POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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Pier Luigi Zinzani

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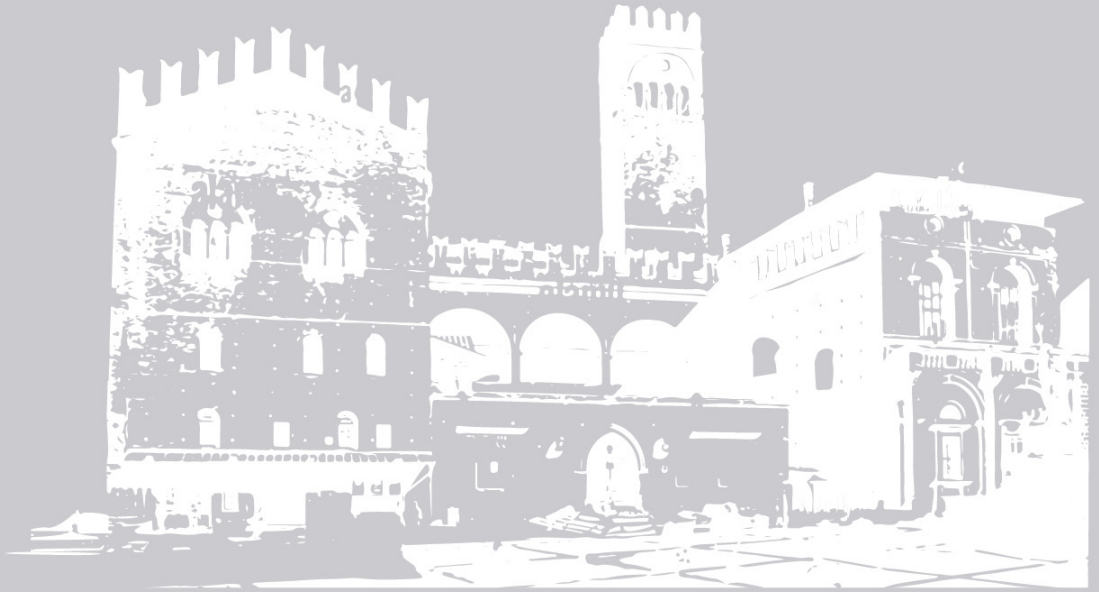


Carlo Visco

Linfoma mantellare

Verona

Disclosure Visco

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AbbVie	X				X	X	
Kite-Gilead						X	
Janssen	x		x		X	X	
Gentili					X	X	
Novartis						X	
Pfizer			x		X	X	
Roche						X	
Incyte					X	X	
Servier					X		
Astra Zeneca					X		
BMS						X	
Kyowa Kirin					X		
Lilly			x		X	X	

First line younger patients

- Long-term *TRIANGLE*
- Benefit of rituximab maintenance

First line elderly patients

- *ENRICH* (CIT vs I+R)
- Update *ECHO* (BR vs A+BR)

Relapsed setting

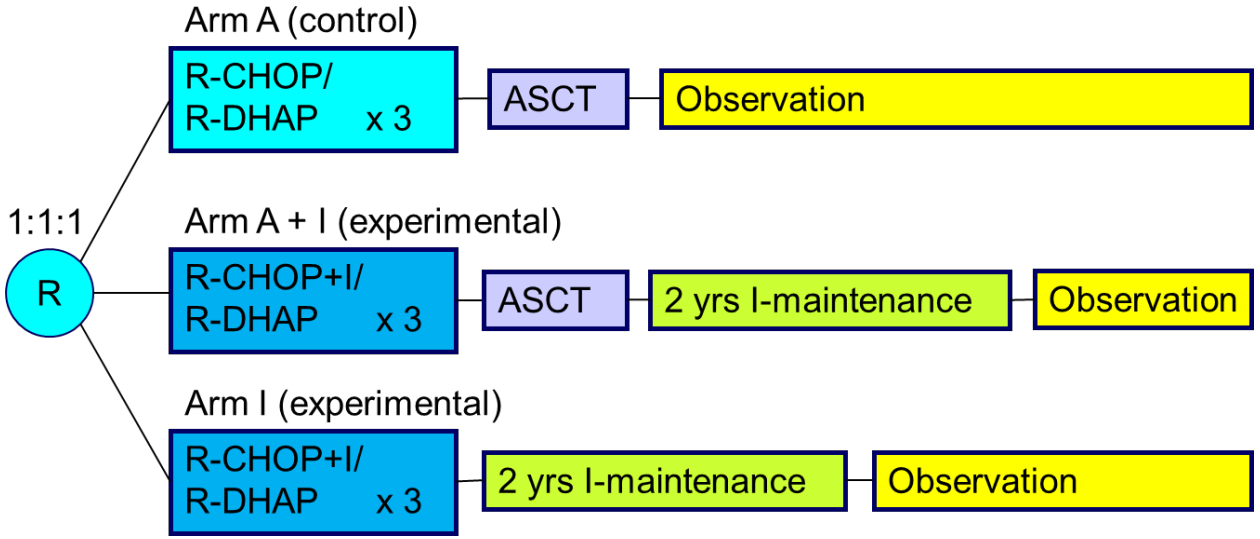
- Post-CarT outcome

Remaining open questions from TRIANGLE 2022

- longer follow-up (from 31 to 55 months)
- significance of OS ?
- ASCT in the era of ibrutinib containing regimens ?
- R maintenance in the era of ibrutinib containing regimens ?

TRIANGLE: Trial Design

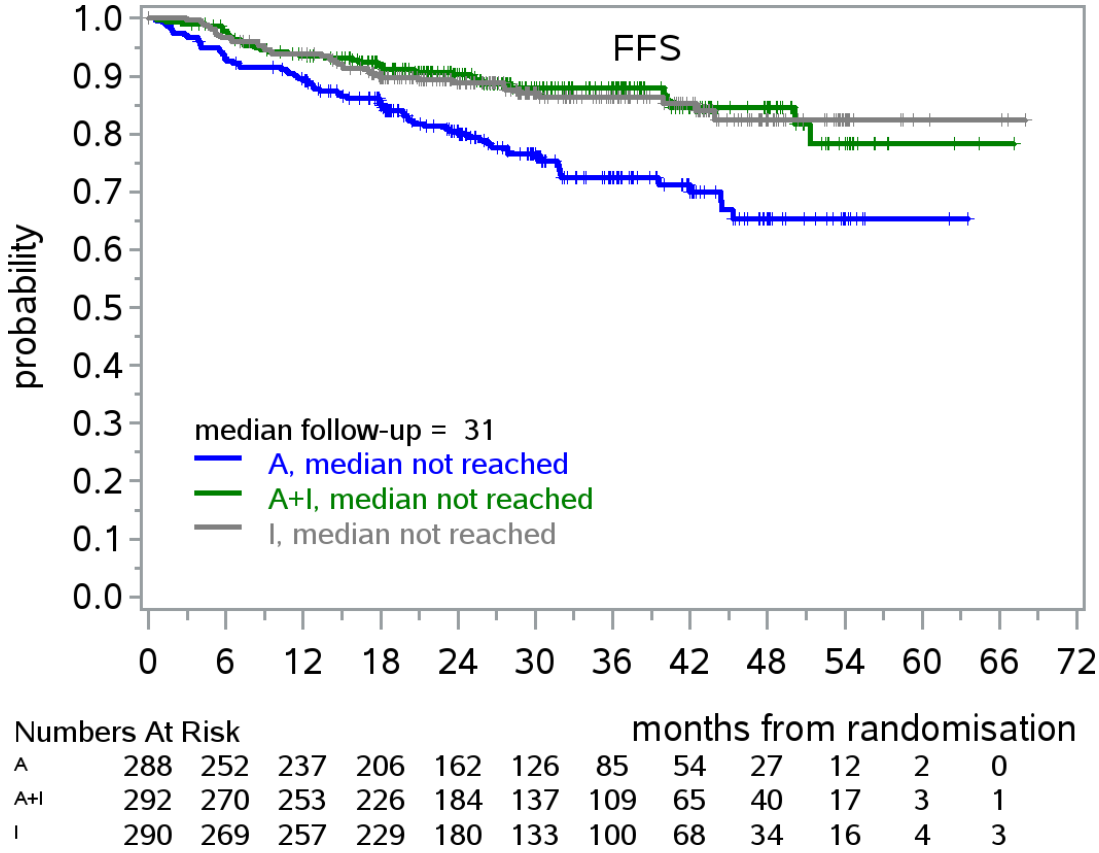
- MCL patients
- previously untreated
- stage II-IV
- younger than 66 years
- suitable for HA and ASCT
- ECOG 0-2



