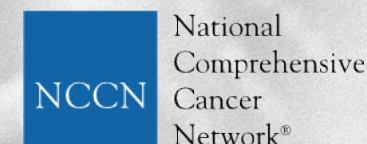
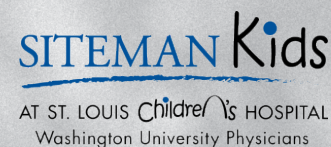
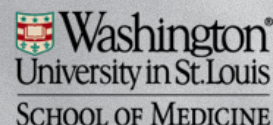


# My Older MCL Patient is in Remission: Now What?

*Brad Kahl, MD*  
*Professor of Medicine*



# Disclosures

- Consulting
  - Abbvie, Acerta, Astra Zeneca, ADCT, BeiGene, BMS, Genentech, Genmab, Gilead, Incyte, Janssen, MEI, Morphosys, Pharmacyclics
- Research Funding
  - Genentech, ADCT, Acerta, Celgene, BeiGene

# A Case

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- 72 yo man presents with left axillary adenopathy
- Bx shows MCL, typical morphology. cyclin D1+. t(11;14). Ki-67 25%. No p53.
- PET shows widespread disease with largest node of 7 cm in mesentery.
- Marrow shows 30% involvement by MCL.
- Blood counts normal. LDH normal. No B symptoms, but fatigue and lack of stamina for several months.
- PMHx includes HTN, elevated cholesterol, CAD s/p stenting, moderate obesity.
- You decide to treat. What is your preferred induction?

## Some induction options for an older MCL patient:

1. BR (probably most widely used in US)
2. R-CHOP
3. VR-CAP
4. R-BAC
5. R<sup>2</sup> (lenalidomide-rituximab) (not FDA approved)
6. BR plus Ibrutinib (ala SHINE)



# MCL older: Induction strategies

- BR (without maintenance) generates remissions lasting 3-4 years on average
- Became US standard with remarkably little data
  - StiL trial N = 47
- Subsequent data supports BR in older MCL
  - BRIGHT trial, Rummel data, BCCA data, E1411, Shine

# Summary of non intensive induction regimens\*

	N	Age	ORR	CR	mPFS
R-CHOP	244	66	89%	42% (CT)	14.4 mo
VR-CAP	243	65	92%	53% (CT)	24.7 mo
BR**	188	70	~90%	~45% (CT)	35-42 mo
RBAC <sub>500</sub>	57	71	91%	91% (PET)	> 7 yrs

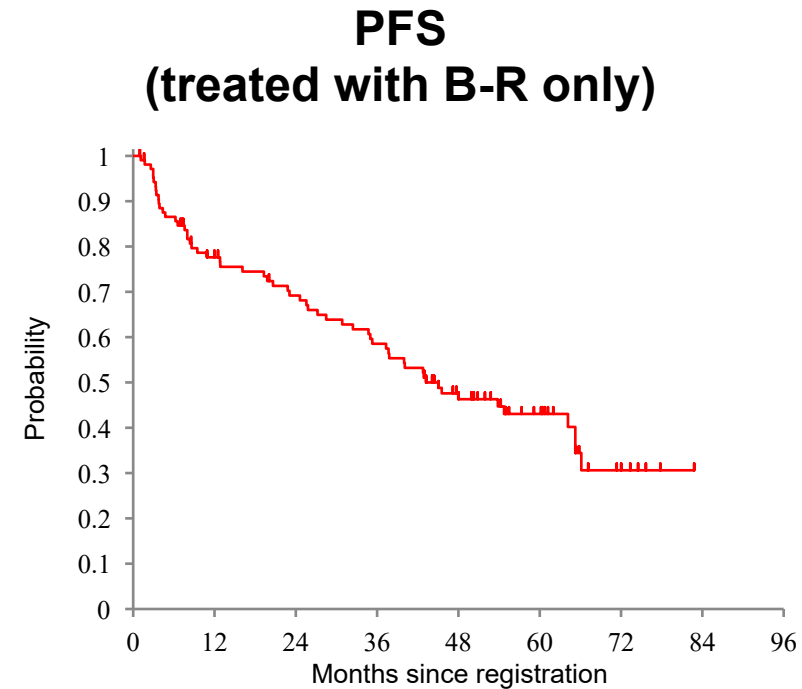
\*no maintenance therapy

\*\*pooled data from 3 trials

# BR induction in older MCL patients

- N = 106
- Median age 70
- Median PFS
  - 43.2 months

Rummel et al, ASCO 2016



# What if?

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- Your older patient has highly proliferative disease shown by Ki-67 staining?
  - BR performs consistently less well in these cases
  - Consider R-BAC regimen
  - Consider VR-CAP
- Your older patient is p53 mutated (or even 17p deleted)?
  - No data to guide us here
  - Consider BTKi (if available)
  - Consider BR – expect short remission
    - Be ready with 2<sup>nd</sup> line BTK or CART



