Mantle Cell Lymphoma - What did we learn in 2022?

Brad Kahl, MD

Professor of Medicine

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Reasonable Standards of Care in 2022

FRONTLINE MANAGEMENT

- Younger/Fit
  - High dose cytarabine containing induction
  - ASCT in 1st remission
  - Maintenance Rituximab for 3 years
- Older/Less Fit
  - Bendamustine-Rituximab (BR) Induction
  - ± Maintenance Rituximab

RELAPSED/REFRACTORY

- BTK inhibitors
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
- Lenalidomide-Rituximab (R2)
- Brexucabtagene Autoleucel (brexu-cel)

New in 2022 (Frontline Management)

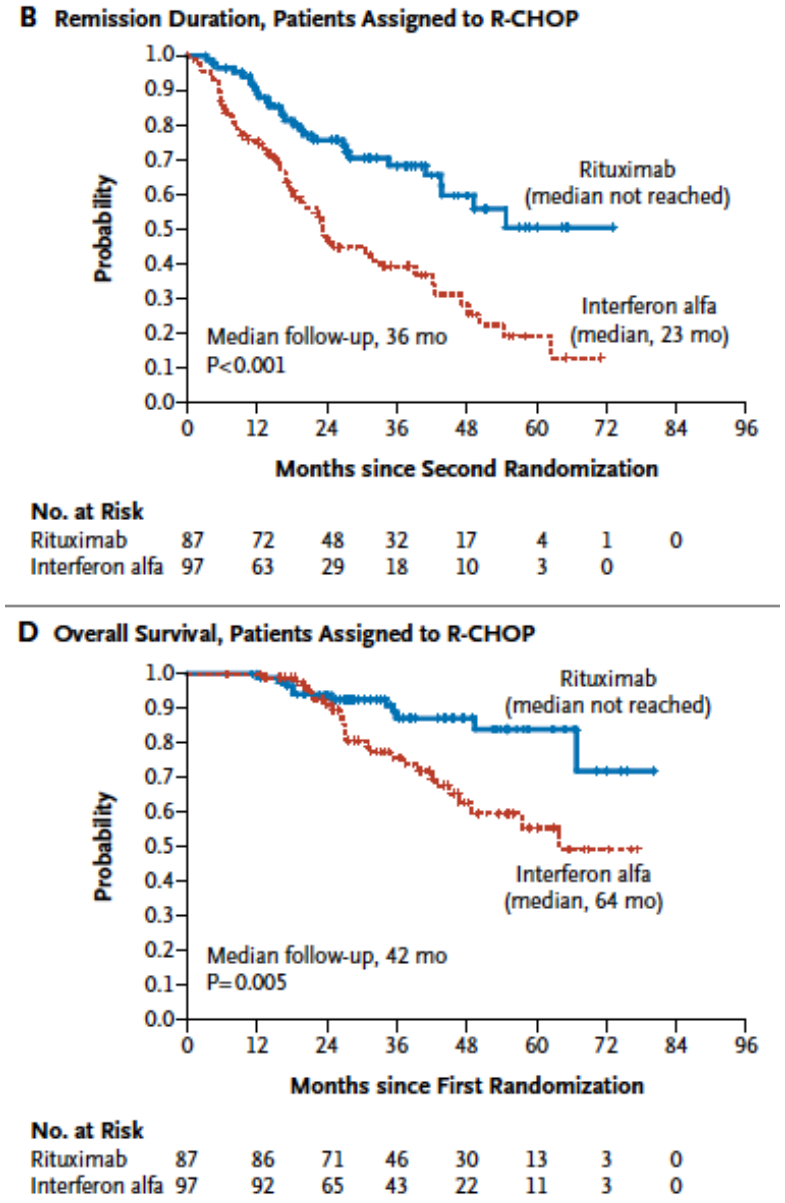
1. Solid evidence supporting MR after BR
   - Flatiron Database analysis (Martin et al, JCO 2022)

