Best of ASCO 2022

Lymphoid Malignancies

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Disclosures

- **Consulting, Advisory Boards, steering committees or data safety monitoring committees:** Abbvie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, Beigene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate therapeutics, MEI pharma and Atara Biotherapeutic.

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Selected studies

1. Hodgkin Lymphoma: Brentuximab-vedotin + chemo for first line (ECHELON-1)

2. CLL: Ibrutinib and Venetoclax for first line (CAPTIVATE FD)

3. Mantle cell: Ibrutinib and BR for first line (SHINE)

2022 ASCO® ANNUAL MEETING

FIRST-LINE BRENTUXIMAB VEDOTIN PLUS CHEMOTHERAPY IMPROVES OVERALL SURVIVAL IN PATIENTS WITH STAGE III/IV CLASSICAL HODGKIN LYMPHOMA: AN UPDATED ANALYSIS OF ECHELON-1

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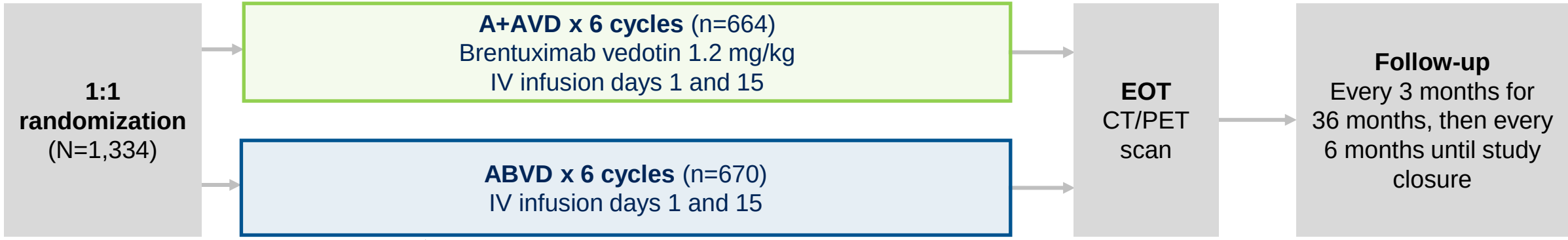
Background

- For the last decade, standard treatments (e.g., ABVD) have set a high bar for survival for patients with advanced cHL, in part due to the improved ability to salvage patients who relapse[1]
- Although various approaches including PET-adapted strategies and BEACOPP-based regimens have succeeded in improving tolerability or disease control versus ABVD, none have yet shown a meaningful OS advantage[2]
- In the phase 3 ECHELON-1 study (NCT01712490), analyses after a 5-year follow-up supported a long-term PFS benefit with first-line A+AVD vs ABVD[3]
- Here we report an alpha-controlled, prespecified OS analysis for patients in the ECHELON-1 study after approximately 6 years follow-up, as well as updates to long-term safety outcomes: second malignancies, pregnancies, and PN

A+AVD, brentuximab vedotin + doxorubicin, vinblastine, and dacarbazine; ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; cHL, classical Hodgkin lymphoma; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; PN, peripheral neuropathy.

1. Canellos GP, et al. N Engl J Med 1992;327:1478–84.
2. Kreissl S, et al. Lancet Haematol 2021;8:e398–409.
3. Straus DJ, et al. Lancet Haematol 2021;8:e410–21.

Phase 3 ECHELON-1 study design



Primary endpoint: modified PFS per IRF (previously reported[1])

Key secondary endpoint: alpha-controlled, event-driven analysis of OS

Long-term follow-up assessments:

- Exploratory analysis of OS among patients who were PET2-positive and PET2-negative
- PFS per investigator
- Subsequent treatment use
- Safety outcomes including:
  - Second malignancies
  - Outcomes of pregnancy among patients and their partners
  - PN resolution and improvement rates

Data cut-off for current analysis, June 1, 2021.
CT, computerized tomography; EOT, end of treatment; IRF, independent review facility; ITT, intention to treat; IV, intravenous; PET2, PET status at the end of cycle 2.