- Primary outcome: FFS

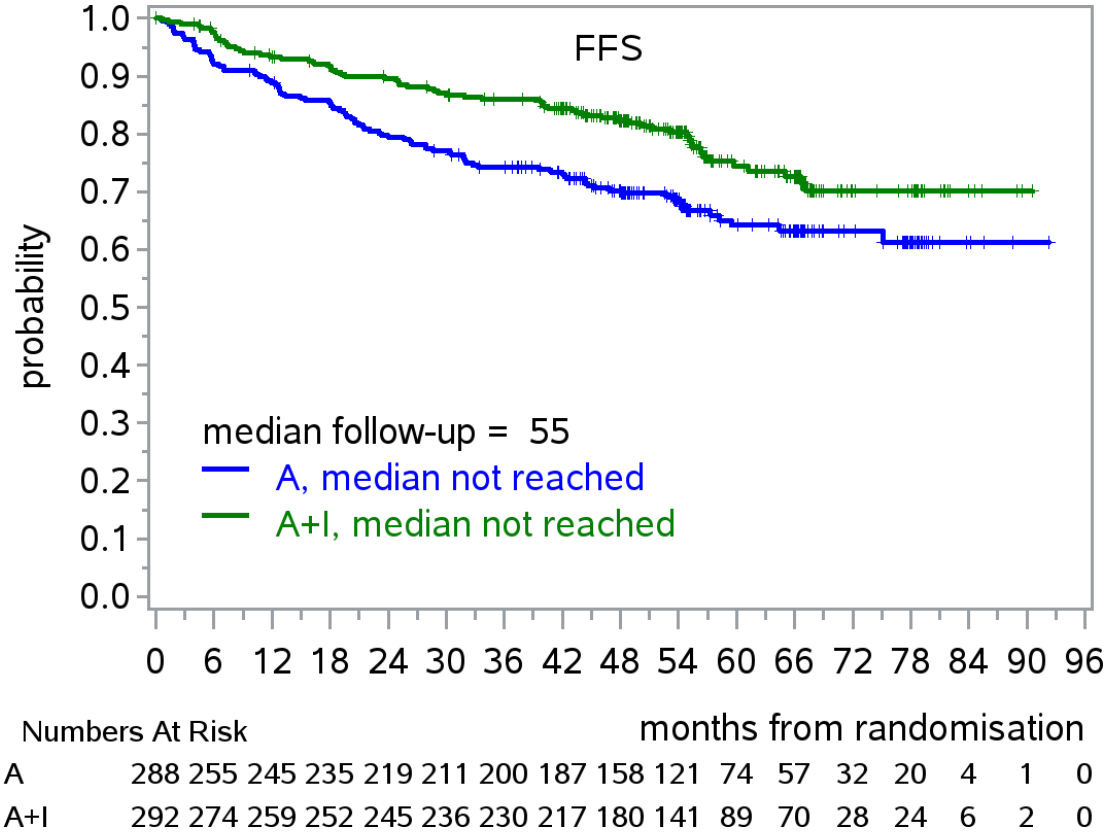
R maintenance following national guidelines in all 3 arms

Dreyling, ASH 2022: #1

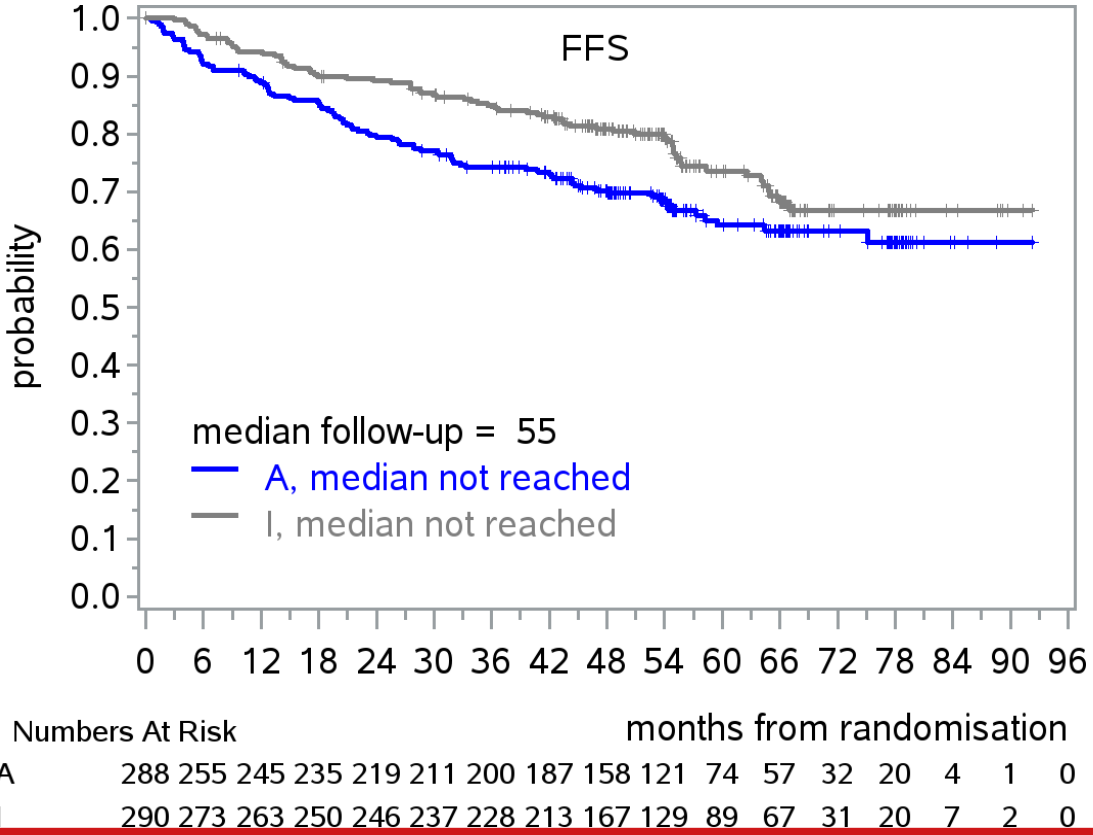


- Test A+I vs. I ongoing, no decision yet

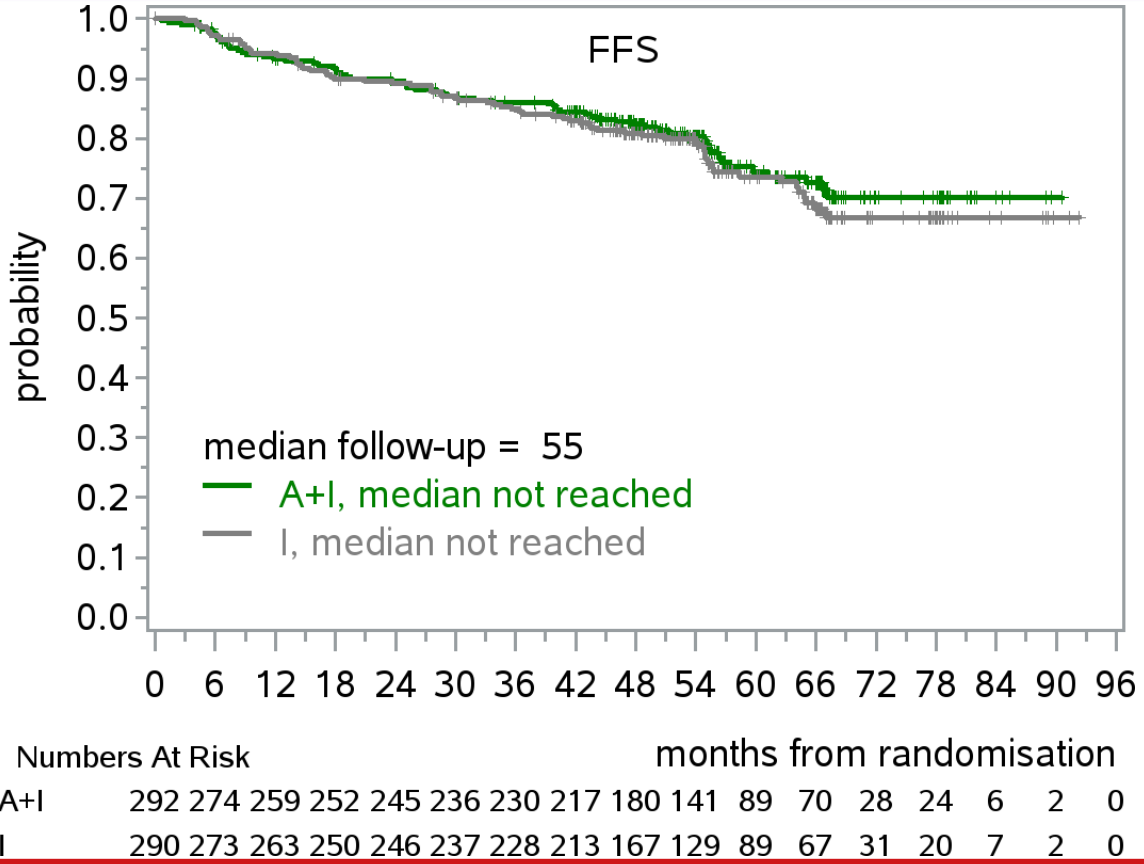
Next lymphoma treatment (among patients with first treatment failure)	A (n=68)		A+I (n=35)		I (n=37)	
Treatment with Ibrutinib	34	79%	4	24%	3	11%
Treatment without Ibrutinib	9	21%	13	76%	24	89%
No treatment	25		18		10	