2. Data for BR plus BTKi in Older MCL
   - SHINE Trial (Wang et al, ASCO 2022, NEJM 2022)

3. Data for BTKi added to intensive therapy in Younger MCL
   - TRIANGLE TRIAL (Dreyling et al, ASH 2022)

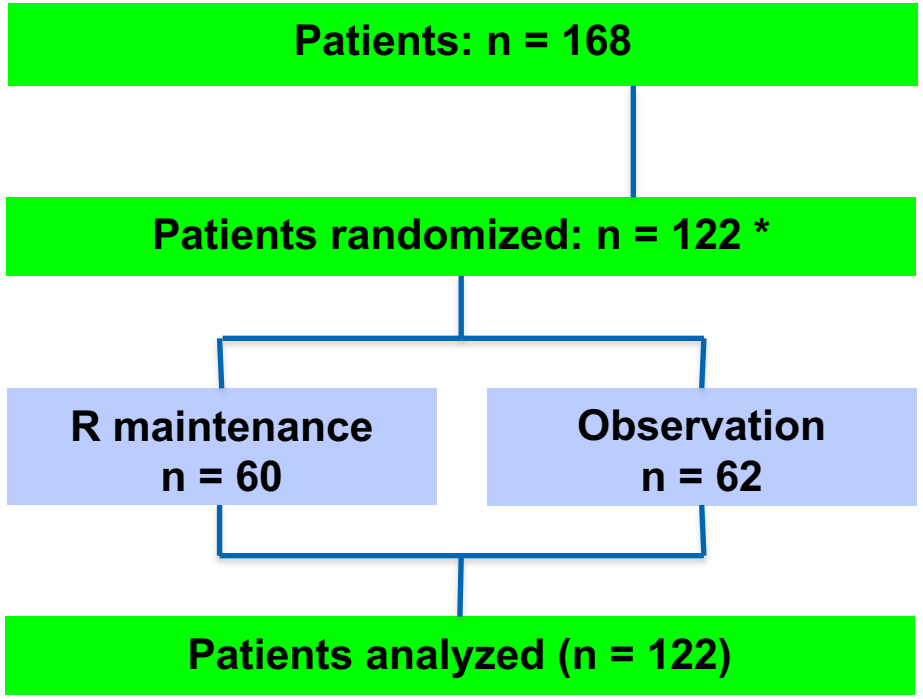
Maintenance Rituximab

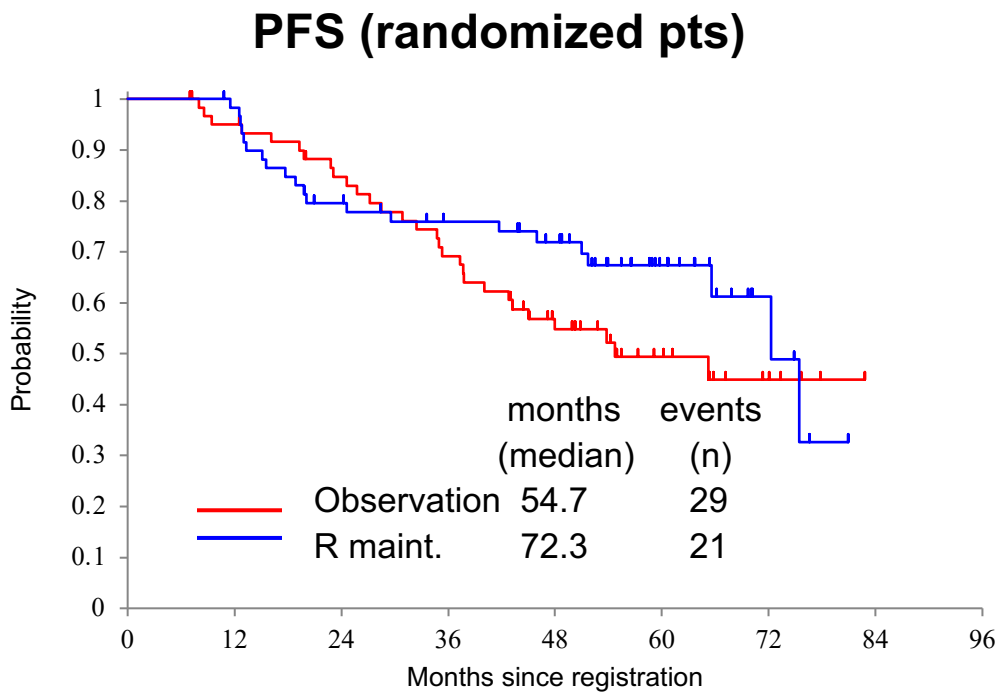
- European MCL Network Study
- N = 532. Median age 70.
- R-CHOP > FCR as induction strategy
- Responding patients randomized to interferon alfa vs. MR given indefinitely
- MR not beneficial after FCR
- What about after BR???



Kluin-Nelemans et al, NEJM, 2012

How about MR after bendamustine-rituximab?



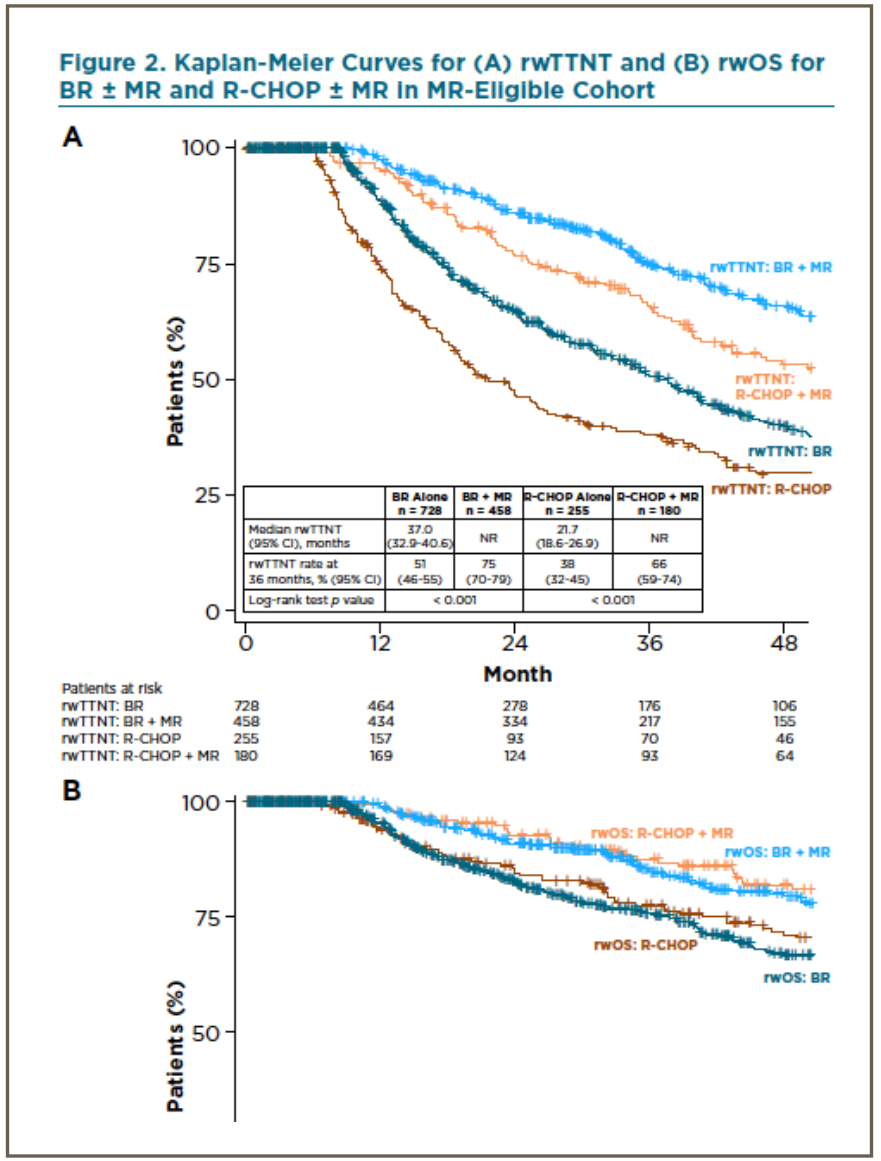


Rummel et al, ASCO 2016

Flatiron Database

- “Real world” analysis of 1621 patients
- Show large benefit for MR
  - TTNT
  - OS
  - After both R-CHOP and BR

