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

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ORIGINAL ARTICLE

Ibrutinib plus Bendamustine and Rituximab in Untreated Mantle-Cell Lymphoma

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BR as First-line MCL Treatment in Older Patients

- Older patients with newly diagnosed mantle cell lymphoma (MCL) are usually treated with chemo-immunotherapy regimens such as bendamustine-rituximab (BR), R-CHOP, or VR-CAP[1-4]
  - BR has become the most commonly used first-line regimen[5]

- BR alone:
  - Improved progression-free survival (PFS) compared with R-CHOP (35 vs 22 months)[6] and has a better safety profile[6,7]

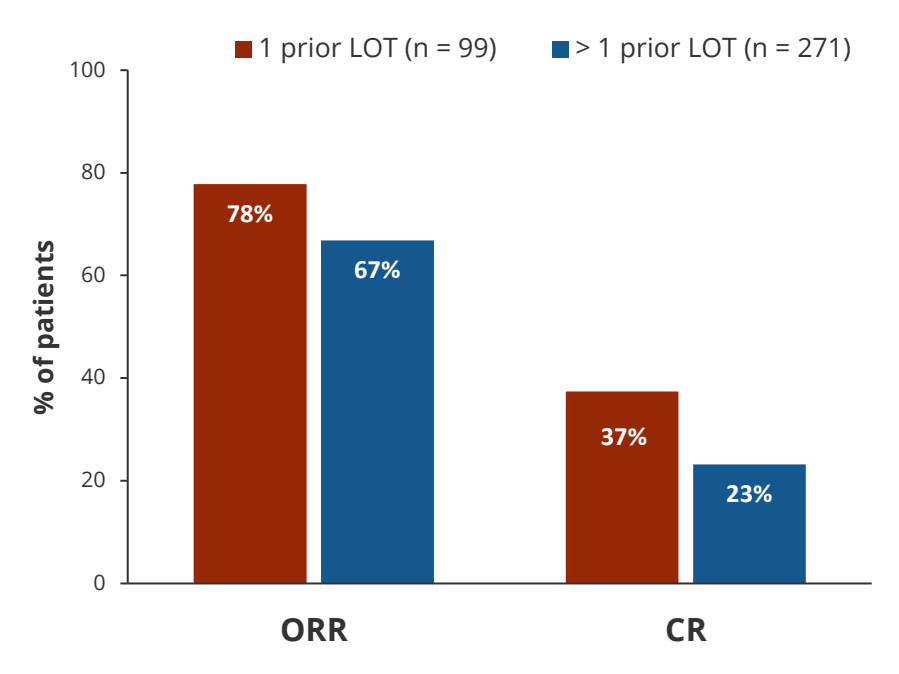
- BR with rituximab maintenance:
  - Significantly improved PFS compared with BR alone in 2 independent real world studies[5,8]

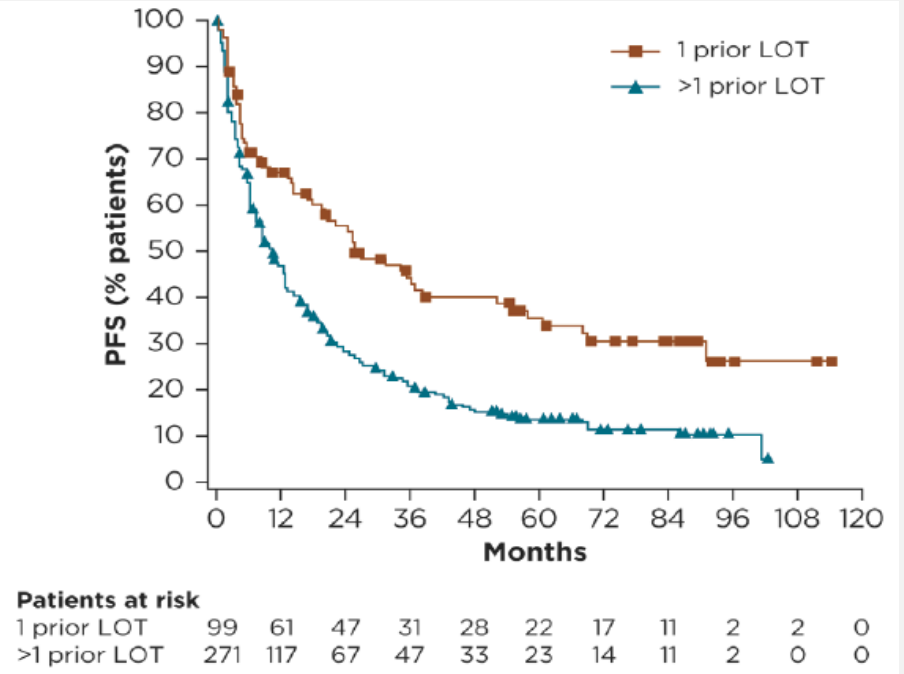
R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

1. Hermine O, et al. *Lancet*. 2016;388:565-575. 2. Le Gouill S, et al. *N Engl J Med*. 2017;377:1250-1260. 3. Robak T, et al. *Leuk Lymphoma*. 2019;60:2622-2634. 4. Monga N, et al. *Crit Rev Oncol Hematol*. 2021;158:103212. 5. Martin P, et al. *J Clin Oncol*. 2021;39(suppl 15):7504. 6. Rummel MJ, et al. *Lancet*. 2013;381:1203-1210. 7. Flinn IW, et al. *J Clin Oncol*. 2019;37:984-991. 8. Hill BT, et al. *Hematol Oncol*. 2019;37:405-407.