1. Connors JM, et al. N Engl J Med 2018;378:331–44.

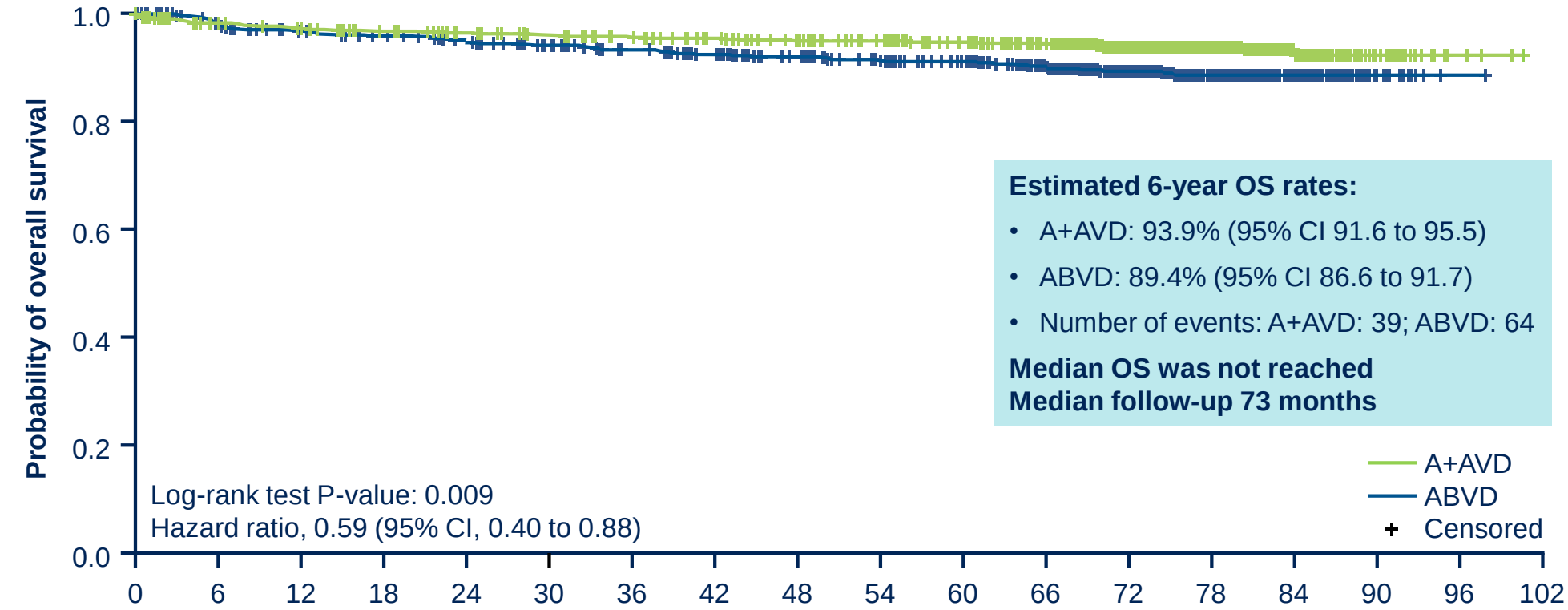
Key patient characteristics in ECHELON-1[1]

Characteristic	A+AVD (n=664)	ABVD (n=670)	Total (N=1,334)
Male sex, n (%)	378 (57)	398 (59)	776 (58)
Median age, years (interquartile range)	35 (26 to 51)	37 (27 to 53)	36 (26 to 52)
Aged <60 years, n (%)	580 (87)	568 (85)	1148 (86)
Aged ≥60 years, n (%)	84 (13)	102 (15)	186 (14)
Ann Arbor stage at initial diagnosis — n (%)*			
Stage II†	1 (<1)	0	1 (<1)
Stage III	237 (36)	246 (37)	483 (36)
Stage IV	425 (64)	421 (63)	846 (64)
Not applicable/unknown/missing	1 (<1)	3 (<1)	4 (<1)
IPS‡, n (%)			
0–1	142 (21)	141 (21)	283 (21)
2–3	355 (53)	357 (53)	712 (53)
4–7	167 (25)	172 (26)	339 (25)
PET2 status#, n (%)			
Positive	47 (7)	58 (9)	105 (8)
Negative	588 (89)	578 (86)	1166 (87)
Unknown/unavailable	29 (4)	34 (5)	63 (5)

*The Ann Arbor staging system ranges from I to IV, with higher stages indicating more widespread disease; †Patients in this category have major protocol violation; ‡The IPS ranges from 0 to 7, with higher scores indicating increased risk of treatment failure: low-risk, 0–1; intermediate-risk, 2–3; high-risk, 4–7; #PET status was assessed at post-index whereas other patient characteristics were assessed at baseline.
IPS; International Prognostic Score.