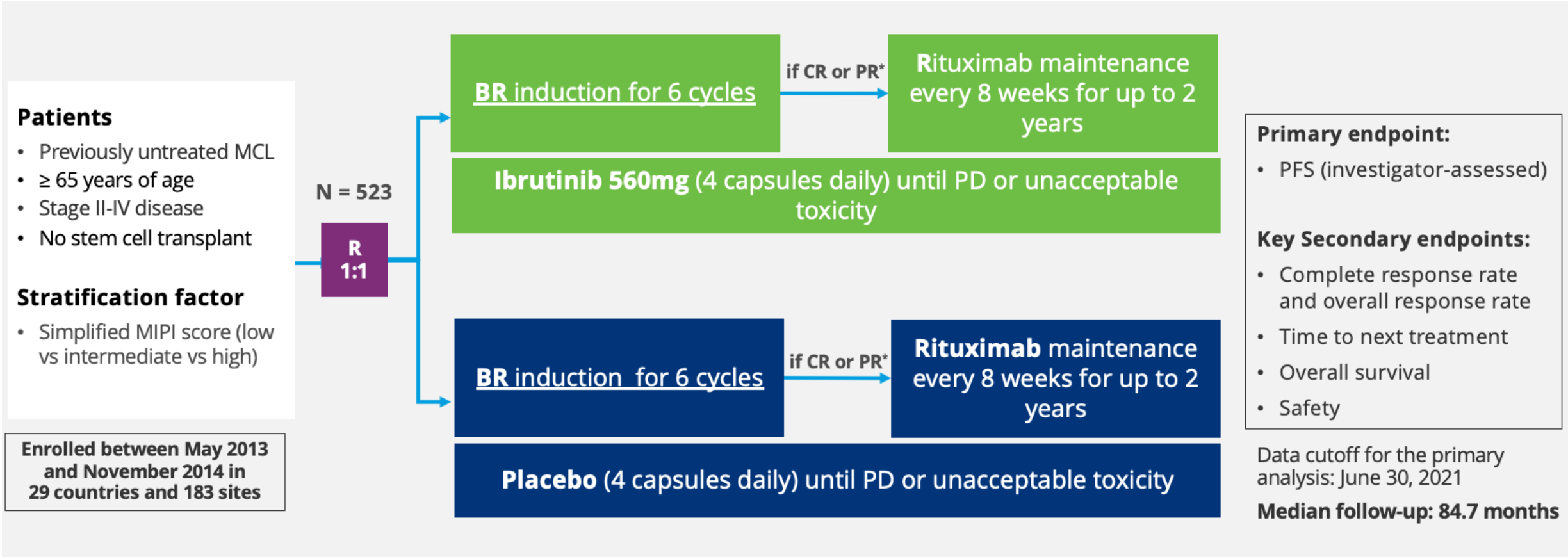
Martin et al, JCO 2022



Thoughts on Maintenance Rituximab

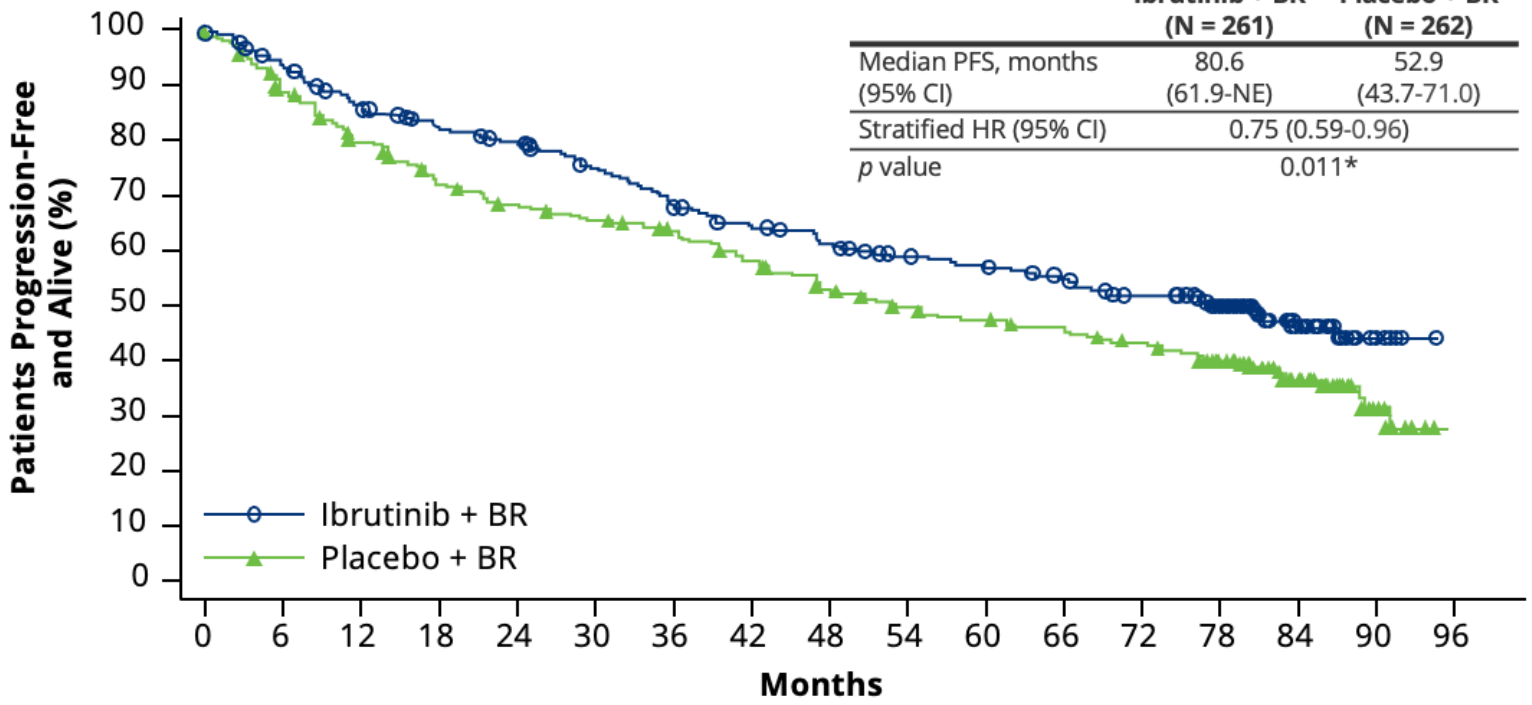
- Preponderance of data suggests major benefit in MCL
- Actually impacts OS, not just PFS (as in follicular lymphoma)
- Still unclear regarding “optimal duration”
  - 2 yrs vs. 3 yrs vs. 5 yrs vs. indefinite?
- COVID 19 Pandemic has created new challenges
  - Prolonged B cell depletion leads to worse infections and inability to vaccinate