Ibrutinib Is a First-in-Class Once-Daily BTK Inhibitor

- Ibrutinib has transformed the care of patients with relapsed/refractory MCL; it is particularly effective and durable at first relapse[1-5]





- Ibrutinib + BR has demonstrated activity in first-line MCL in a phase 1b study[6]

BTK, Bruton's tyrosine kinase; LOT, line of therapy.

1. Wang ML, et al. *N Engl J Med*. 2013;369:507-516. 2. Rule S, et al. *Leukemia*. 2018;32:1799-1803. 3. Rule S, et al. *Blood*. 2019;134(suppl 1):1538. 4. Rule S, et al. *Haematologica.* 2019;104:e214.
5. Dreyling M, et al. *HemaSphere*. 2022;6:e712. 6. Maddocks K, et al. *Blood*. 2015;125:242-248.

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

Patients

- Previously untreated MCL
- ≥ 65 years of age
- Stage II-IV disease
- No planned stem cell transplant

Stratification factor

- Simplified MIPI score (low vs intermediate vs high)

Enrolled between May 2013 and November 2014 at 183 sites

N = 523

R 1:1

BR induction for 6 cycles → **if CR or PR** → **R**ituximab maintenance every 8 weeks for 12 cycles

Ibrutinib 560 mg (4 capsules daily) until PD or unacceptable toxicity

BR induction for 6 cycles → **if CR or PR** → **R**ituximab maintenance every 8 weeks for 12 cycles

Placebo (4 capsules daily) until PD or unacceptable toxicity

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

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

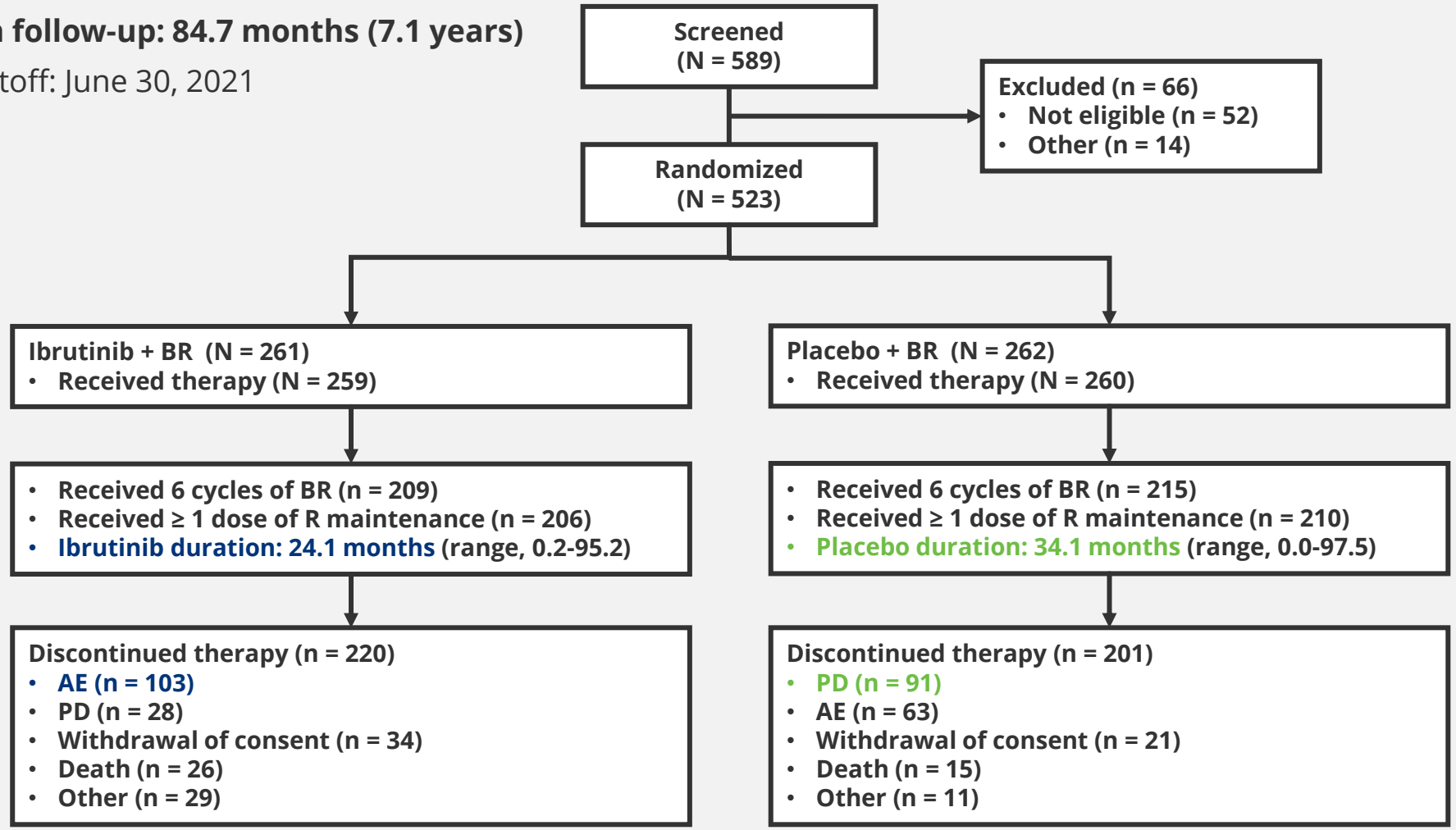
Induction: **B**endamustine 90 mg/m2 Days 1 and 2, **R**ituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.