- Superiority of A+I vs. A
  - 4-year FFS A+I: 82%
  - 4-year FFS A: 70%
- p-value (overrunning, one-sided): p=0.0026
- HR (A+I vs. A): HR=0.64

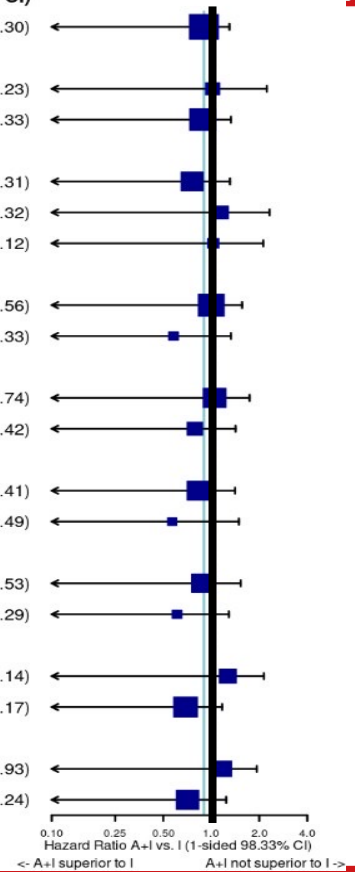


- Superiority of A vs. I rejected
  - 4-year FFS A: 70%
    (MCL Younger: 70%)
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided):
  p=0.9890
- HR (A vs. I): HR=1.29
- Superiority of I
  (two-sided, retrospective)
  p=0.0208



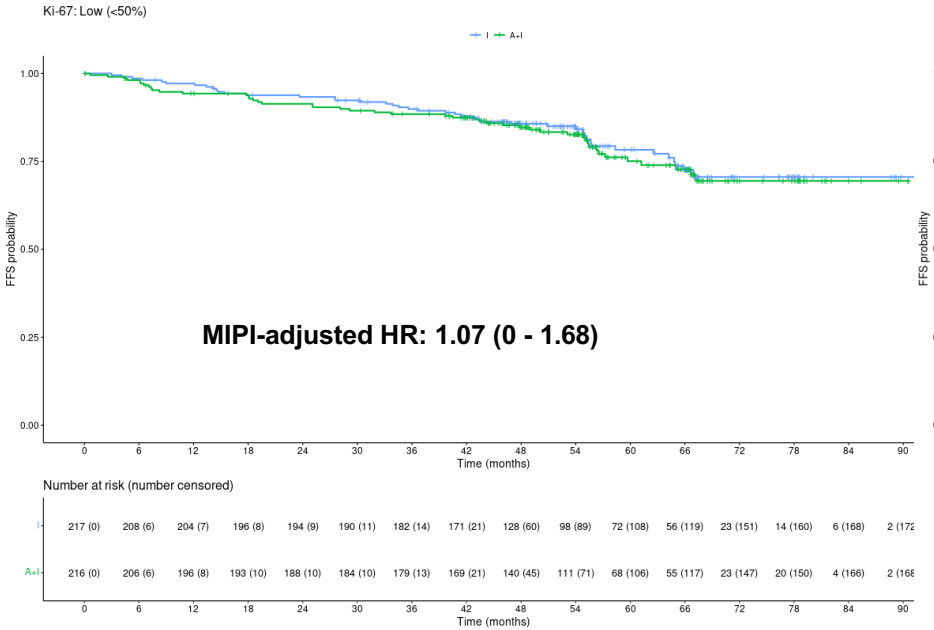
- Superiority of A+I vs. I rejected
  - 4-year FFS A+I: 82%
  - 4-year FFS I: 81%
- p-value (overrunning, one-sided): p=0.21
- HR (A+I vs. I): HR=0.83

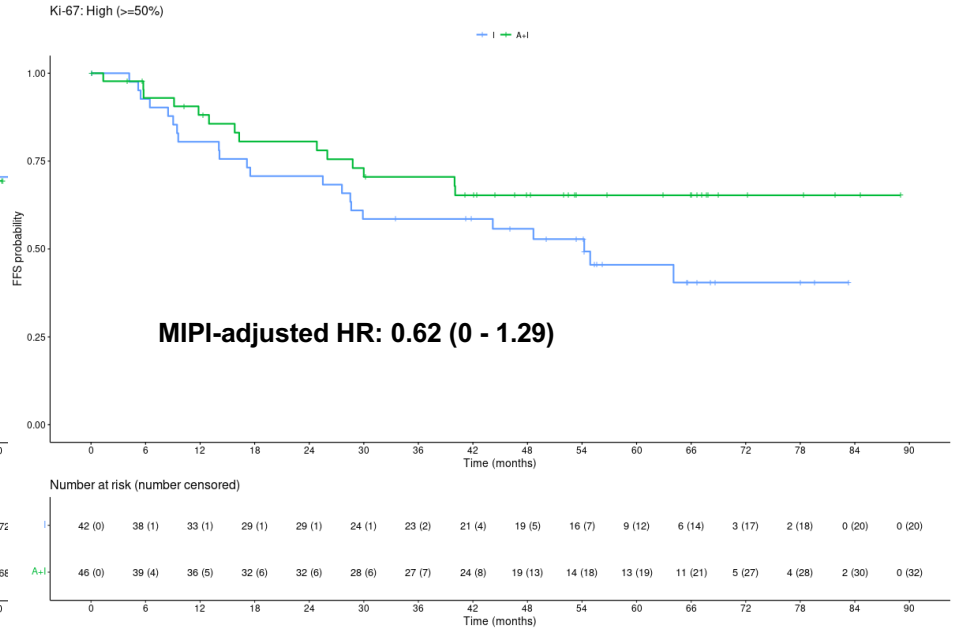
Subgroup (interaction p-value)	No. of patients	No. of events	Hazard ratio (1-sided 98.33% CI)
All	582	134	0.90 (0 - 1.30)
Sex (p=0.71)			
Female	138	30	1.02 (0 - 2.23)
Male	444	104	0.88 (0 - 1.33)
MIPI			
Low	336	62	0.76 (0 - 1.31)
Intermediate (p=0.33)	157	37	1.15 (0 - 2.32)
High (p=0.56)	89	35	1.03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



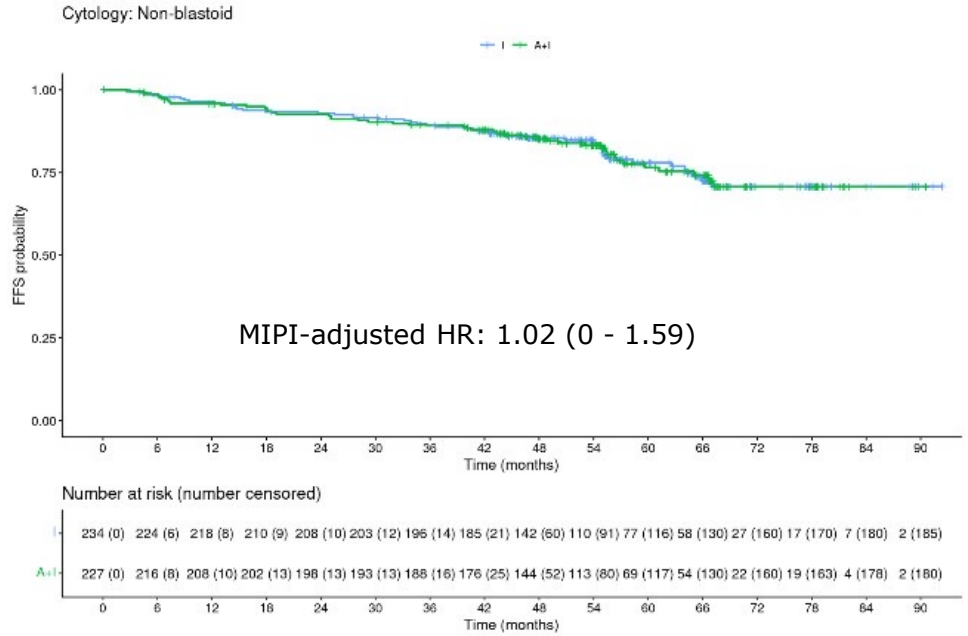
- trend towards superiority of A+I over I in patients in high risk patients:
  - Ki-67 >30%
  - blastoid cytology or
  - high p53 expression