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



Wang et al, NEJM 2022

Progression Free Survival



	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*	

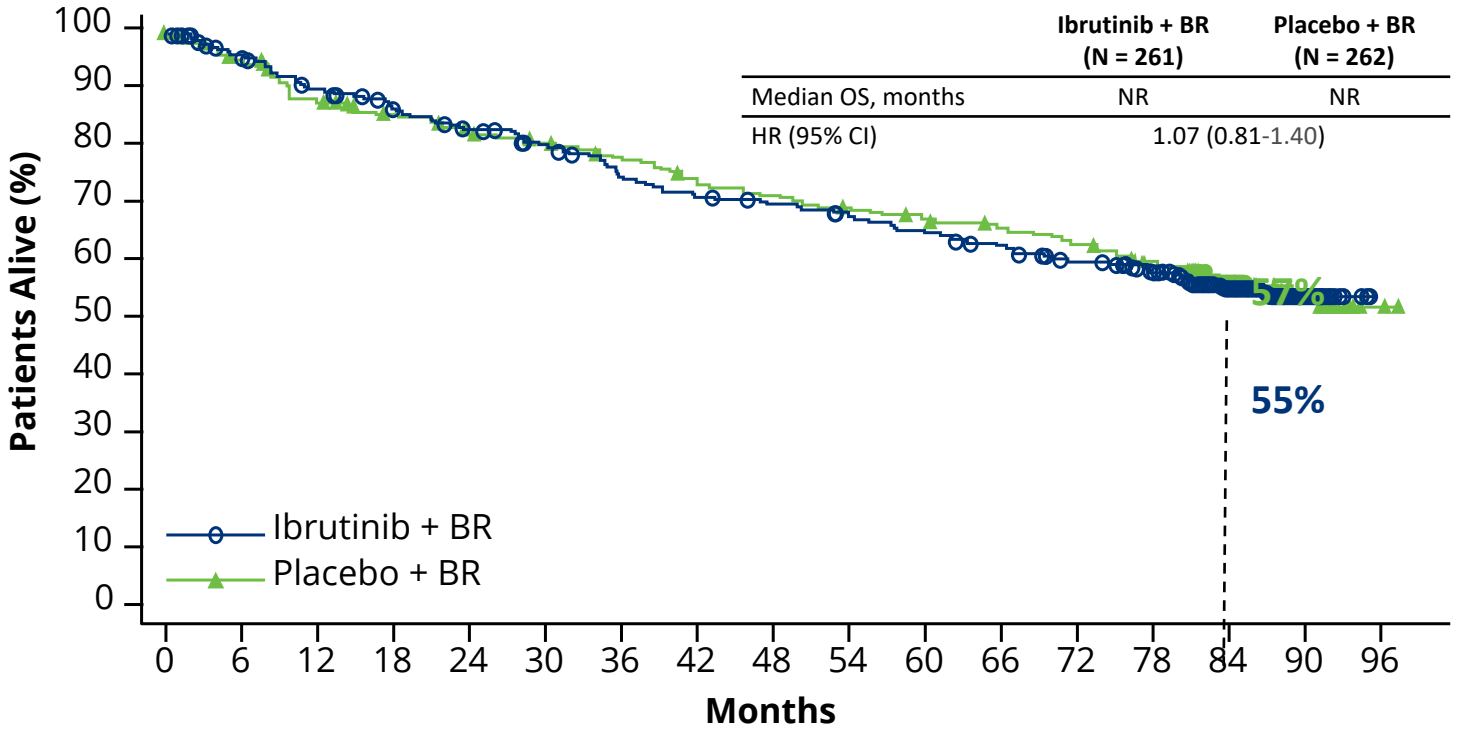
Patients at Risk

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 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) **(Δ=2.3 years)**

Wang et al, ASCO 2022

Overall Survival Similar in Both Arms



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

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%)
Total deaths	**104 (39.8%)**	**107 (40.8%)**

*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.

Wang et al, ASCO 2022

NR, not reached.

SHINE: My thoughts

- 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 2nd line therapy

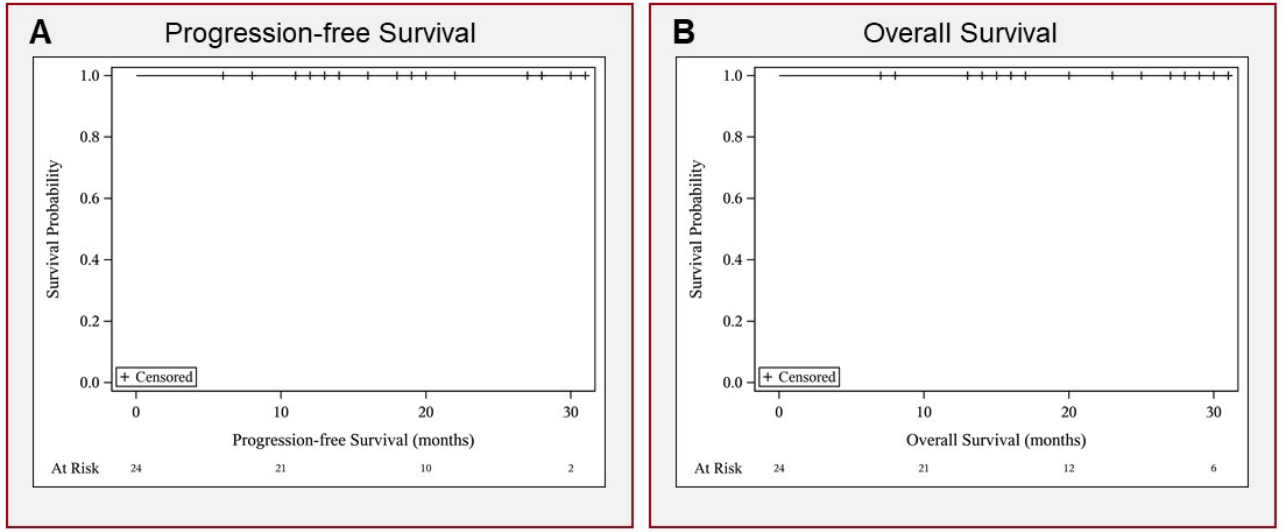
- I will discuss with patients but do not see myself recommending it

MCL Treatment: The Horizon for Older MCL

1. SHINE trial: BR ± ibrutinib until PD
2. ECHO: BR ± acalabrutinib until PD
3. E1411: BR ± bortezomib. R maintenance ± lenalidomide
4. MANGROVE: Zanubrutinib-R vs. BR
5. ENRICH: Ibrutinib-R vs. BR/R-CHOP