# My patient is in CR after BR x 6. Now what?

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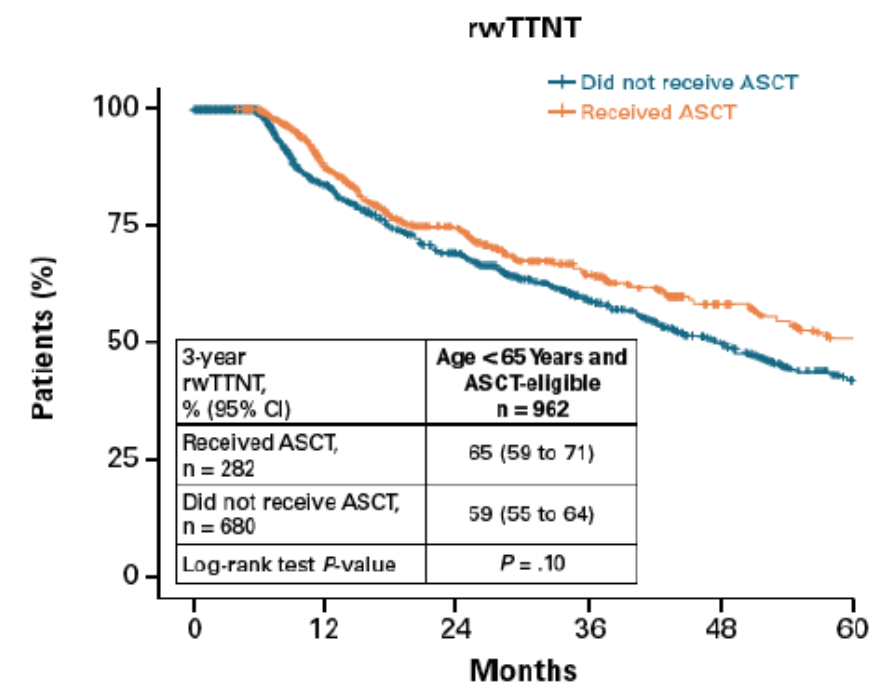
1. Observe
2. Maintenance Rituximab
3. ASCT
4. ASCT plus MR
5. BTKi
6. MR plus ibrutinib (Shine)
7. Lenalidomide plus Rituximab

# Intensive strategies for older MCL patients

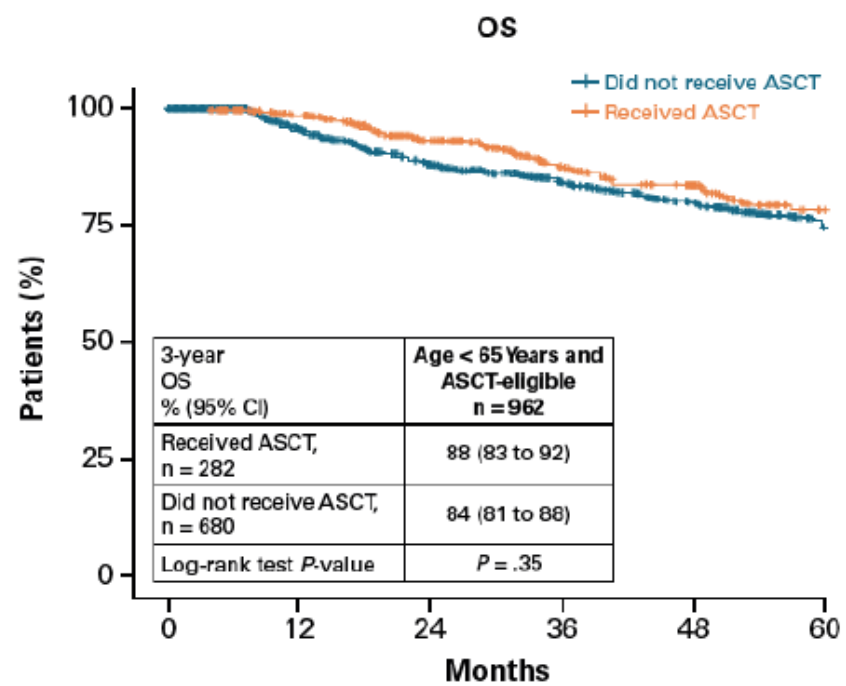
- MD Anderson experience (Fayad et al, Clin Lymph 2007)
  - Conventional R-hyperCVAD
    - $\leq 65$  mPFS 5.5 years (N = 65)
    - $> 65$  mPFS 3.0 years (N = 32)
- U Penn experience (Frosch et al, Clin Lymph 2015)
  - Median age 65 (60-75)
  - R-CHOP plus ASCT or R-hyperCVAD
    - Median PFS 3.2 years
- Not my favorite strategy for older patients

# Flatiron Database

A



Patients at risk	690	451	331	228	164	106
Did not receive ASCT	690	451	331	228	164	106
Received ASCT	282	222	160	112	81	59

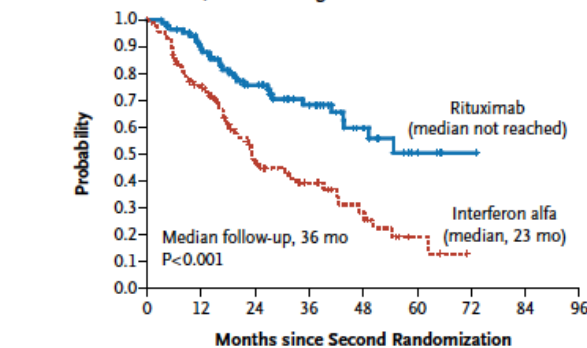


Patients at risk	690	616	418	319	251	186
Did not receive ASCT	690	616	418	319	251	186
Received ASCT	282	251	194	144	112	86

# Maintenance Rituximab

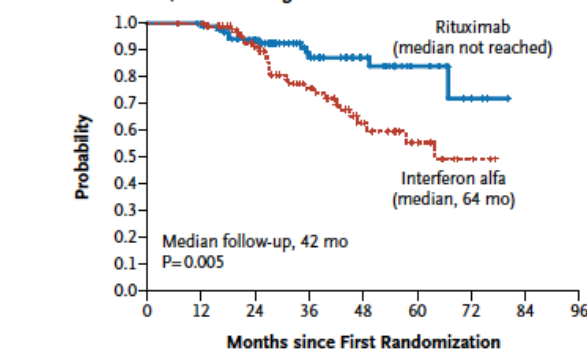
- European MCL Network Study
- N = 532. Median age 70.
- R-CHOP > FCR as induction strategy
- Responding patients randomized to interferon alfa vs. MR given indefinitely
- MR not beneficial after FCR
- What about after BR???