CR, complete response; ITT, intent-to-treat; MIPI, Mantle Cell Lymphoma International Prognostic Index; PD, progressive disease; PFS, progression-free survival; PR, partial response.

Patient Disposition and Treatment Exposure

Median follow-up: 84.7 months (7.1 years)

Data cutoff: June 30, 2021



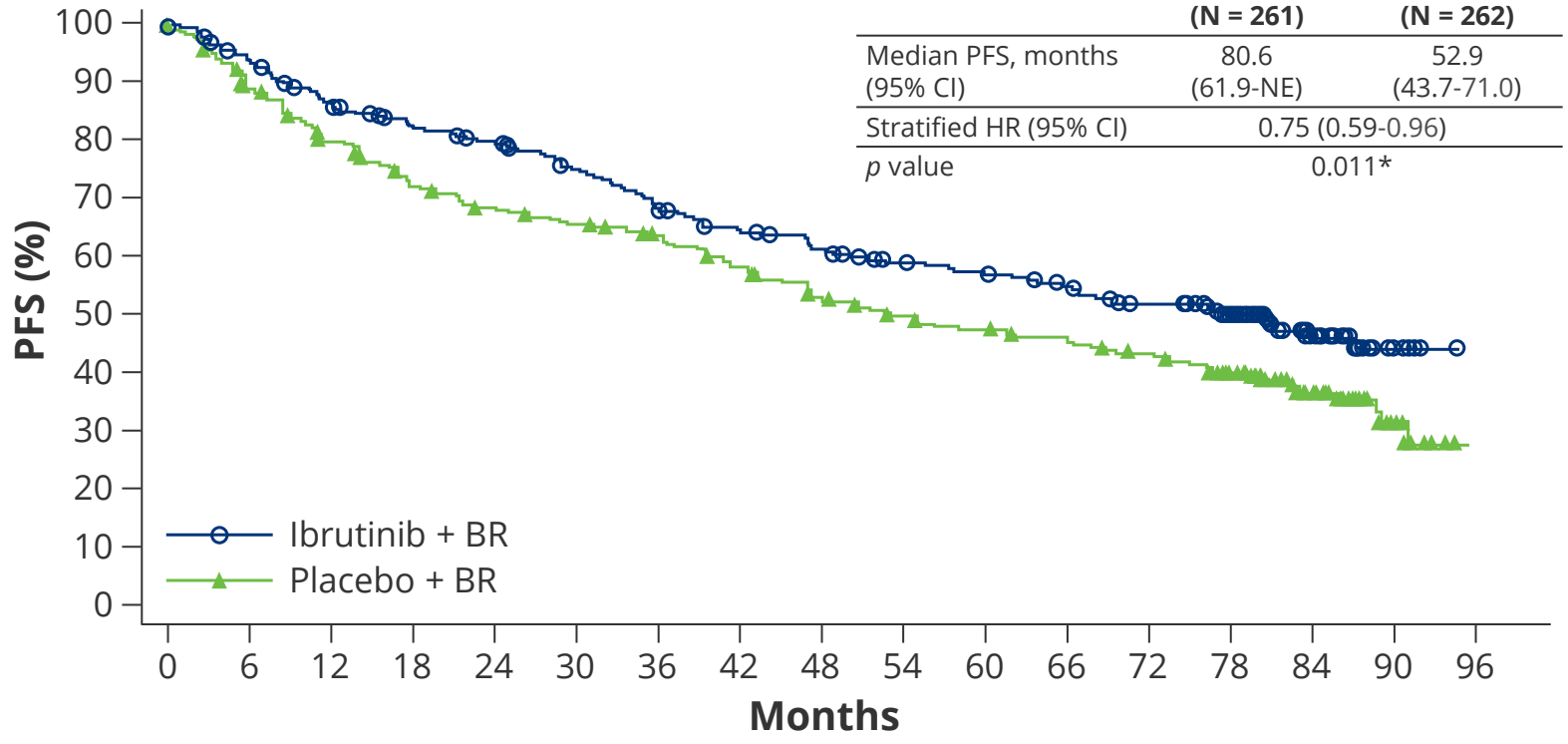
AE, adverse event; PD, progressive disease.

Baseline Characteristics

		Ibrutinib + BR (N = 261)	Placebo + BR (N = 262)
Median age (range), years		71 (65-86)	71 (65-87)
≥ 75 years, n (%)		74 (28.4)	82 (31.3)
Male, n (%)		178 (68.2)	186 (71.0)
ECOG PS 1, n (%)		127 (48.7)	118 (45.0)
Simplified MIPI, n (%)	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, n (%)		198 (75.9)	200 (76.3)
Blastoid/pleomorphic histology, n (%)		19 (7.3)	26 (9.9)
Extranodal, n (%)		234 (89.7)	226 (86.3)
Bulky (≥ 5 cm), n (%)		95 (36.4)	98 (37.4)
TP53 mutated, n (%)		26 (10.0)	24 (9.2)
TP53 mutation status unknown, n (%)		121 (46.4)	133 (50.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, Mantle Cell Lymphoma International Prognostic Index.