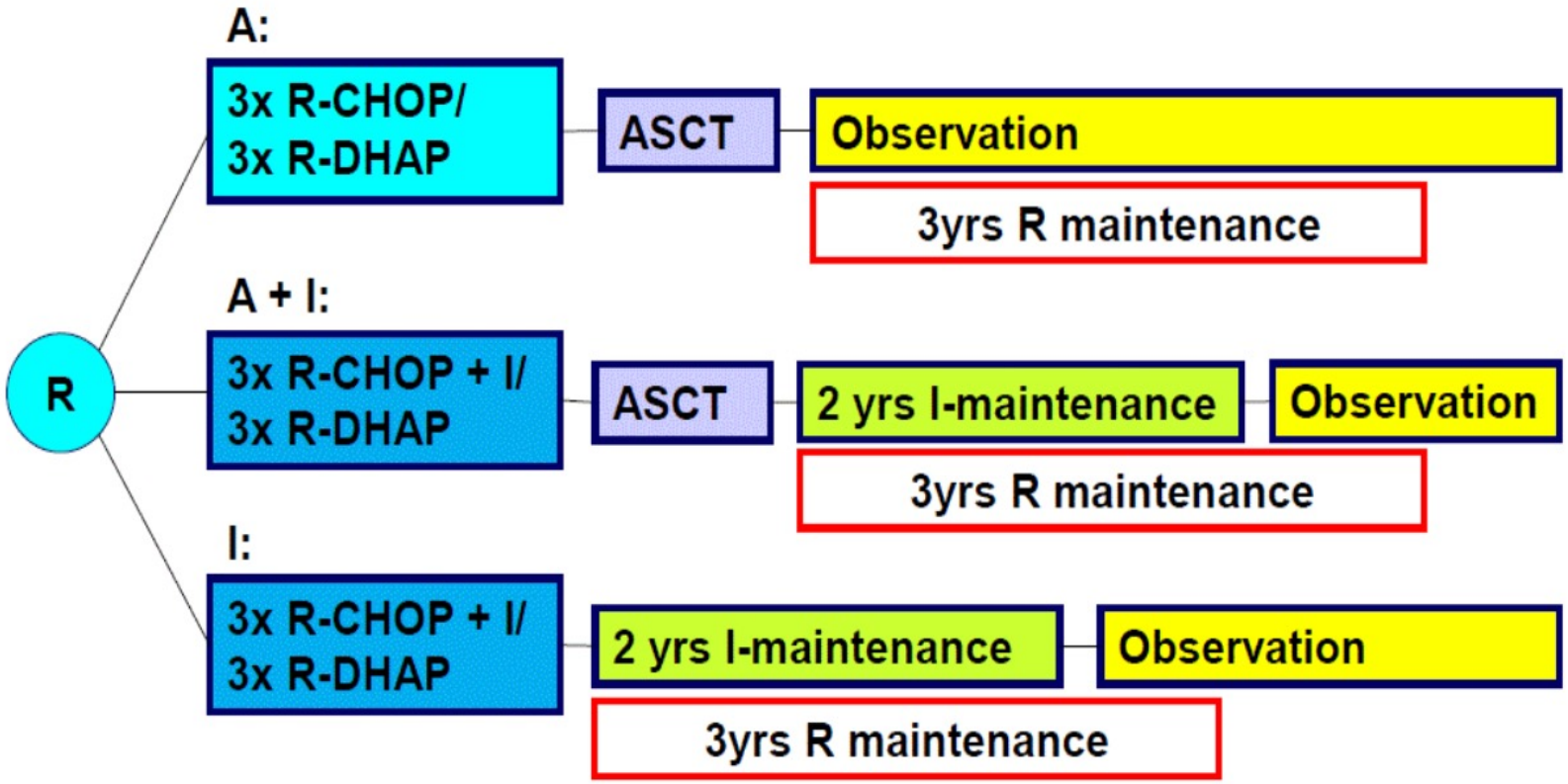
R2 plus Acalabrutinib for Untreated MCL. Ruan et al. #73

- N = 24. Median age 64.
- MIPI low/int/high = 37/42/21%
- P53 mutations in 7 patients
- <u>RESULTS</u>
  - ORR 100%. CR 90%.
  - MRD negative at 12 months in 71%
  - No unexpected toxicities
  - Rash 42%

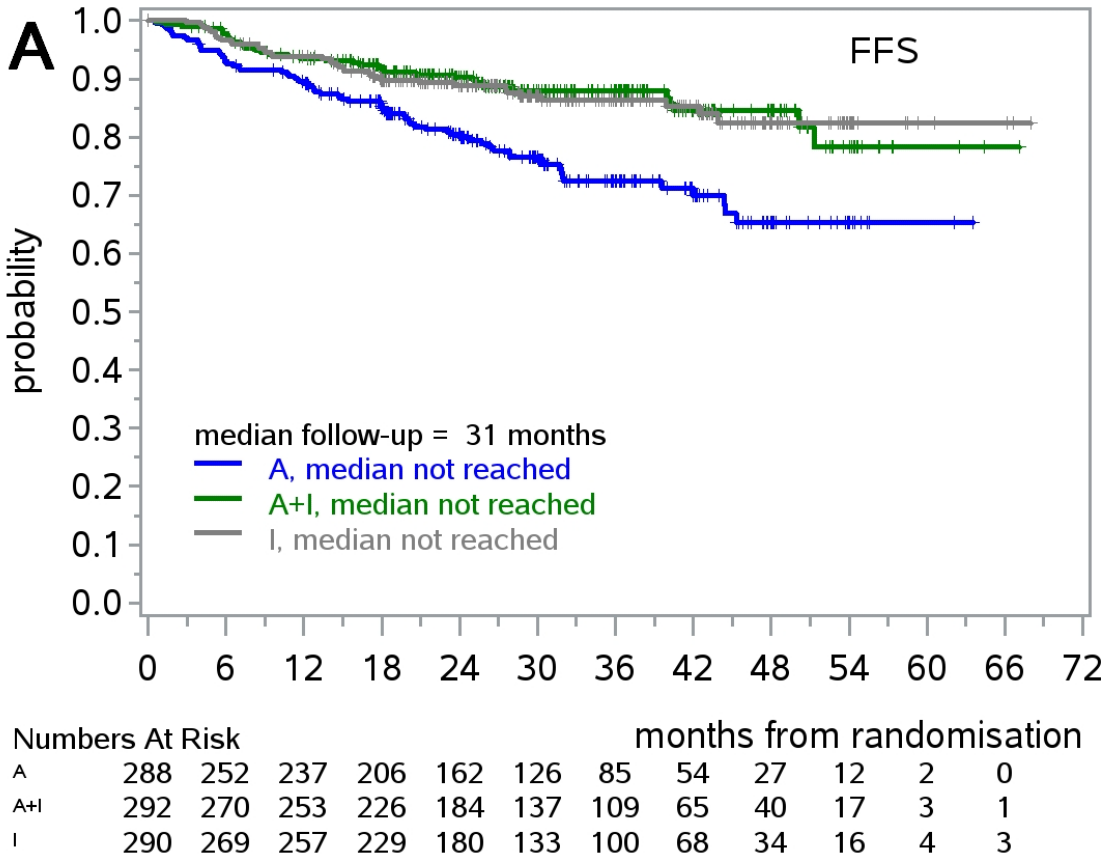


TRIANGLE Trial (European MCL Network)

- Target 870 pts (290 per arm)
- Activated Oct 2017
- Completed accrual Dec 2020
- 1st results ASH 2022