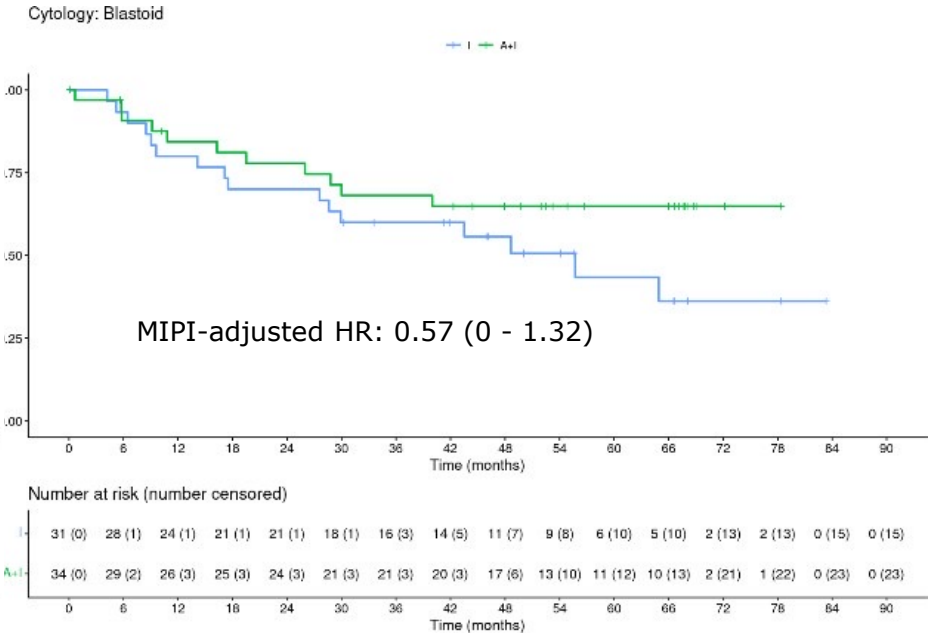
TRIANGLE: A+I vs. I (FFS) and **Ki-67** (50% cut-off)



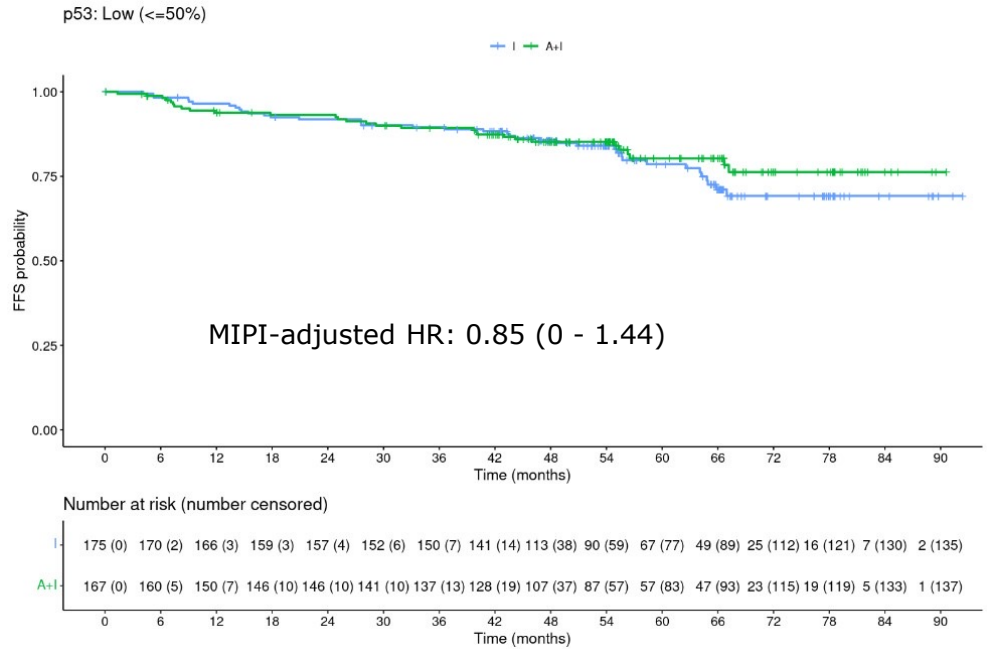


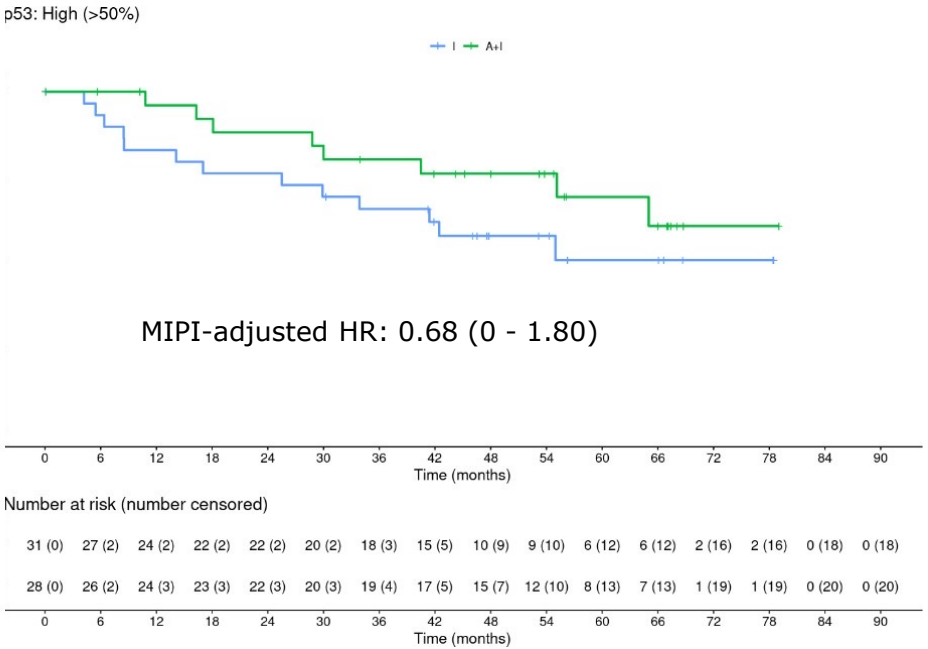
TRIANGLE: A+I vs. I (FFS) and **blastoid variant**