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

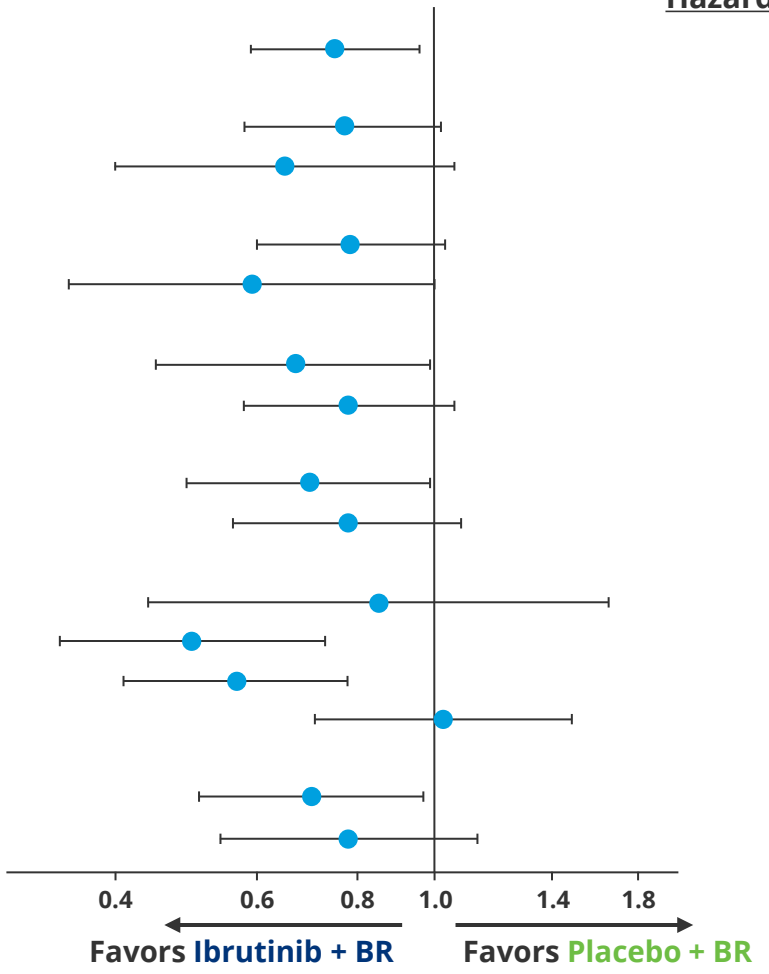
Ibrutinib + BR and R maintenance achieved:

- **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 $p < 0.023$.

PFS Hazard Ratio in Subgroups

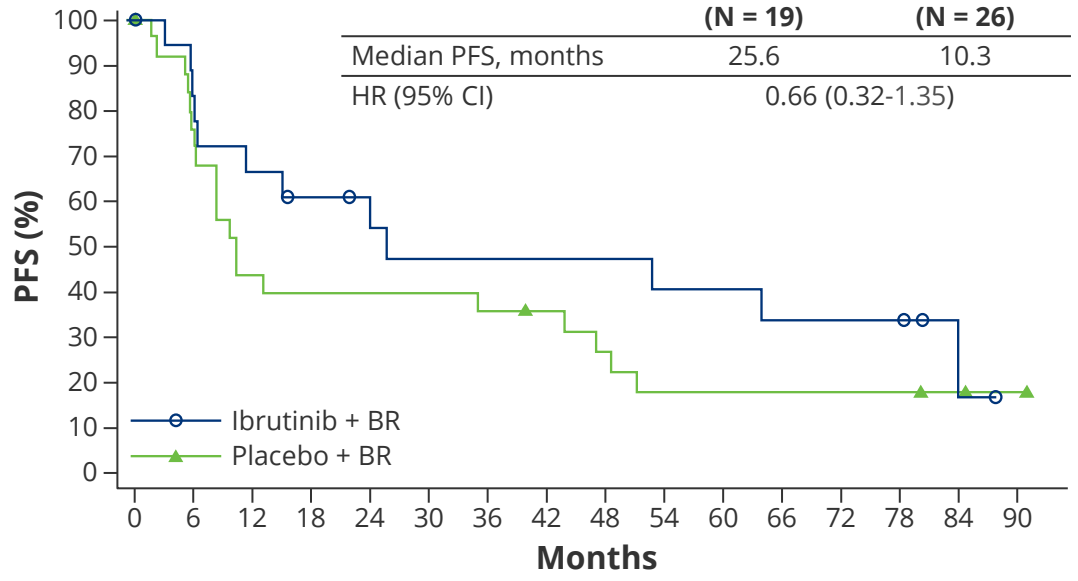
Characteristic, n/N	Ibrutinib + BR	Placebo + BR	Hazard Ratio (HR)	95% CI
All patients	116/261	152/262	**0.75**	0.59-0.96
Sex				
Male	88/178	111/186	**0.77**	0.58-1.02
Female	28/83	41/76	**0.65**	0.40-1.06
Race				
White	92/199	118/206	**0.78**	0.60-1.03
Non-white	24/62	34/56	**0.59**	0.35-1.00
Age				
< 70 years	39/99	62/108	**0.67**	0.45-0.99
≥ 70 years	77/162	90/154	**0.78**	0.58-1.06
ECOG PS				
0	53/134	72/141	**0.69**	0.49-0.99
1-2	63/127	80/121	**0.77**	0.56-1.08
Simplified MIPI at baseline				
Low risk (0-3)	15/44	21/46	**0.85**	0.44-1.65
Intermediate risk (4-5)	42/124	76/129	**0.50**	0.34-0.73
Low/intermediate risk (0-5)	57/168	97/175	**0.57**	0.41-0.78
High risk (6-11)	59/93	55/87	**1.02**	0.71-1.48
Tumor bulk				
< 5 cm	64/165	90/163	**0.71**	0.51-0.97
≥ 5 cm	51/95	62/98	**0.78**	0.54-1.13



ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, Mantle Cell Lymphoma International Prognostic Index; CI, confidence interval.

PFS in High-Risk Subgroups

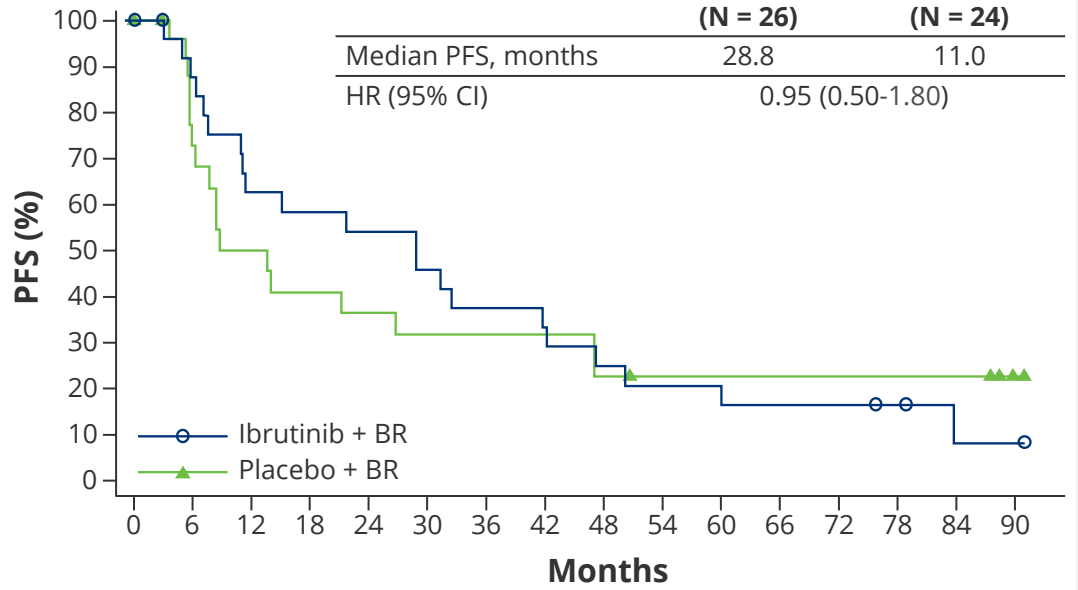
Blastoid/pleomorphic histology



Patients at Risk

Ibrutinib + BR	19	14	12	10	8	7	7	7	7	6	6	5	5	5	1	0
Placebo + BR	26	19	11	10	10	10	9	8	6	4	4	4	4	4	3	1