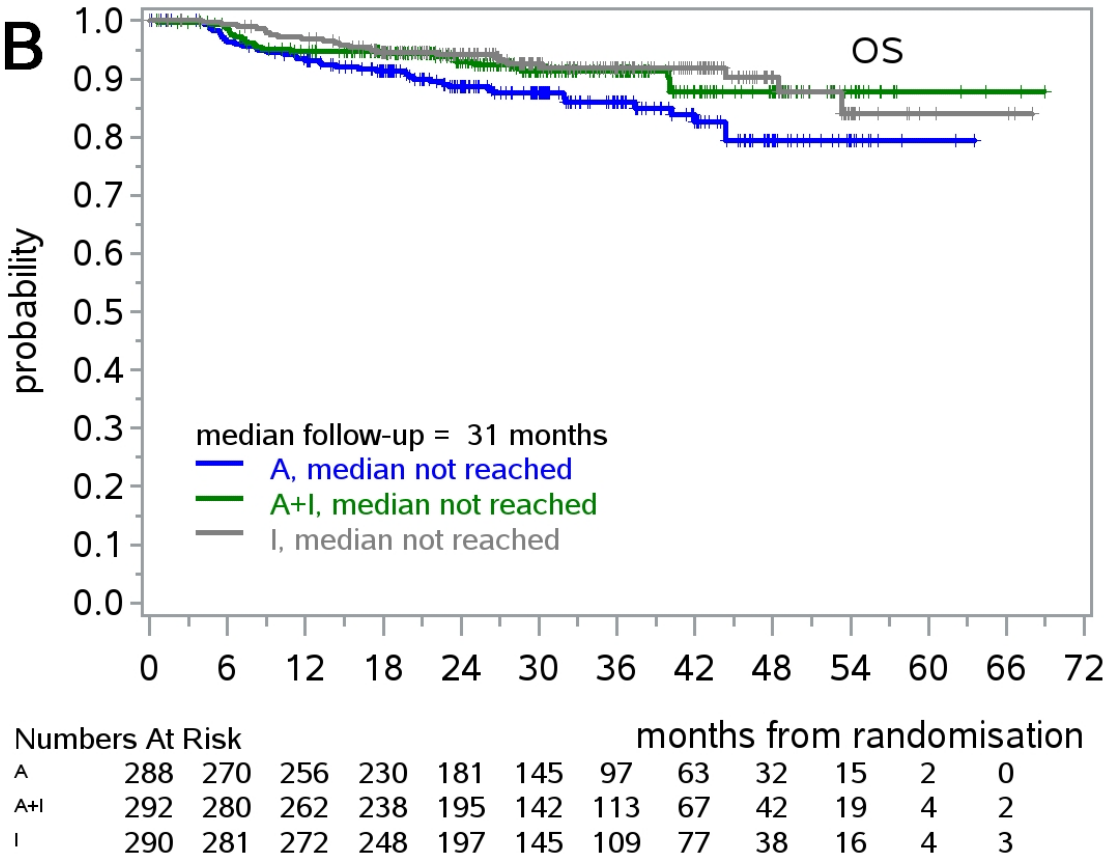


TRIANGLE Trial, Dreyling et al, Abstract #1



Numbers At Risk

A	288	252	237	206	162	126	85	54	27	12	2	0
A+I	292	270	253	226	184	137	109	65	40	17	3	1
I	290	269	257	229	180	133	100	68	34	16	4	3



Numbers At Risk

A	288	270	256	230	181	145	97	63	32	15	2	0
A+I	292	280	262	238	195	142	113	67	42	19	4	2
I	290	281	272	248	197	145	109	77	38	16	4	3

TRIANGLE TRIAL Details and Potential Impact

Toxicity

- Ibrutinib did not increase R-CHOP/R-DHAP toxicity
- Ibrutinib did increase serious infection risk after ASCT
  - A+I more toxic than A or I alone

Conclusions

- Arm C (ibrutinib and no ASCT) appears to be the winner
  - Best combination of efficacy and toxicity
- Addition of ibrutinib during induction and for 2 years as maintenance allows for the subtraction of ASCT in 1st remission

Three FDA-approved BTK inhibitors in R/R MCL

	Ibrutinib	Acalabrutinib	Zanubrutinib
Approval Date	November 13, 2013	October 31, 2017	November 14, 2019
Dose	560 mg QD	100 mg BID	160 mg BID or 320 QD
Trial Size	N = 111	N = 124	N = 86
ORR	68%	89%	84%
CR	21%	48%	78%
mDOR	~18 months	~28 months	~36 months

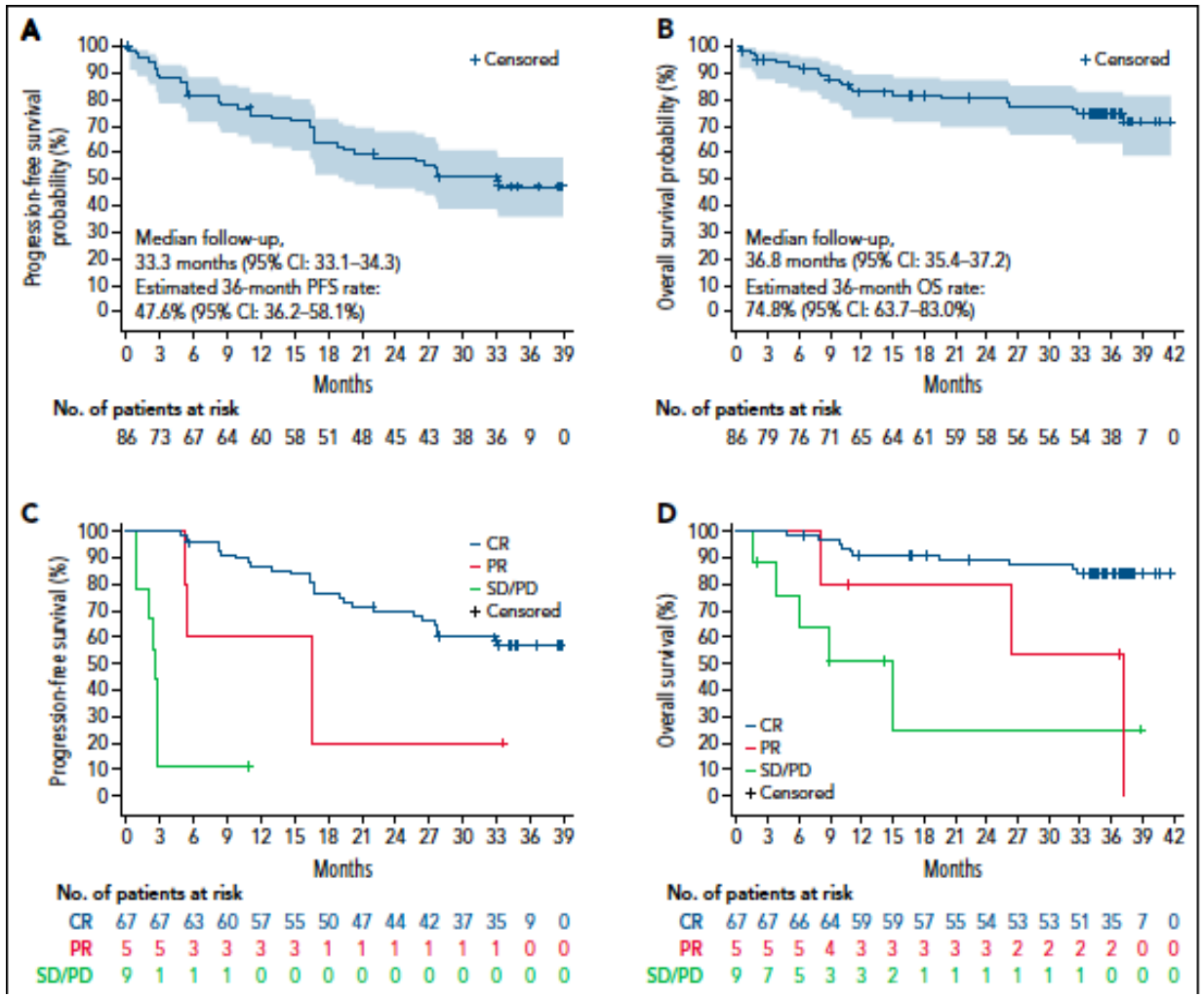
CLINICAL TRIALS AND OBSERVATIONS

Zanubrutinib in relapsed/refractory mantle cell lymphoma: long-term efficacy and safety results from a phase 2 study