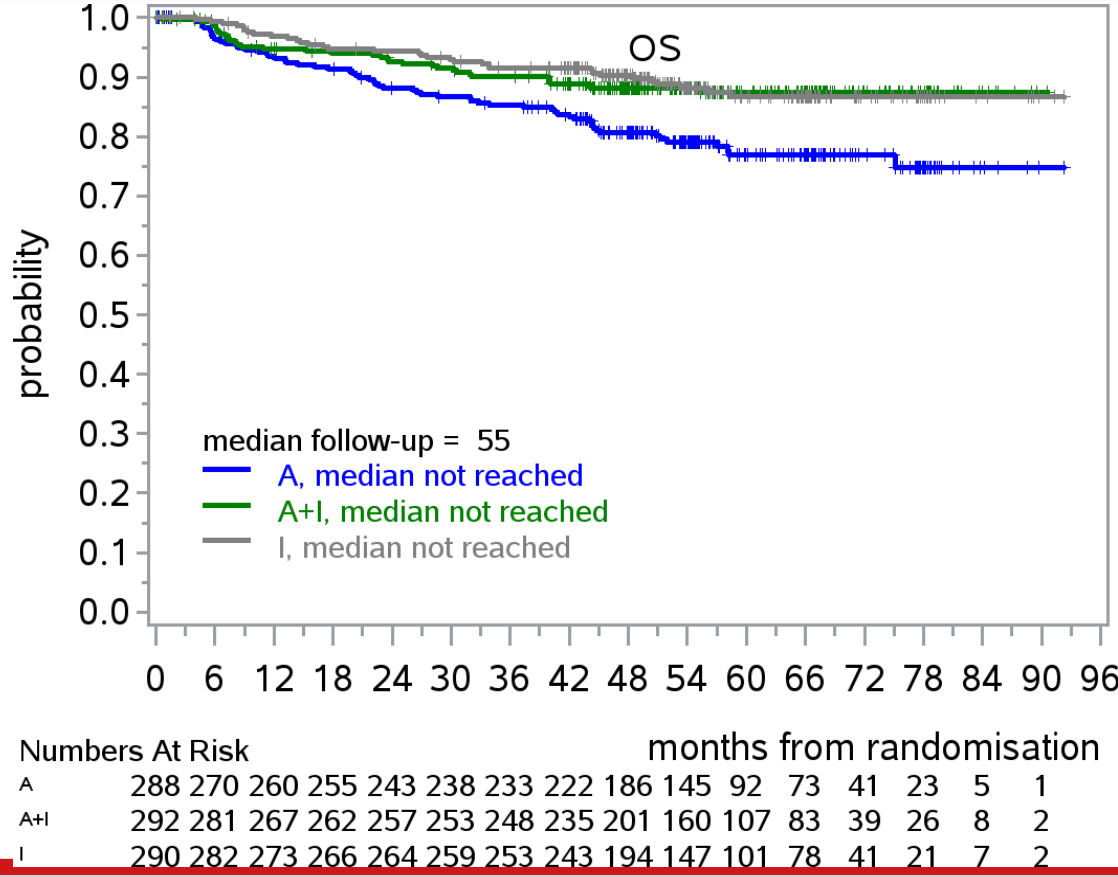




TRIANGLE: A+I vs. I (FFS) and **p53 high expression**







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

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

Impact of Rituximab Maintenance Added to Ibrutinib-Containing Regimens with and without ASCT in Younger, Previously Untreated MCL Patients: An Analysis of the Triangle Data Embedded in the Multiply Project

ASH Meeting, San Diego CA
USA 7th December 2024

Marco Ladetto*, Katja Gutmair* , Jeanette Doorduijn, Eva Giné, Mats Jerkeman, Jan Walewski, Martin Hutchings, Ulrich Mey, Jon Riise, Marek Trneny, Vibeke KJ Vergote, Piero Maria Stefani, Netanel A. Horowitz, Maria Gomes da Silva, Sirpa Leppä, Linmiao Jiang, Christiane Pott, Wolfram Klapper, Christian Schmidt, Michael Unterhalt , Martin Dreyling#, and Eva Hoster#,

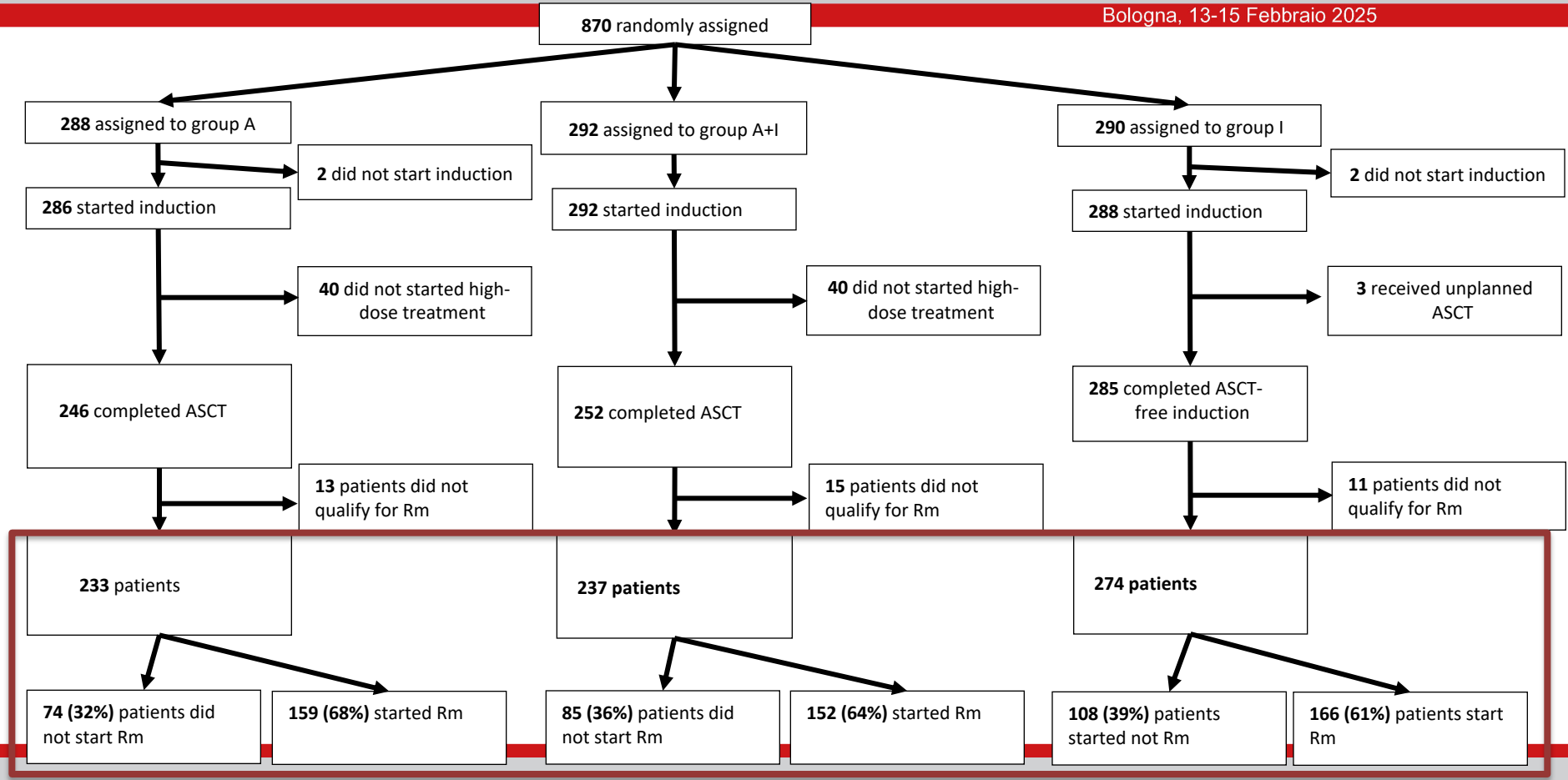
*On behalf of European MCL Lymphoma Network (*shared first authorship, # shared last authorship)*

Presenting Author: Marco Ladetto MD Università del Piemonte Orientale and AO SS Antonio e Biagio e Cesare Arrigo

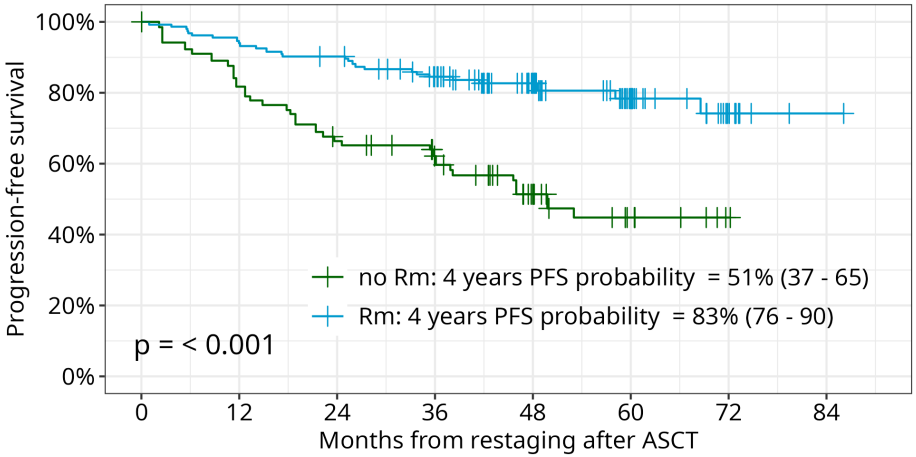
Azienda Ospedaliera Nazionale
SS. Antonio e Biagio e Cesare Arrigo
Alessandria

UPO
UNIVERSITÀ DEL PIEMONTE ORIENTALE

FIL FONDAZIONE ITALIANA LINFOMI


870 randomly assigned
288 assigned to group A
292 assigned to group A+I
290 assigned to group I
2 did not start induction
2 did not start induction
286 started induction
292 started induction
288 started induction
40 did not started high-dose treatment
40 did not started high-dose treatment
3 received unplanned ASCT
246 completed ASCT
252 completed ASCT
285 completed ASCT-free induction
13 patients did not qualify for Rm
15 patients did not qualify for Rm
11 patients did not qualify for Rm
233 patients
237 patients
274 patients
74 (32%) patients did not start Rm
159 (68%) started Rm
85 (36%) patients did not start Rm
152 (64%) started Rm
108 (39%) patients started not Rm
166 (61%) patients start Rm

