either autologous HSCT or interferon alfa maintenance therapy.
- Median age 55 years
- R-CHOP induction was used in 68 (39%) of 174 patients.
- The median follow-up was 14 years
- Median PFS 3.3 years ASCT vs 1.5 years in the interferon maintenance group
- No benefit PFS for Rituximab treated patients

Interpretation Our results confirm the long-term efficacy of autologous HSCT to treat mantle cell lymphoma established in the pre-rituximab era. The suggested reduced efficacy after immunochemotherapy supports the need for its re-evaluation now that antibody maintenance, high-dose cytarabine, and targeted treatments have changed the standard of care for patients with mantle cell lymphoma.

Zoellner, et al Lancet Hem, 2021