Yuqin Song,[1] Keshu Zhou,[2] Dehui Zou,[3] Jianfeng Zhou,[4] Jianda Hu,[5] Haiyan Yang,[6] Huilai Zhang,[7] Jie Ji,[8] Wei Xu,[9] Jie Jin,[10] Fangfang Lv,[11] Ru Feng,[12] Sujun Gao,[13] Haiyi Guo,[14] Lei Zhou,[15] Jane Huang,[16] William Novotny,[16] Pil Kim,[16] Yiling Yu,[14] Binghao Wu,[14] and Jun Zhu[1]

Table 1. Summary of investigator-assessed efficacy

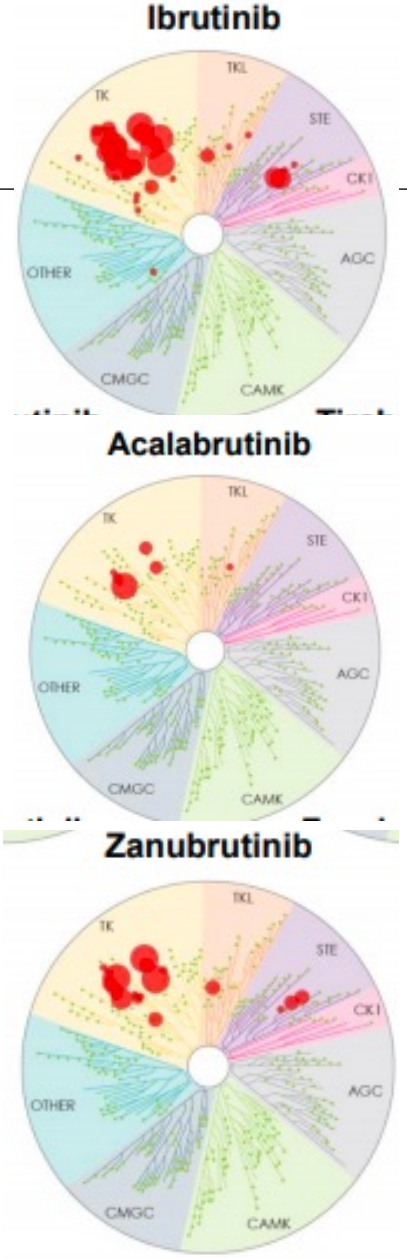
Efficacy variable	n = 86
ORR (CR + PR), % (95% CI)*	83.7 (74.2-90.8)
Best response, n (%)	
CR	67 (77.9)
PR	5 (5.8)
SD	1 (1.2)
PD	8 (9.3)
Discontinued before first assessment	5 (5.8)
Time to response (mo)	
Median (range)	2.7 (2.5-3.0)
Time to CR (mo)	
Median (range)	2.8 (2.5-16.7)
Response duration (mo)	
Median† (range)	NE (2.3-36.2+)
95% CI	(24.9-NE)
Event-free rates‡ at 30 mo (%)	57.3
95% CI	(44.9-67.9)



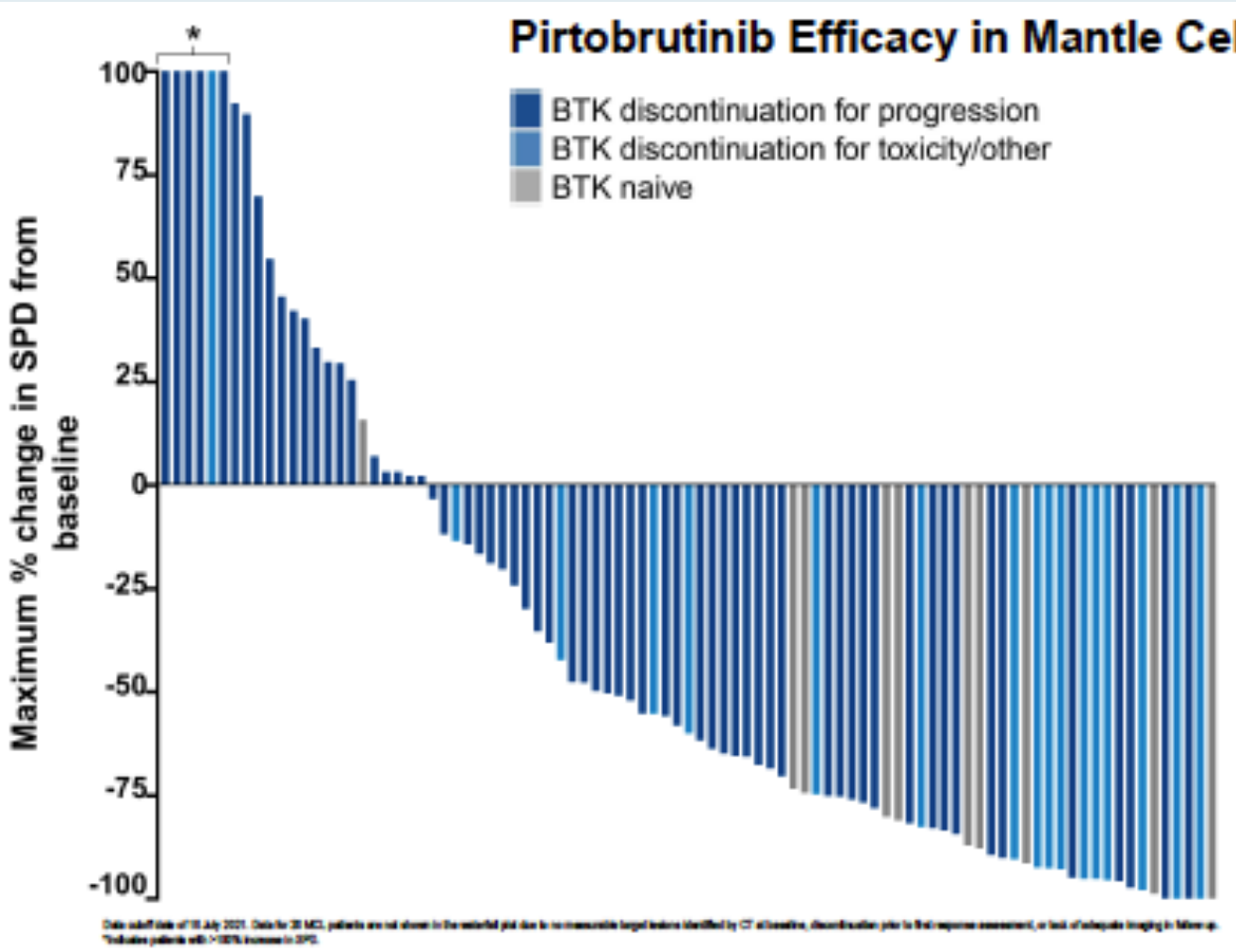
Blood, May 2022

BTKi Comparisons

- Acalabrutinib and Zanubrutinib better tolerated than Ibrutinib in CLL and WM
  - ELEVATE R/R trial
  - ALPINE Trial
  - ASPEN Trial
- Zanubrutinib more active than ibrutinib in CLL
  - ALPINE Trial
- Zanubrutinib vs. Acalabrutinib never done
  - Cross trial comparisons suggest similar efficacy and tolerability
- I prefer zanubrutinib/acalabrutinib over ibrutinib for MCL