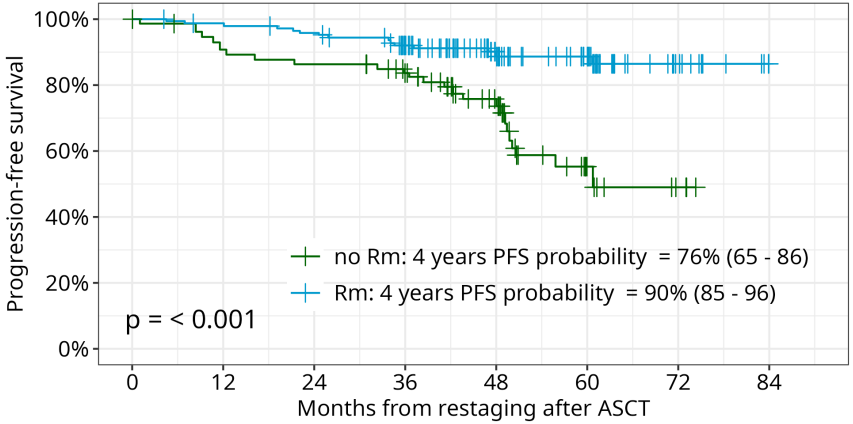
Arm A (ASCT, no I): PFS



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

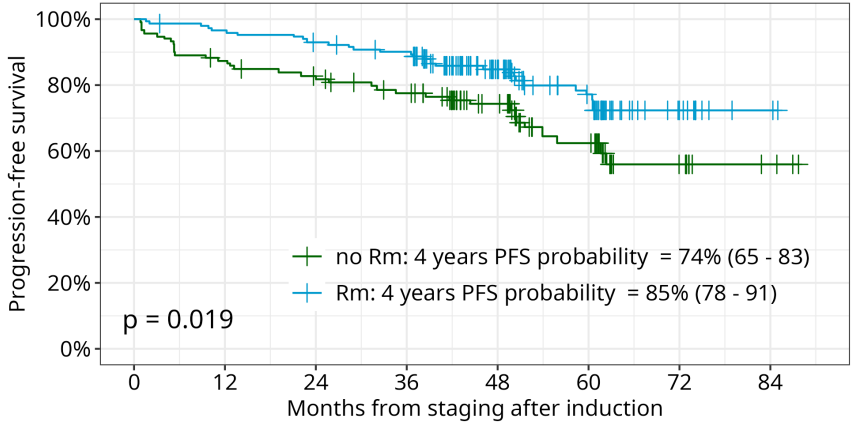
*Propensity Score including MIPI single variables, response after induction (arm I)/ after ASCT (arm A, A+I), Ki67, cytology

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

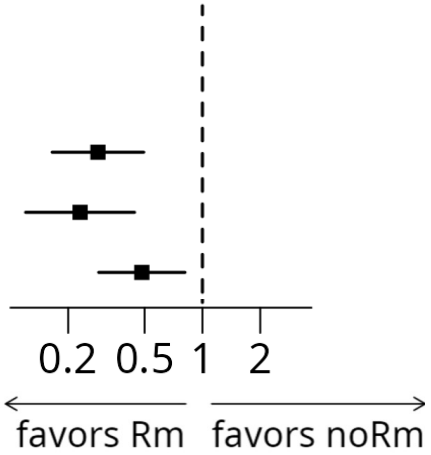


	noRm group							
At risk	116.7	100.7	92.5	82.6	59.8	38.2	19.3	6
Event	0	14.1	20.2	26.2	29.2	35.8	37.7	37.7
	Rm group							
At risk	157.2	148.3	141.5	135.3	87.3	57.9	23	3.9
Event	0	7	12.8	16.9	22.8	28.7	30.6	30.6

*Propensity Score including MIPI single variables, response after induction (arm I) after ASCT (arm A, A+I), Ki67, cytology

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)



RM is beneficial in all three arms, but the benefit appears greater in A and A+I arms compared with arm I.

Conclusions: TRIANGLE results (after 55 months)

- Both Ibrutinib including arms superior to A for FFS and OS
- A+I not superior to I (*trend in HR groups in favour of A+I*, but higher toxicity)
- Rm significantly prolongs PFS in all treatment arms (++ in A including arms, no OS)
- Rm associated with modest increase in infections and hemo-toxicity in arm A

Arm I (*A+I*) may represent the preferred first-line treatment in younger MCL patients

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.

Trial design

Inclusion criteria

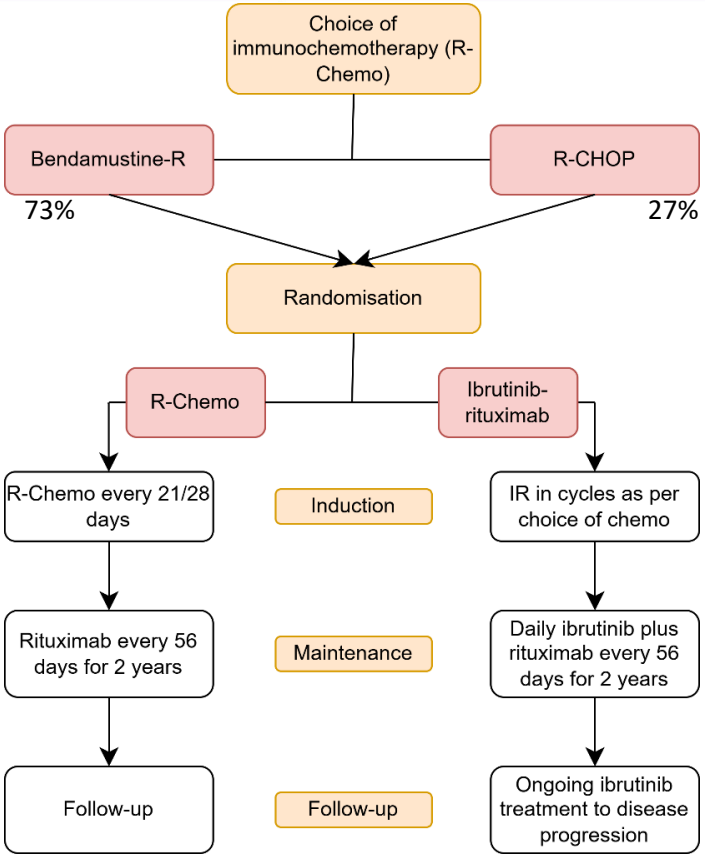
- 60 years or older
- Previously untreated, measurable (>1.5cm), stage II-IV MCL in need of treatment
- ECOG 0-2