TP53 mutation present

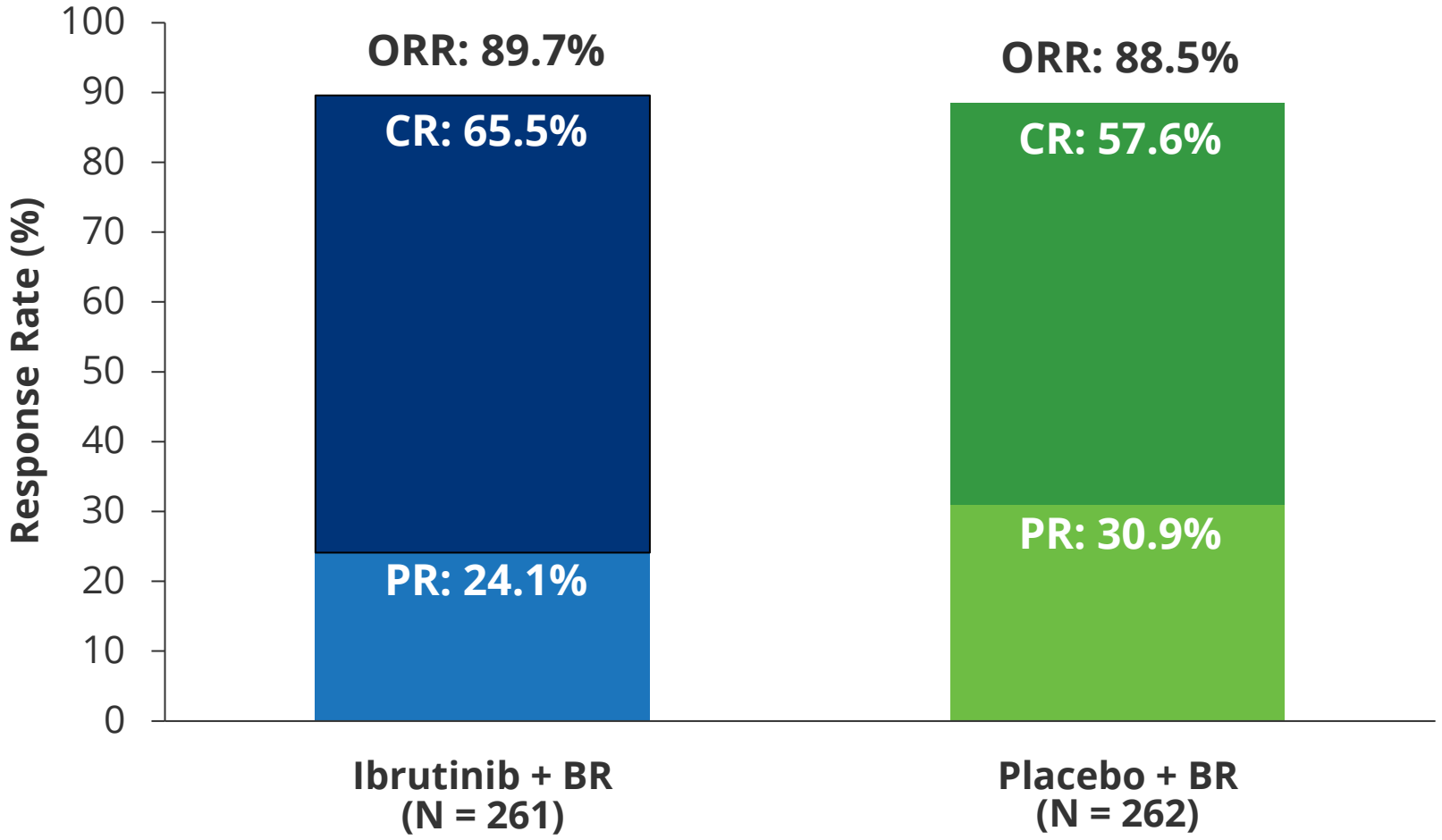


Patients at Risk

Ibrutinib + BR	26	21	15	14	13	11	9	7	6	5	4	4	4	3	1	1
Placebo + BR	24	16	11	9	8	7	7	7	5	4	4	4	4	4	4	1