**B Remission Duration, Patients Assigned to R-CHOP**



No. at Risk								
Rituximab	87	72	48	32	17	4	1	0
Interferon alfa	97	63	29	18	10	3	0	0

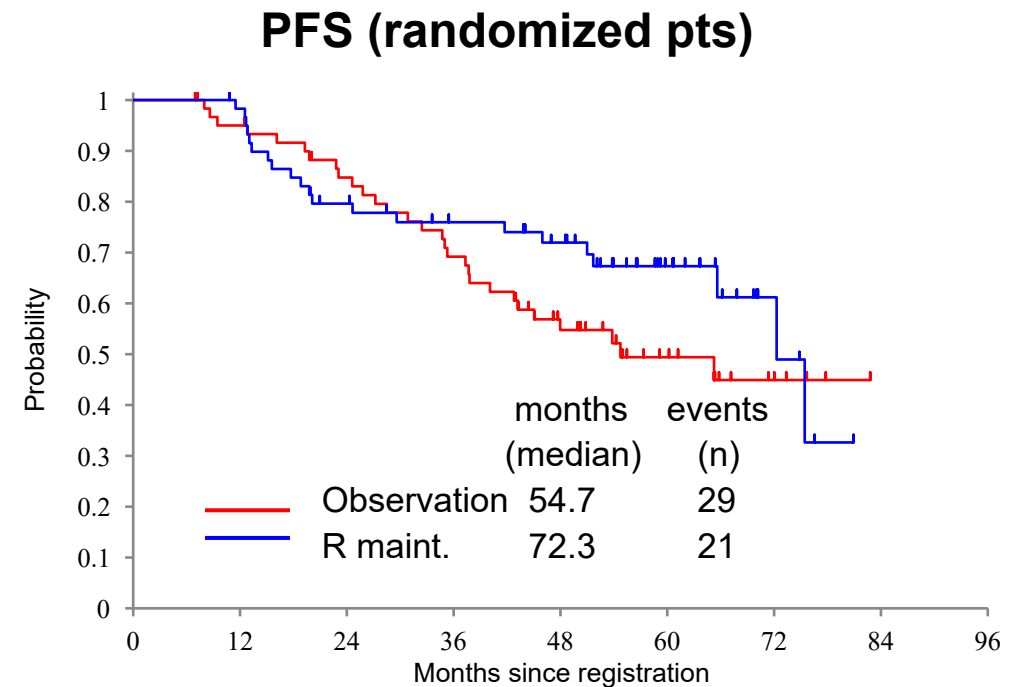
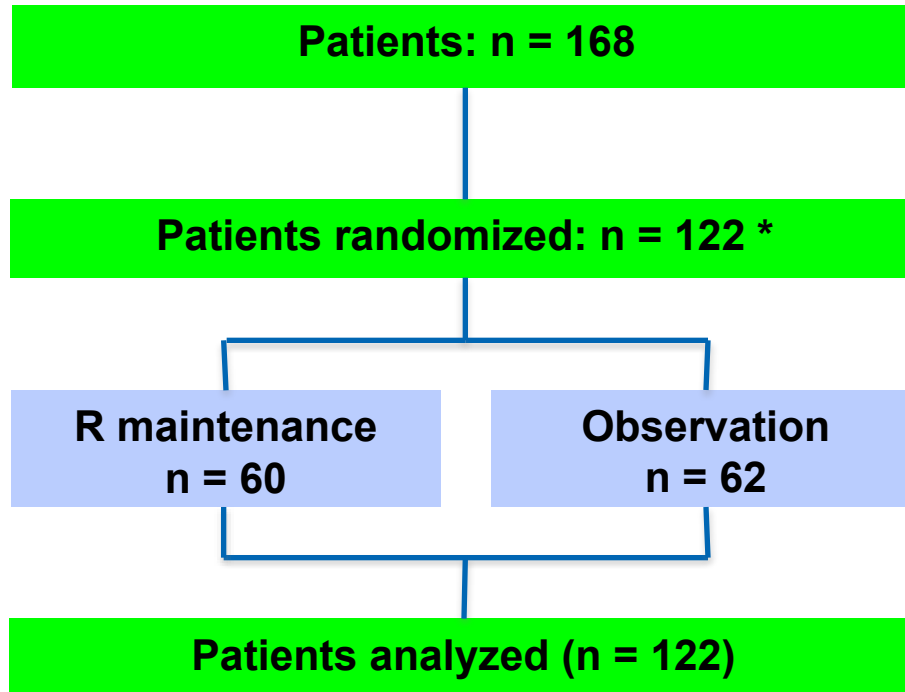
**D Overall Survival, Patients Assigned to R-CHOP**



No. at Risk								
Rituximab	87	86	71	46	30	13	3	0
Interferon alfa	97	92	65	43	22	11	3	0