Primary endpoint: PFS

Recruitment open December 2015 - June 2021

Patients from 66 sites in UK, Nordics

ENRICH



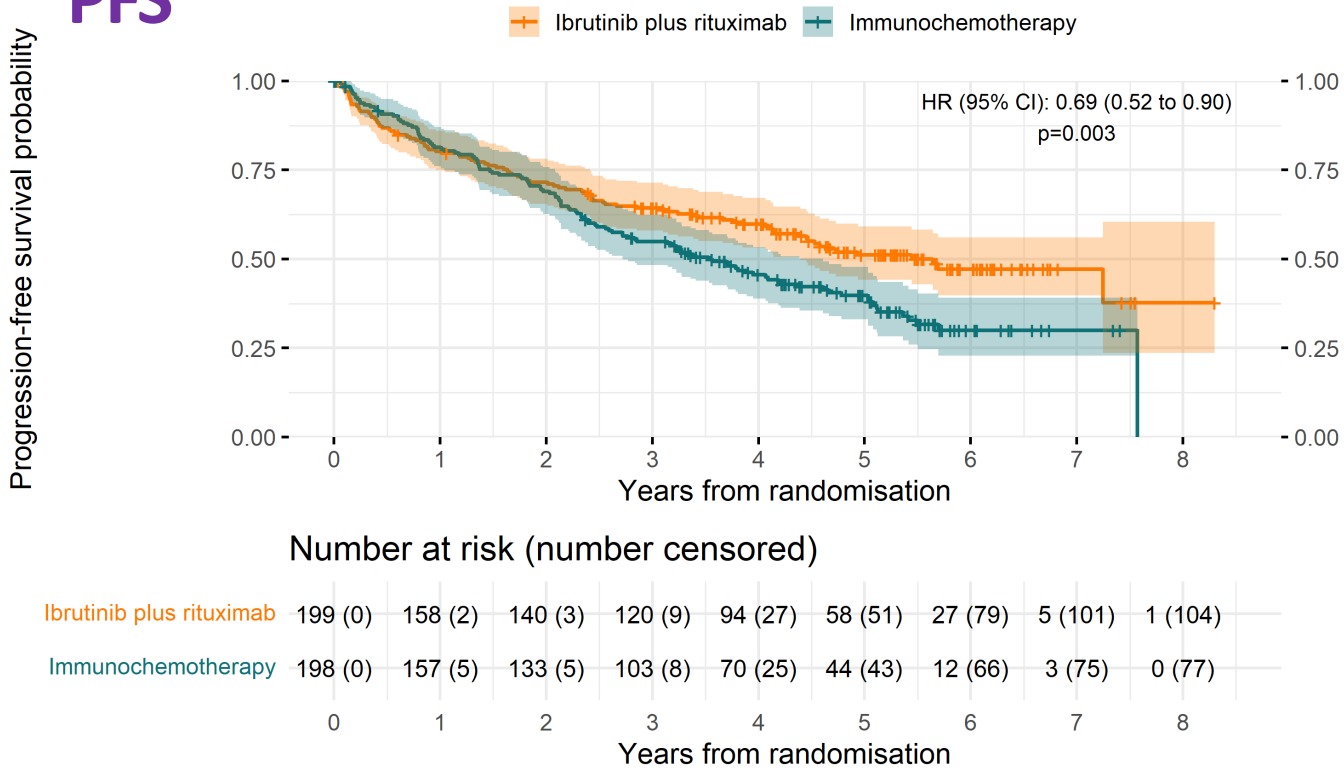
Patient characteristics

ENRICH

		Immunochemotherapy, N = 198	Ibrutinib plus rituximab, N = 199
Age (median, IQR)		74 (70, 78)	74 (70, 77)
Male		146 / 198 (73.7%)	150 / 199 (75.4%)
ECOG	**0**	107 / 198 (54.0%)	124 / 199 (62.3%)
	1	80 / 198 (40.4%)	64 / 199 (32.2%)
	2	11 / 198 (5.6%)	11 / 199 (5.5%)
Stage IV		183 / 198 (92.4%)	175 / 199 (87.9%)
Blastoid		15 / 192 (7.8%)	10 / 178 (5.6%)
Ki67 ≥ 30%		71 / 157 (45.2%)	55 / 142 (38.7%)
MIPI	**Low**	23 / 195 (11.8%)	23 / 198 (11.6%)
	Intermediate	61 / 195 (31.3%)	64 / 198 (32.3%)
	High	111 / 195 (56.9%)	111 / 198 (56.1%)
TP53 mutation		18 / 75 (24.0%)	22 / 80 (27.5%)

PFS

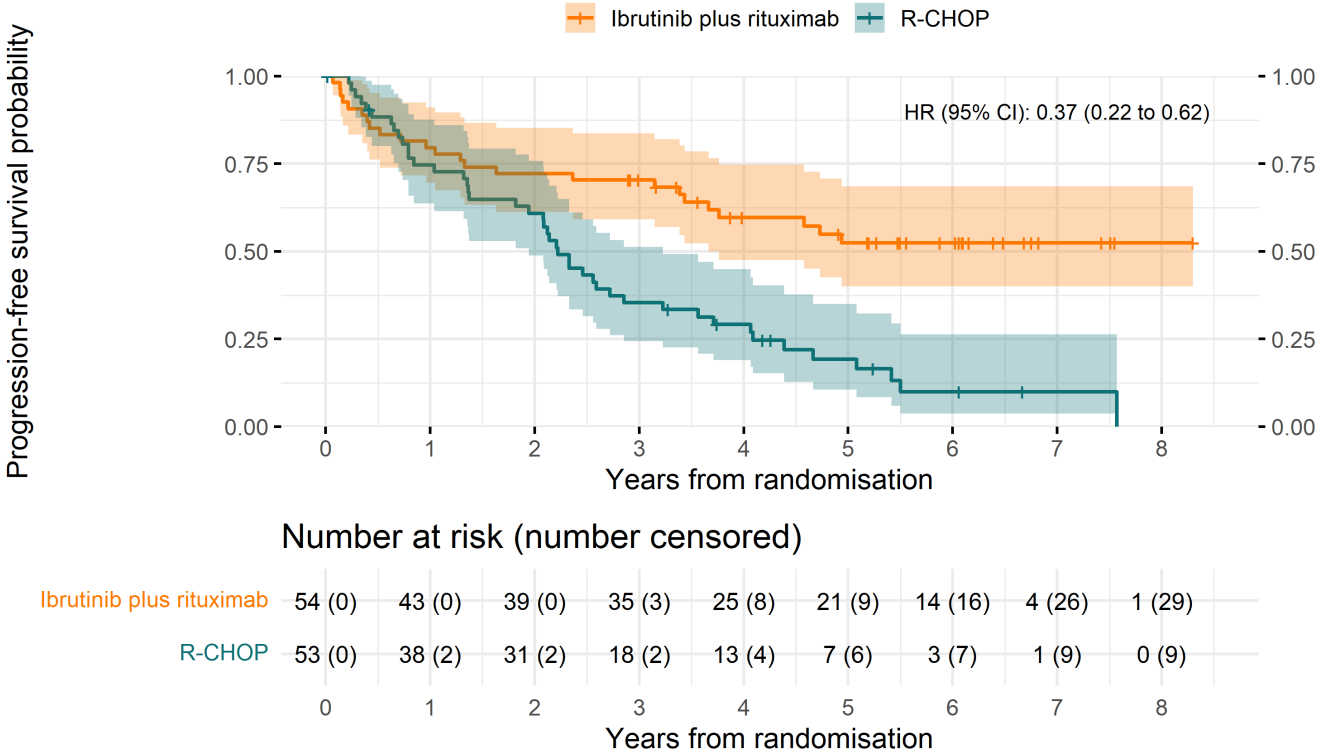
ENRICH



Median f/u 47.9 months

PFS for R-CHOP choice

ENRICH



PFS for BR choice

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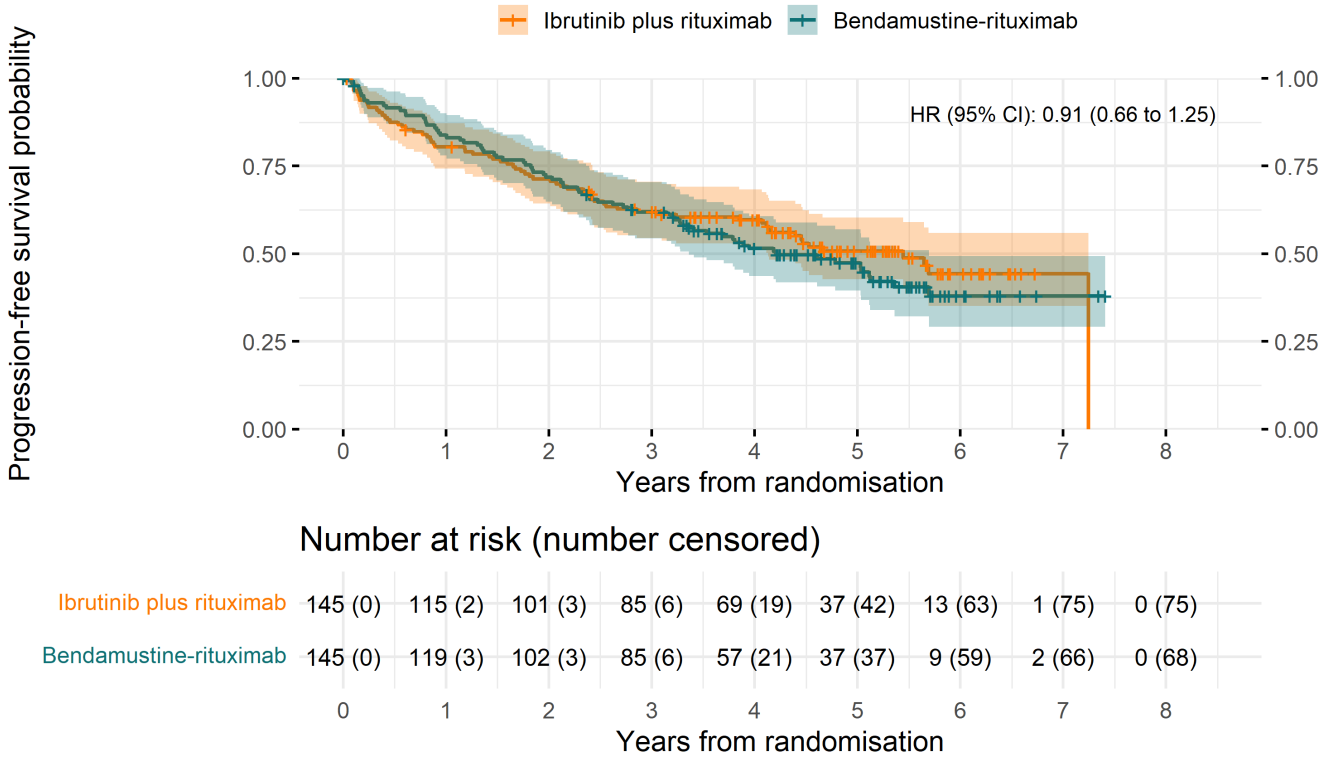
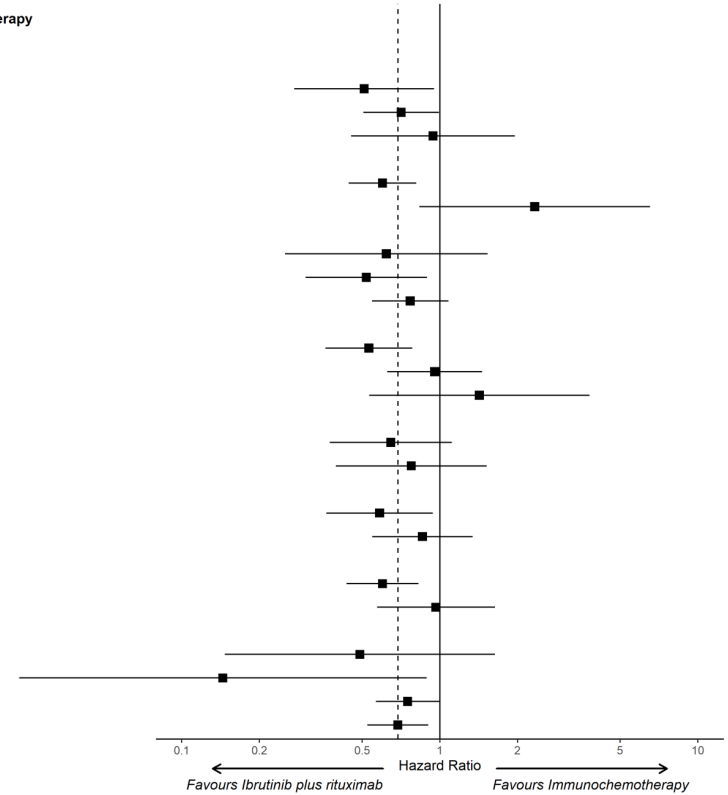