1. Straus DJ, et al. Lancet Haematol 2021;8:e410–21.

A+AVD significantly improved OS with a 41% reduction in risk of death compared with ABVD

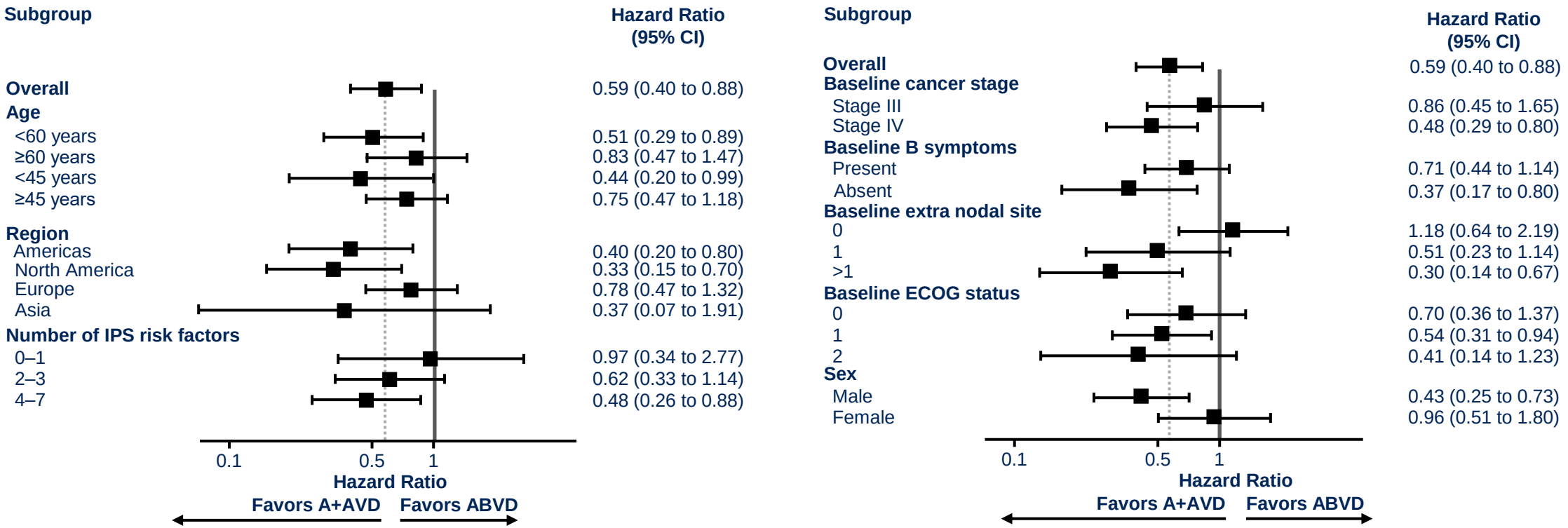


Number of patients at risk

A+AVD	664	638	626	612	598	584	572	557	538	517	494	461	350	209	97	27	4	0
ABVD	670	634	614	604	587	567	545	527	505	479	454	411	308	191	84	11	1	0

CI, confidence interval.