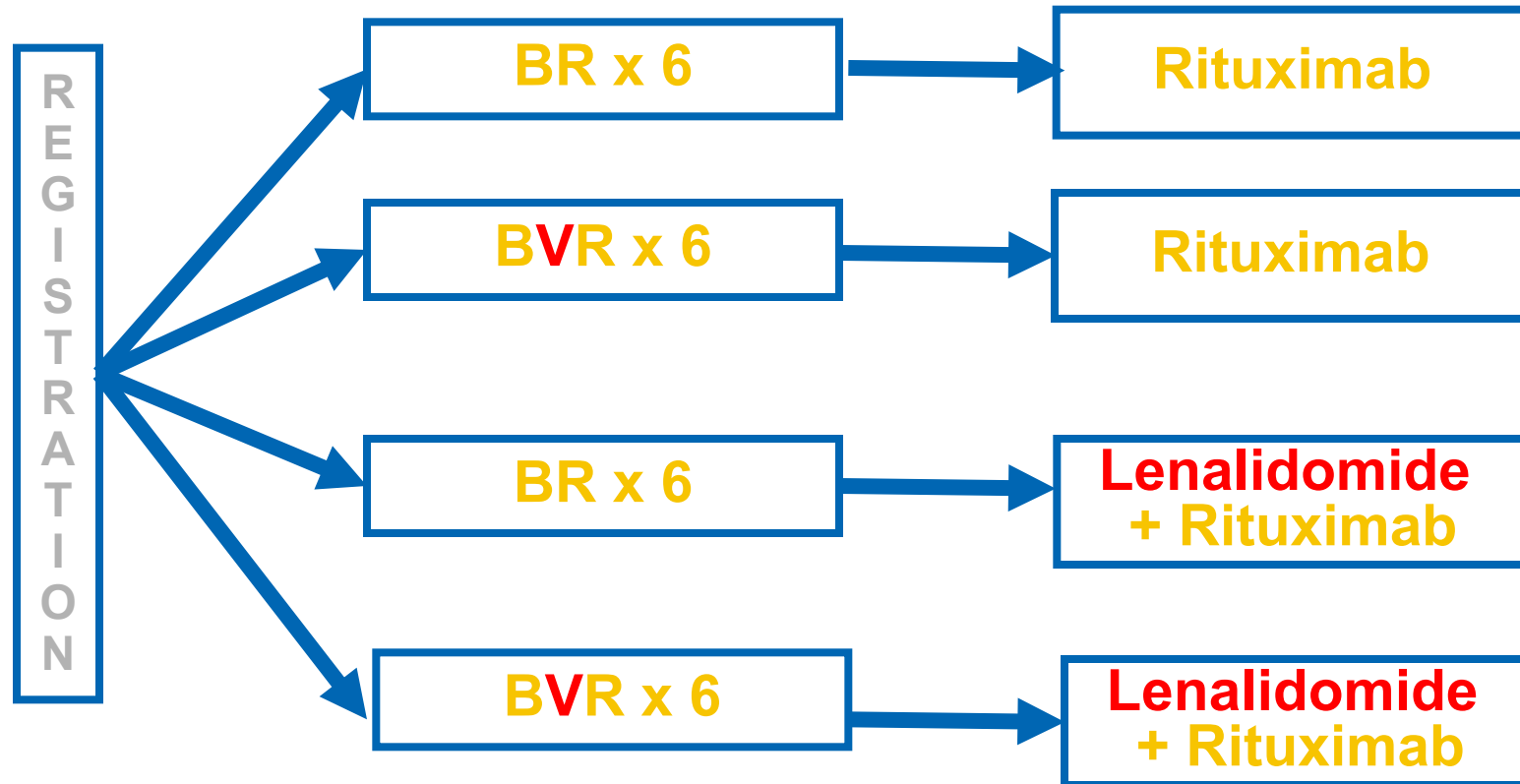


## How about MR after bendamustine-rituximab?



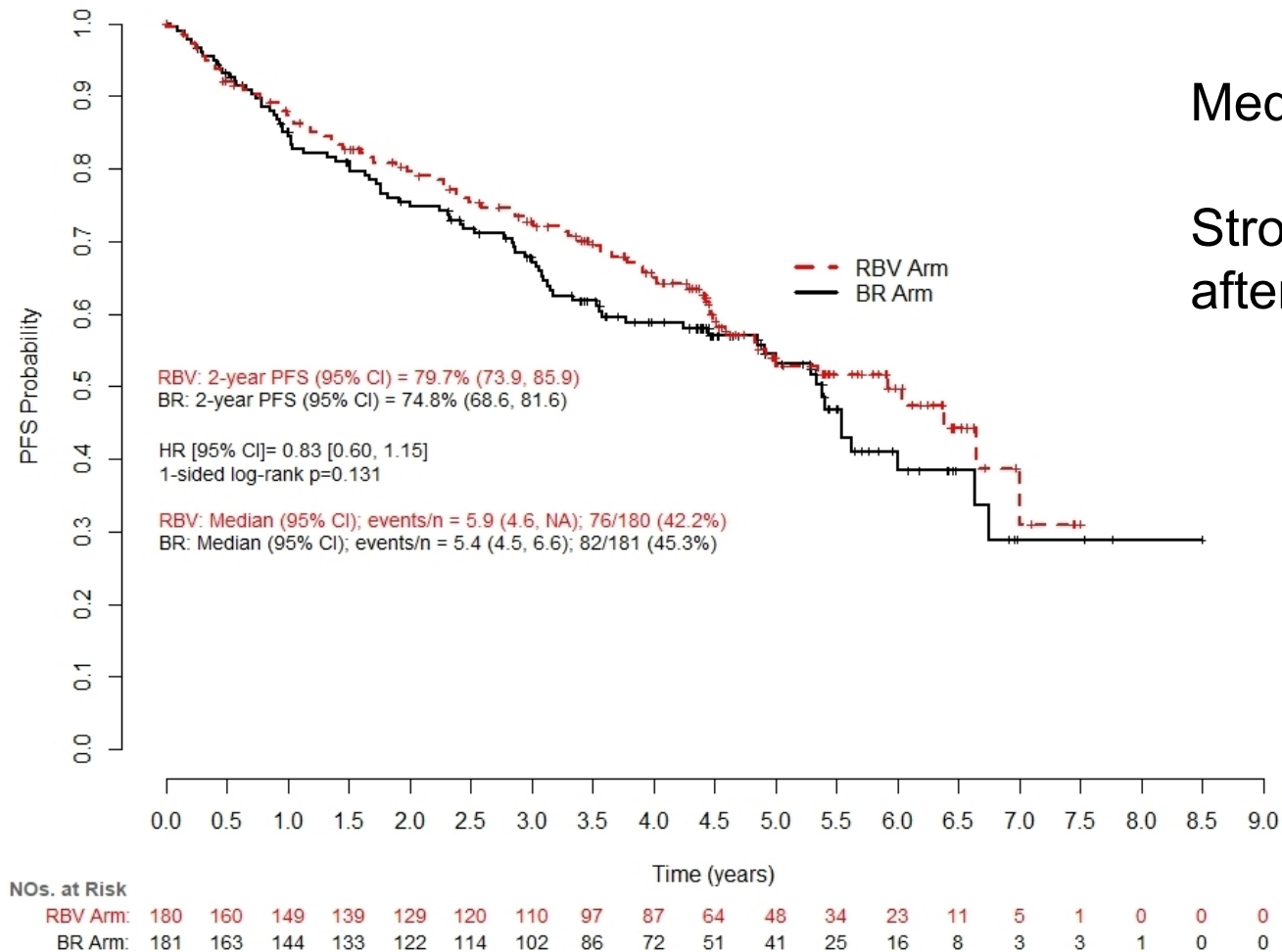
Rummel et al, ASCO 2016

## E1411: Randomized Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma



N = 372

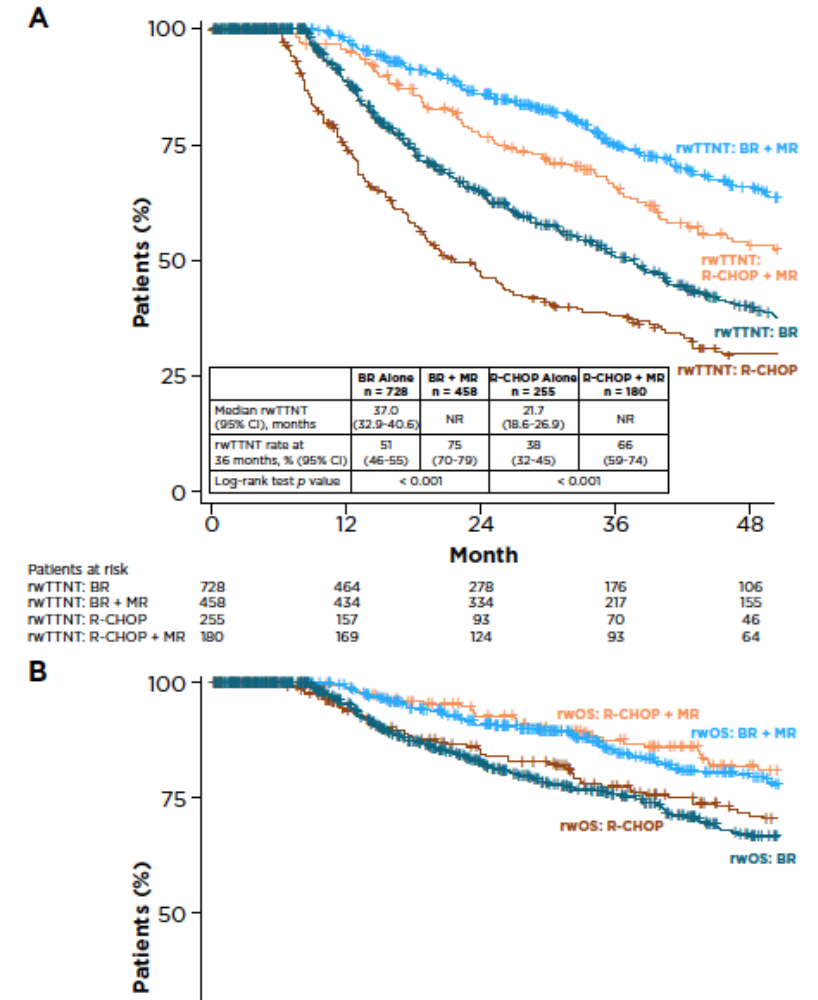
# PFS: BR vs RBV



# Flatiron Database

- “Real world” analysis of 1621 patients
- Show large benefit for MR
  - TTNT
  - OS
  - After both R-CHOP and BR
- Presented ICML 2021 (Salles et al)
- Martin et al, JCO 2022

Figure 2. Kaplan-Meier Curves for (A) rwTTNT and (B) rwOS for BR ± MR and R-CHOP ± MR in MR-Eligible Cohort