PFS subgroups

ENRICH

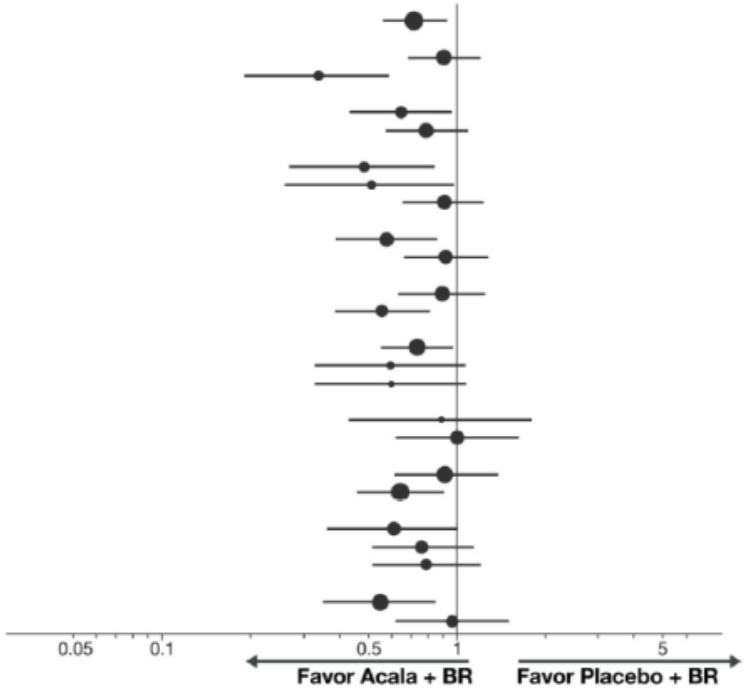
	Ibrutinib plus rituximab	Immunochemotherapy	Hazard Ratio (95% CI)
	no. of events/no. of patients		
Age category			
[60, 70)	16/51	27/45	0.51 (0.27, 0.95)
[70, 80)	63/129	77/129	0.71 (0.51, 0.99)
[80, 90)	15/19	17/24	0.94 (0.45, 1.95)
Blastoid status			
Non-blastoid	72/168	107/177	0.60 (0.44, 0.81)
Blastoid	9/10	10/15	2.33 (0.83, 6.52)
MIPI			
Low	8/23	12/23	0.62 (0.25, 1.53)
Intermediate	21/64	36/61	0.52 (0.30, 0.89)
High	65/111	71/111	0.77 (0.55, 1.08)
ECOG			
0	44/124	63/107	0.53 (0.36, 0.78)
1	40/64	50/80	0.96 (0.63, 1.46)
2	10/11	8/11	1.42 (0.53, 3.80)
TP53			
Non-mutated	22/58	32/57	0.65 (0.37, 1.11)
Mutated	20/22	16/18	0.77 (0.40, 1.52)
Ki67			
< 30%	29/87	44/86	0.58 (0.36, 0.94)
≥ 30%	34/55	49/71	0.86 (0.55, 1.34)
Gender			
Male	68/150	90/146	0.60 (0.44, 0.83)
Female	26/49	31/52	0.97 (0.57, 1.63)
Disease stage			
II	5/14	6/9	0.49 (0.15, 1.64)
III	2/10	5/6	0.14 (0.02, 0.89)
IV	87/175	110/183	0.75 (0.57, 1.00)
All participants	**94/199**	**121/198**	**0.69 (0.52, 0.90)**



PFS subgroups

Phase 3 ECHO

Subgroup	Number of Events/Patients Acala + BR	Placebo + BR
Overall		
Primary analysis	110/299	137/299
Sex		
Male	93/214	94/209
Female	17/85	43/90
Age category, y		
<70	42/123	57/117
≥70	68/176	80/182
Geographic region[a]		
North America	19/82	35/83
Western Europe	14/46	24/46
Other	77/171	78/170
Baseline ECOG PS score		
0	42/156	60/140
1 or 2	68/141	75/155
Tumor bulk		
<5 cm	62/187	68/186
≥5 cm	48/112	69/113
MCL type		
Classic type	82/238	107/243
Blastoid variant/pleomorphic variant	21/41	24/38
Other	0/0	2/5
TP53 mutation		
Positive	14/22	17/29
Negative	36/97	31/83
Ki-67		
<30%	45/133	47/126
≥30%	56/139	80/147
Simplified MIPI score[a]		
Low risk (0–3)	24/99	39/101
Intermediate risk (4–5)	46/128	52/125
High risk (6–11)	40/72	46/73
COVID-19 vaccine status		
Yes	34/164	53/147
No	39/76	40/79



Grade 3-4 Adverse events

ENRICH

N participants (% of safety population)	Ibrutinib plus rituximab, N=198	Bendamustine-rituximab, N=143	R-CHOP, N=52
Total	125 (63.1%)	97 (67.8%)	36 (69.2%)
All Cardiac AEs	44 (22.2%)	7 (4.9%)	7 (13.5%)
All bleeding AEs	10 (5.1%)	3 (2.1%)	3 (5.8%)
Atrial Fibrillation	12 (6.1%)	1 (0.7%)	0
Neutropenia	18 (9.1%)	27 (18.9%)	11 (21.2%)
Neutropenic sepsis	6 (3.0%)	2 (1.4%)	8 (15.4%)
Corona virus infection	10 (5.1%)	10 (7.0%)	0

Grade 3 and 4 adverse events during induction treatment and maintenance
Safety population - patients who had at least one cycle of treatment

Conclusions

ENRICH

- ENRICH is the first randomised study to demonstrate an improved PFS for IR versus immunochemotherapy in previously untreated MCL
  - Primarily driven by improved PFS for IR versus RCHOP
  - PFS for IR versus BR broadly similar
- Adverse event profile in keeping with known AE profile of ibrutinib
- Subgroup analysis suggests IR ++ if*: <70, ECOG=0, Ki67<30%, non blastoid, low-int MIPI [BR+Acala better than BR also in HR] **Phase 3 ECHO**

- Ibrutinib-rituximab can be considered a standard of care in (*low risk*) previously untreated MCL

Grazie
per l’attenzione