CI, confidence interval

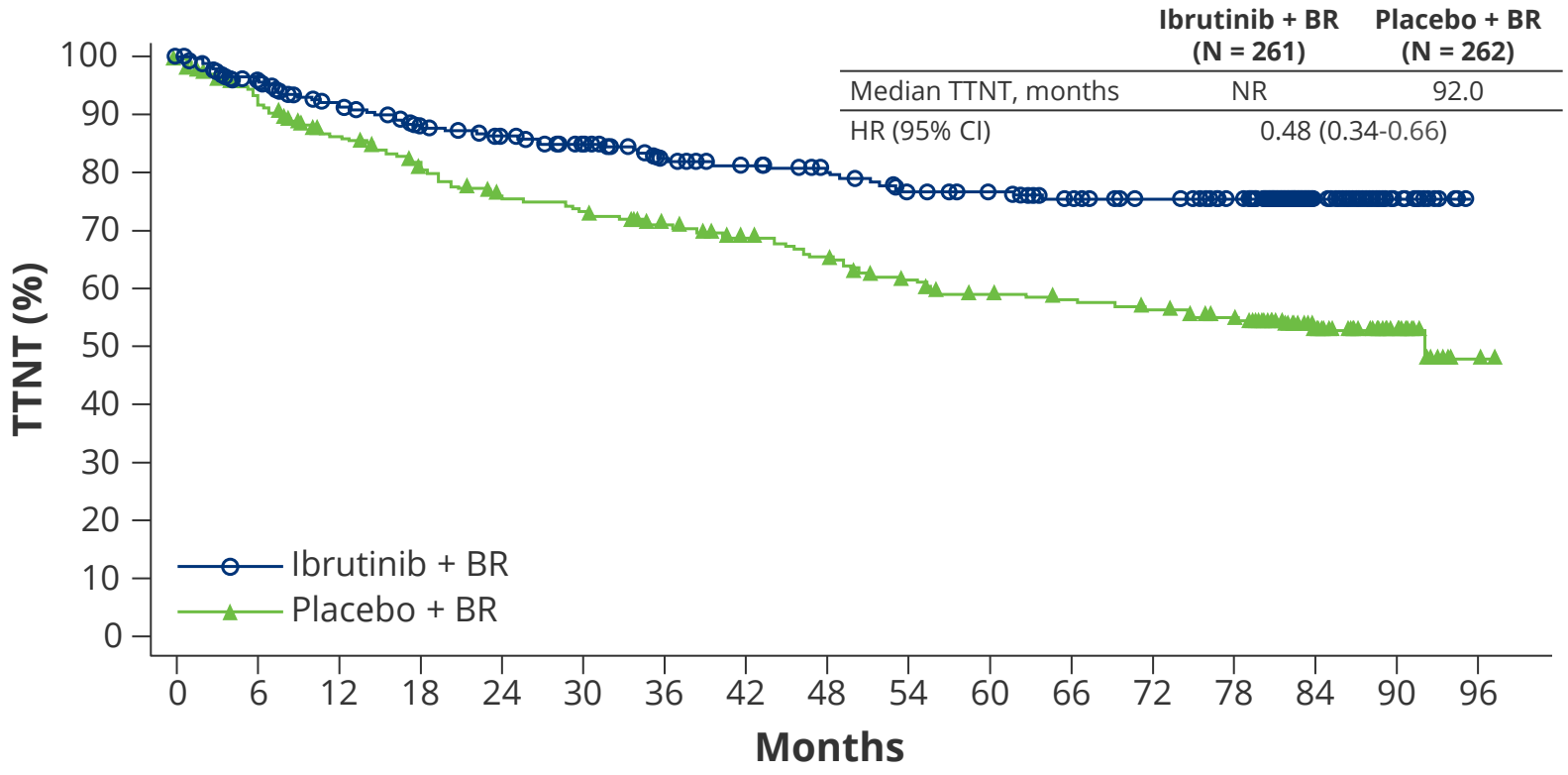
Response Rate



- **CR rate was numerically higher in the ibrutinib arm (65.5% vs 57.6%; *p* = 0.057)**

ORR, objective response rate; CR, complete response; PR, partial response.

Time To Next Treatment



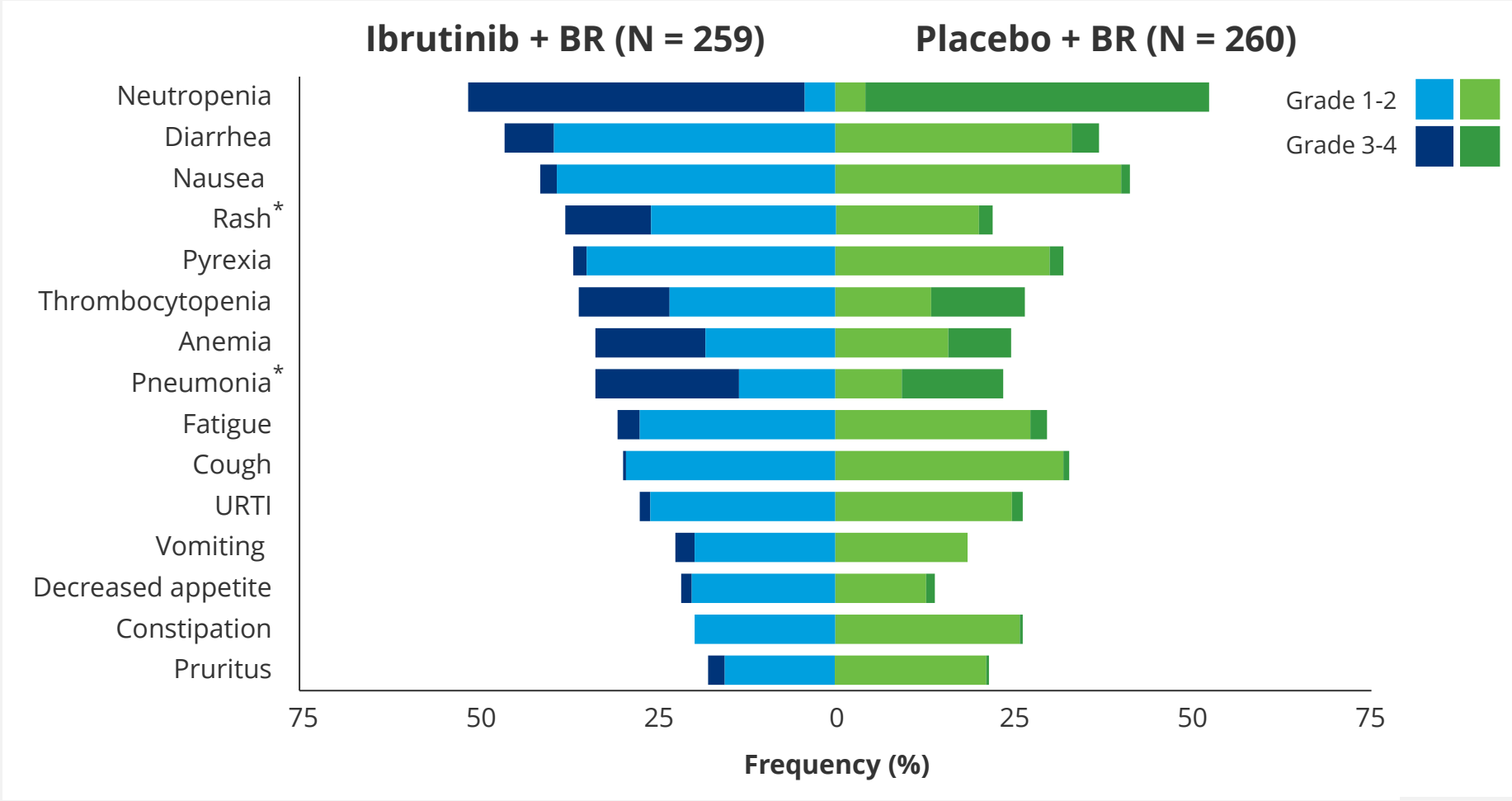
Patients at Risk

Ibrutinib + BR	261	231	209	192	184	174	155	147	140	131	126	119	111	102	60	21	0
Placebo + BR	262	231	203	189	171	167	157	146	137	125	117	113	109	101	67	23	2

- **Subsequent therapy at second-line:**
  - **Ibrutinib arm: 52/261(19.9%)**
    - **BTKi: 6/52 (11.5%)**
  - **Placebo arm: 106/262 (40.5%)**
    - **BTKi: 41/106 (38.7%)**

BTKi, Bruton's tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; NR, not reached; TTNT, time to next treatment.