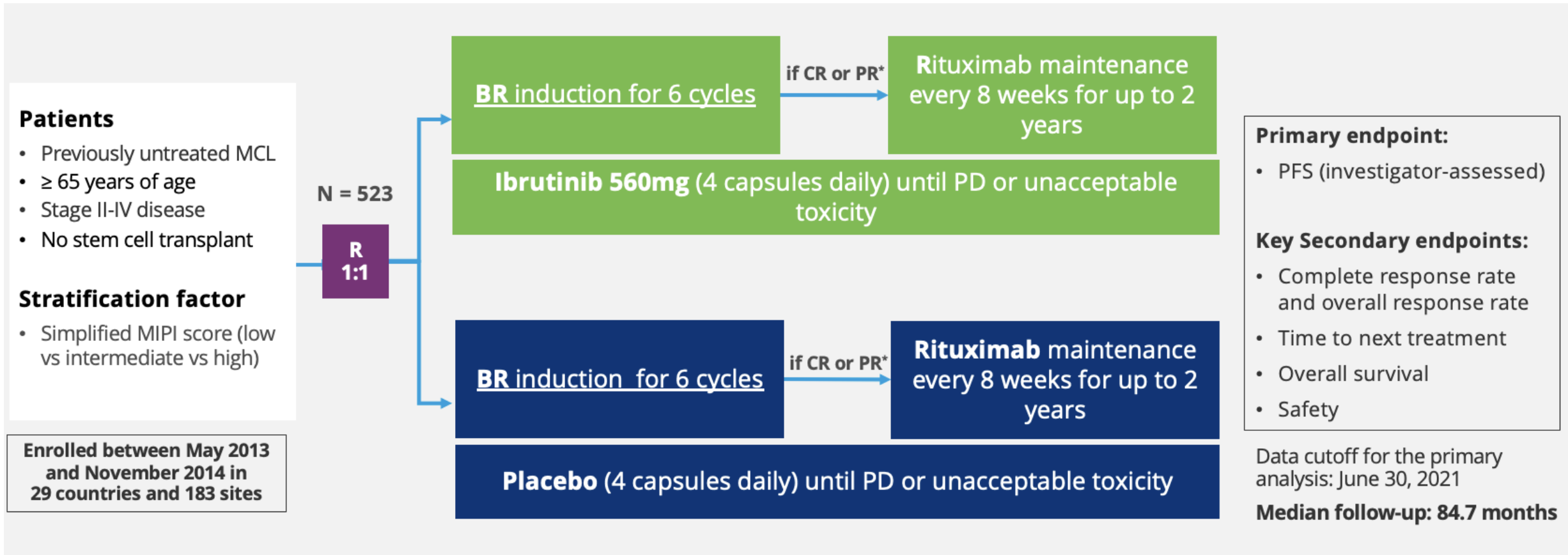


# Thoughts on Maintenance Rituximab

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- Preponderance of data suggests major benefit in MCL
- Actually impacts OS, not just PFS (as in follicular lymphoma)
- Still unclear regarding “optimal duration”
  - 2 yrs vs. 3 yrs vs. 5 yrs vs. indefinite?
- COVID 19 Pandemic has created new challenges
  - Prolonged B cell depletion leads to worse infections and inability to vaccinate
  - Anecdotally, convalescent serum, MoAb rx has been helpful in management
  - Evusheld getting heavy use in our clinics

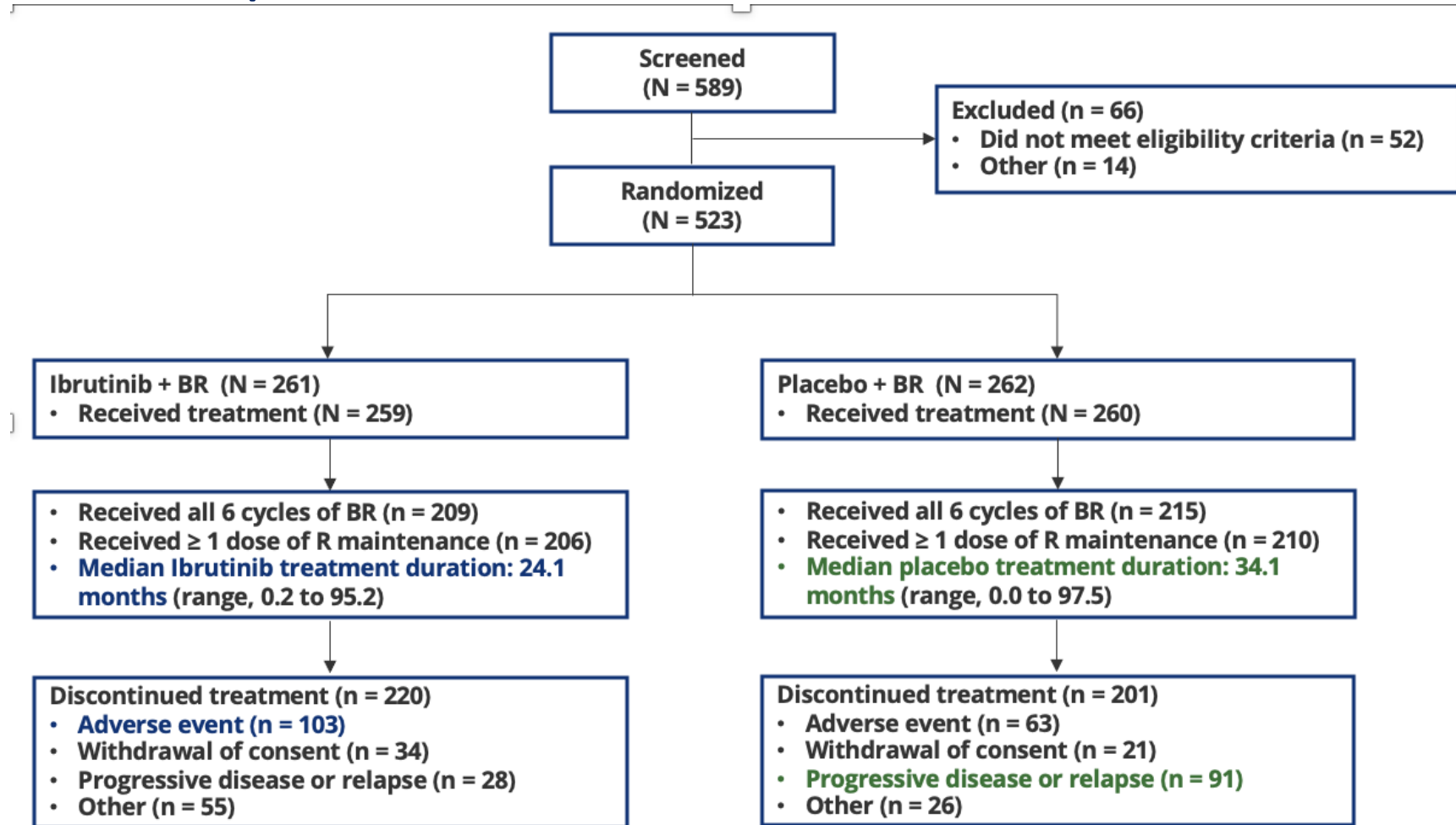
# Primary Results From the Double-Blind, Placebo-Controlled, Phase III SHINE Study of Ibrutinib in Combination With Bendamustine-Rituximab and Rituximab Maintenance as a First-Line Treatment for Older Patients With Mantle Cell Lymphoma