BRUIN: Updated Results with Pirtobrutinib for MCL



BTK Pre-Treated MCL Patients[a]	n=100
Overall Response Rate[b], % (95% CI)	**51% (41-61)**
Best Response	
CR, n (%)	25 (25)
PR, n (%)	26 (26)
SD, n (%)	16 (16)
BTK Naive MCL Patients[a]	**n=11**
Overall Response Rate[b], % (95% CI)	**82% (48-98)**
Best Response	
CR, n (%)	2 (18)
PR, n (%)	7 (64)
SD, n (%)	1 (9)

- Efficacy also seen in patients with prior:
  - Stem cell transplant (n=28): ORR 64% (95% CI: 44-81)
  - CAR-T therapy (n=6): ORR 50% (95% CI: 12-88)

Lewis K et al. Pan Pacific Lymphoma Conference 2022; Cohen JB et al. SOHO 2022;Abstract 133.

BRUIN: Updated Safety Results with Pirtobrutinib for MCL

All Doses and Patients (n=618)							
	Treatment-Emergent AEs, (≥15%), %					Treatment-Related AEs, %	
Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grades 3/4	Any Grade
Fatigue	13%	8%	1%	-	23%	1%	9%
Diarrhea	15%	4%	<1%	<1%	19%	<1%	8%
Neutropenia[a]	1%	2%	8%	6%	18%	8%	10%
Contusion	15%	2%	-	-	17%	-	12%
AEs of special interest[b]							
Bruising[c]	20%	2%	-	-	22%	-	15%
Rash[d]	9%	2%	<1%	-	11%	<1%	5%
Arthralgia	8%	3%	<1%	-	11%	-	3%
Hemorrhage[e]	5%	2%	1%[g]	-	8%	<1%	2%
Hypertension	1%	4%	2%	-	7%	<1%	2%
Atrial fibrillation/flutter[f]	-	1%	<1%	<1%	2%[h]	-	<1%

Lewis K et al. Pan Pacific Lymphoma Conference 2022; Cohen JB et al. SOHO 2022;Abstract 133.

R/R MCL: BTK plus…

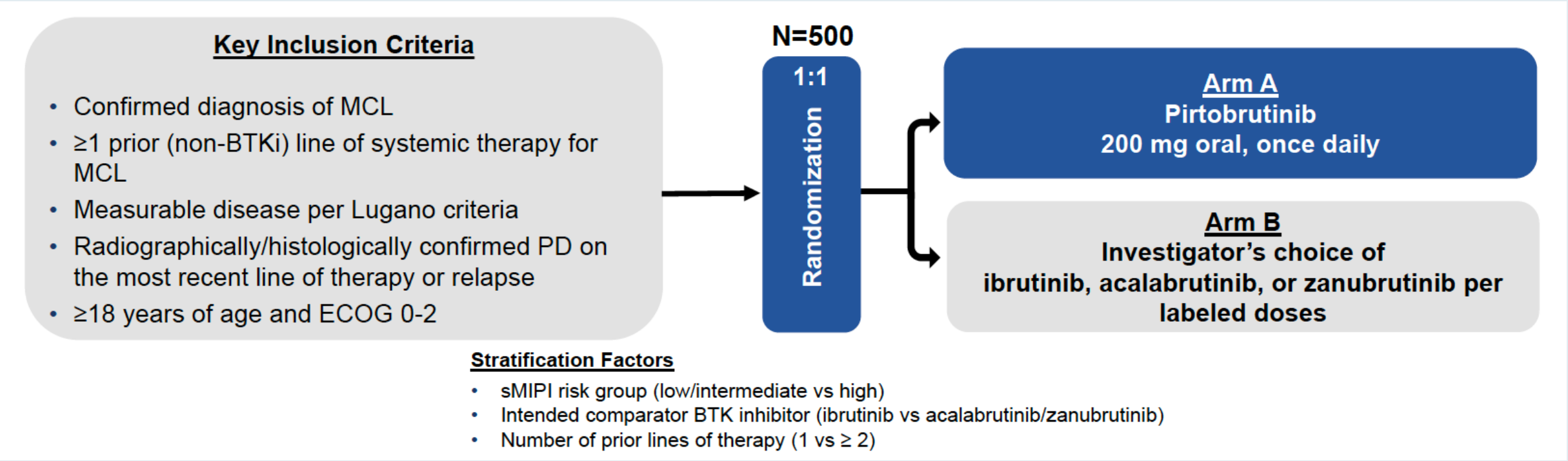
Completed

1. Ibrutinib plus Venetoclax - 71% CR (AIM Study)
2. Ibrutinib + Obinutuzumab + Venetoclax - 67% CR (OASIS study)

Ongoing Phase III Trials

1. Ibrutinib vs. Ibrutinib plus Venetoclax (SYMPATICO)
2. Pirtobrutinib vs. SOC BTK (LOXO 305)

BRUIN MCL-321 Phase III Study Design



Ito R et al. SOHO 2022;Abstract MCL-135.

Glofitamab for R/R MCL. Philips et al. Abstract #74.

Patient Characteristics

- N = 37
- Median Age 72
- Median prior therapy 3 (1-5)

Treatment Schedule

- Obinutuzumab D1
  - 1000 vs 2000 mg
- Glofit step up dosing D 8, 15
- Glofit 30mg q 3w x 12 cycles

Results

- ORR 84%
- CR 73%
- Median f/u 8 months
- Median DOR 12.6 months
- CRS 76%
  - Tocilizumab in 17 patients
- Neurotox 51% (gr 1-2)

R2 plus Venetoclax for R/R MCL. Abstract 76. Zandelisib plus Zanubrutinib for R/R MCL. Abstract 78.

Jerkeman et al, #76

- N = 59, Median age 73
- Median prior lines 2
- Ven 600 mg. Len 15 mg.
- ORR 63%. CR 49%.
- Durability ?
- Grade 3-4 neutropenia in 88%.
- Grade 3-4 thrombocytopenia 36%.
- Grade 3-4 infection 14%.
- Grade 3 rash in 8%.

Soumerai et al, #78

- N = 19. Median age 67.
- Median prior lines 2
- Zandelisib 60 mg. Zanu 80 mg BID.
- ORR 76%. CR 35%.
- Median PFS 10 months
- Diarrhea 32%
- Headache 18%
- Arthralgia 16%
- Rash 16%

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