Common Treatment-Emergent Adverse Events (≥ 20%)



*Difference of ≥ 10% in any grade treatment-emergent adverse event (TEAE).
URTI, upper respiratory tract infection.

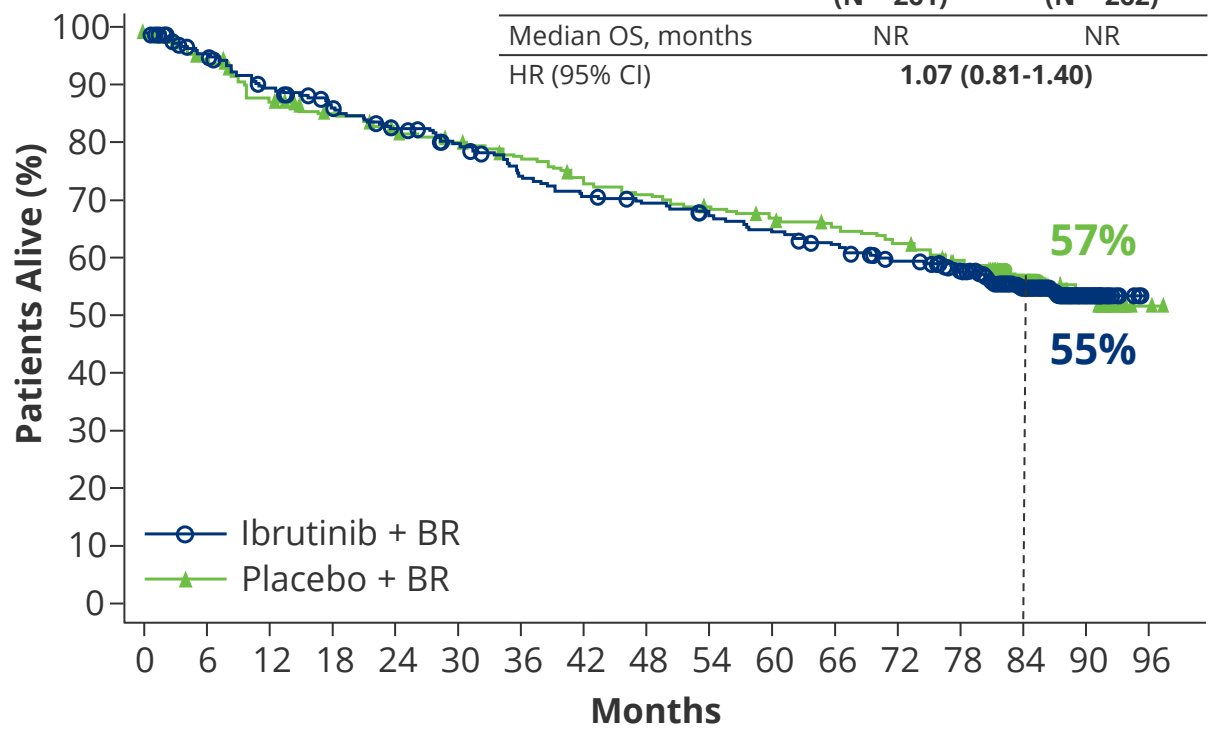
TEAEs of Clinical Interest With BTKis

	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

- These adverse events were generally not treatment limiting
- During the entire study period, second primary malignancies (including skin cancers) occurred in 21% in the ibrutinib arm and 19% in the placebo arm; MDS/AML in 2 and 3 patients, respectively

*Difference of ≥ 5% in any grade TEAE; MDS/AML, myelodysplastic syndromes/acute myeloid leukemia;
Any bleeding is based on Haemorrhage Standardized MedDRA Query (SMQ) (excluding laboratory terms). Major bleeding includes any grade 3 or higher bleeding and serious or central nervous system bleeding of any grade.

Overall Survival



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 and TEAE	**58 (22.2%)**	**70 (26.7%)**
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 excluding PD and TEAEs	**46 (17.6%)**	**37 (14.1%)**
Total deaths	**104 (39.8%)**	**107 (40.8%)**

- Death due to Covid-19: 3 patients in the ibrutinib arm during the TEAE period and 2 patients in the placebo arm after the TEAE period
- Exploratory analysis of cause-specific survival including only deaths due to PD or TEAEs showed an HR of 0.88

*The most common grade 5 TEAE was infections in the ibrutinib and placebo arms: 9 versus 5 patients. Grade 5 TEAE of cardiac disorders occurred in 3 versus 5 patients, respectively.
CI, confidence interval; HR, hazard ratio; NR, not reached; PD, progressive disease; TEAE, treatment-emergent adverse event.

Conclusions

SHINE is the first phase 3 study to show that ibrutinib in combination with chemoimmunotherapy is highly effective in patients with untreated MCL

Median PFS of 6.7 years: a statistically significant and clinically meaningful 2.3-year PFS advantage

Consistent and expected AEs with the known profiles of ibrutinib and BR

A new benchmark for first-line treatment of older patients with MCL or those unsuitable for ASCT

ASCT, autologous stem cell transplantation.

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