# Patient disposition

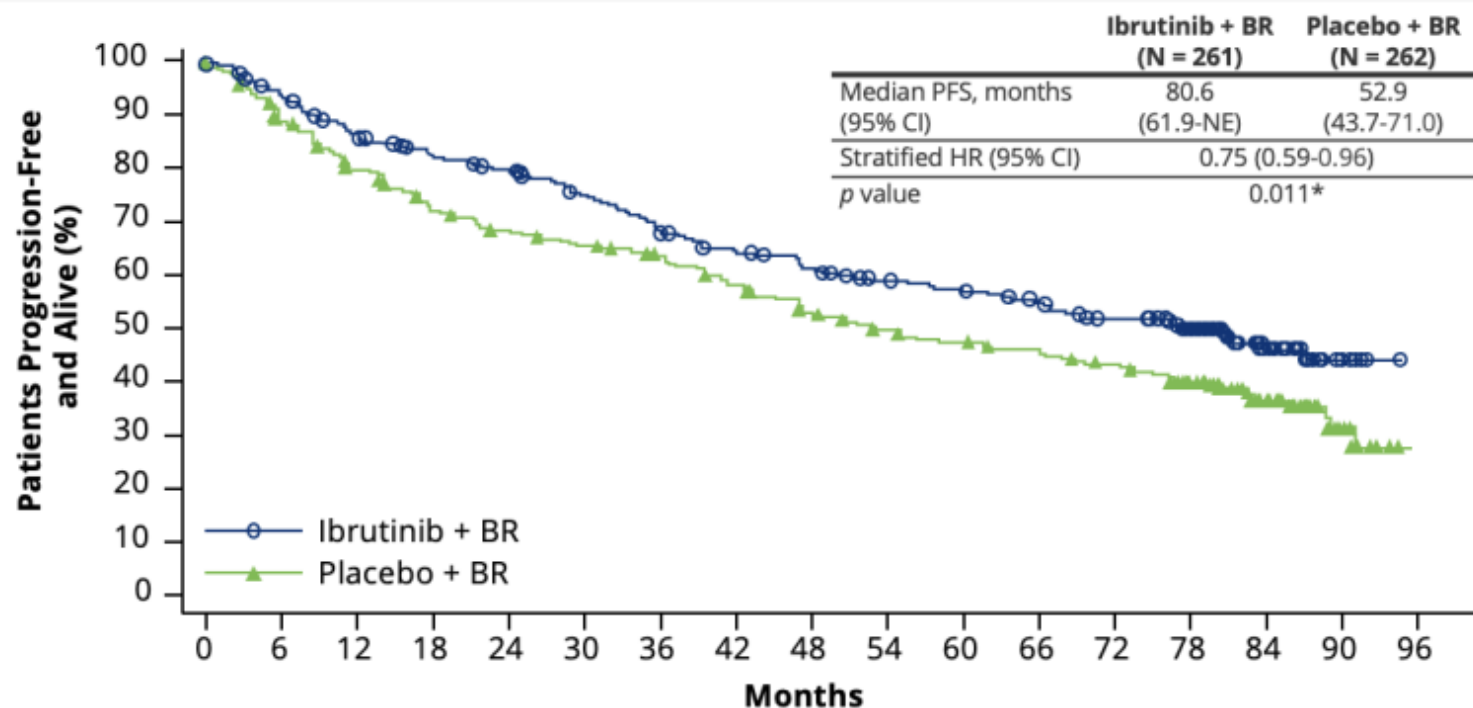
		Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median age (range) — years		71 (65–86)	71 (65–87)
Age, ≥ 75 years — no. (%)		74 (28.4)	82 (31.3)
Sex, male — no. (%)		178 (68.2)	186 (71.0)
ECOG PS 1 or 2 — no. (%)		127 (48.7)	121 (46.2)
Simplified MIPI score — no. (%)	Low risk	44 (16.9)	46 (17.6)
	Intermediate risk	124 (47.5)	129 (49.2)
	High risk	93 (35.6)	87 (33.2)
Bone marrow involvement at study entry — no. (%)		198 (75.9)	200 (76.3)
Blastoid/pleomorphic histology — no. (%)		19 (7.3)	26 (9.9)
Extranodal disease — no. (%)		234 (89.7)	226 (86.3)
Bulky disease (≥ 5 cm) — no. (%)		95 (36.4)	98 (37.4)
TP53 mutated — no. (%)		26 (10.0)	24 (9.2)
TP53 mutation status unknown — no. (%)		121 (46.4)	133 (50.8)

# Patient disposition





# PFS

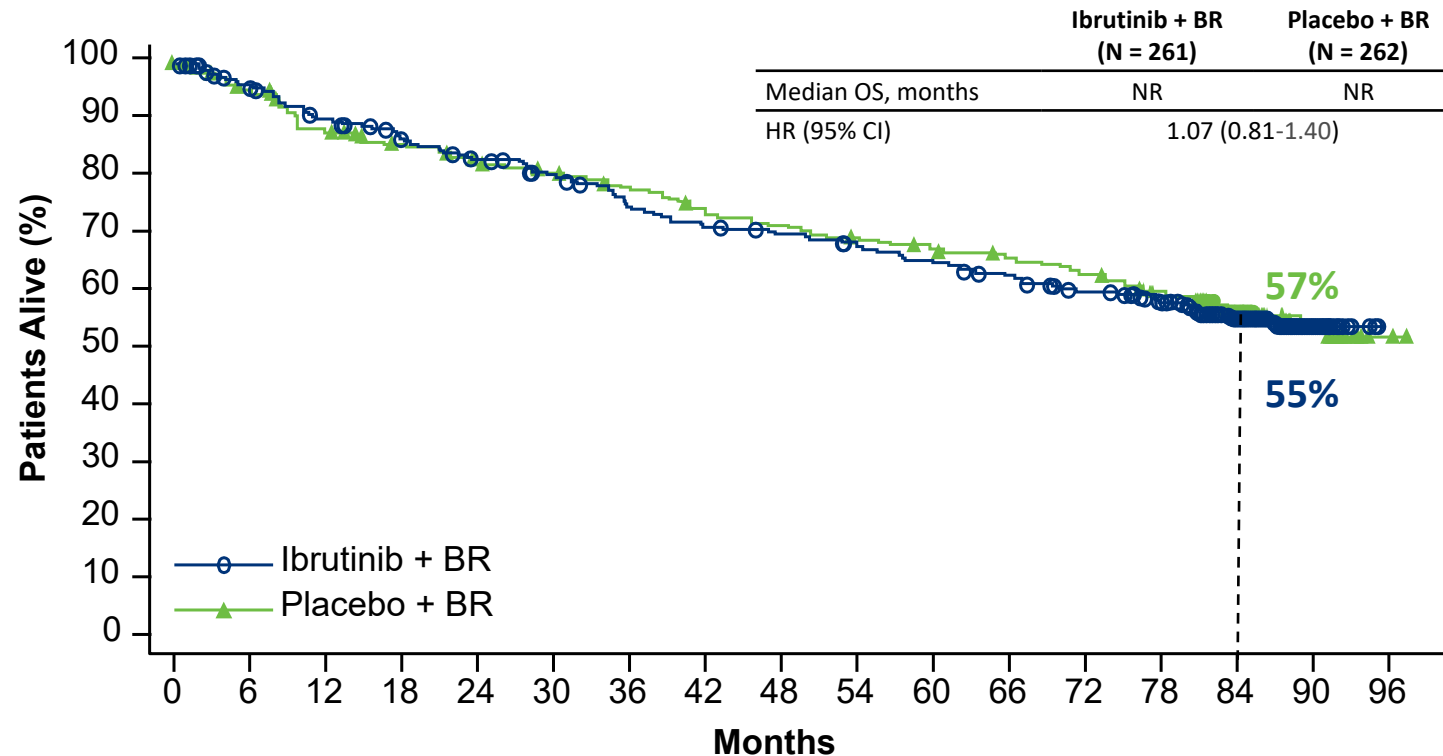


- Ibrutinib combined with BR and R maintenance demonstrated a **25% reduction in the relative risk of disease progression or death** versus BR and R maintenance
- Significant improvement in median PFS:** 80.6 month (6.7 years) versus 52.9 months (4.4 years) ( $\Delta=2.3$  years)

## 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

# Overall Survival Similar in Both Arms



Cause of death	Ibrutinib+BR (N=261)	Placebo+BR (N=262)
Death due to PD	30 (11.5%)	54 (20.6%)
Death due to TEAEs*	28 (10.7%)	16 (6.1%)
Death during post-treatment follow-up period excluding PD	46 (17.6%)	37 (14.1%)
<b>Total deaths</b>	<b>104 (39.8%)</b>	<b>107 (40.8%)</b>

\*The most common Grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 vs 5 patients. Grade 5 TEAE of cardiac disorders in 3 vs 5 patients, respectively.

## 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	137	90	31	2

# SHINE: Kahl Conclusions

- Not a black and white outcome (very gray to me)
- Pro's for adding ibrutinib
  - No question adding ibrutinib improves PFS
  - Significant improvement in median PFS
  - Patients less likely to die from MCL
- Con's for adding ibrutinib
  - 5 yr PFS improves from 50 to 60% (modest)
  - Cost about \$150k/year for this benefit
  - Patients more likely to die of toxicity so no OS benefit
  - Patient will not have BTKi available for 2<sup>nd</sup> line therapy
- I will discuss with patients but do not see myself recommending it

# MCL Treatment: The Horizon for Older MCL

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1. SHINE trial: BR  $\pm$  ibrutinib until PD
2. ECHO: BR  $\pm$  acalabrutinib until PD
3. E1411: BR  $\pm$  bortezomib. R maintenance  $\pm$  lenalidomide
4. MANGROVE: Zanubrutinib-R vs. BR (phase 3)





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