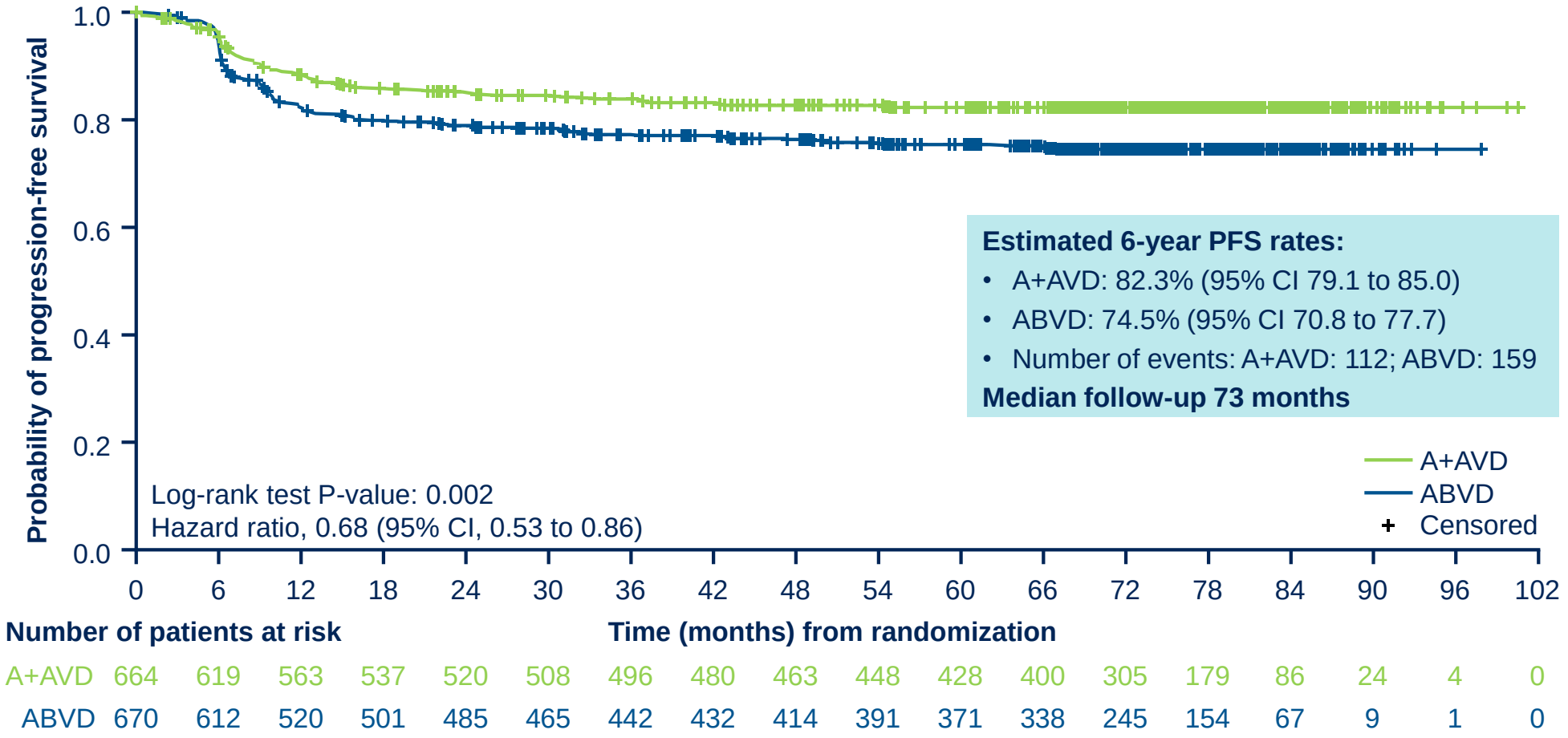
OS benefit was generally consistent across subgroups



- The OS benefit with A+AVD was preserved in a multivariable analysis when simultaneously adjusting for baseline demographic and disease factors (HR 0.53; 95% CI, 0.34 to 0.83)
  - Age, non-white race, ECOG performance status score, and PET2 status were identified as the covariates with greatest evidence of association with overall survival

ECOG, Eastern Cooperative Oncology Group.

A+AVD reduced the risk of progression or death by 32% when compared with ABVD



Fewer patients died from HL and disease- or treatment-related complications with A+AVD vs ABVD

Cause of death per investigator	A+AVD (n=662)	ABVD (n=659)
Total Deaths	**39 (5.9%)**	**64 (9.7%)**
Hodgkin lymphoma or complications	32	45
Second malignancies	1	11
Other causes	**6**	**8**
Unknown cause	1	5*
Accident or suicide	3	0
COVID-19	0	1
Heart failure	1	1
Intracranial hemorrhage	1	0
Lower respiratory tract infection	0	1

*In 2 patients in the ABVD arm, death was reported to be of indeterminate cause, but the event occurred following investigator-documented disease progression.

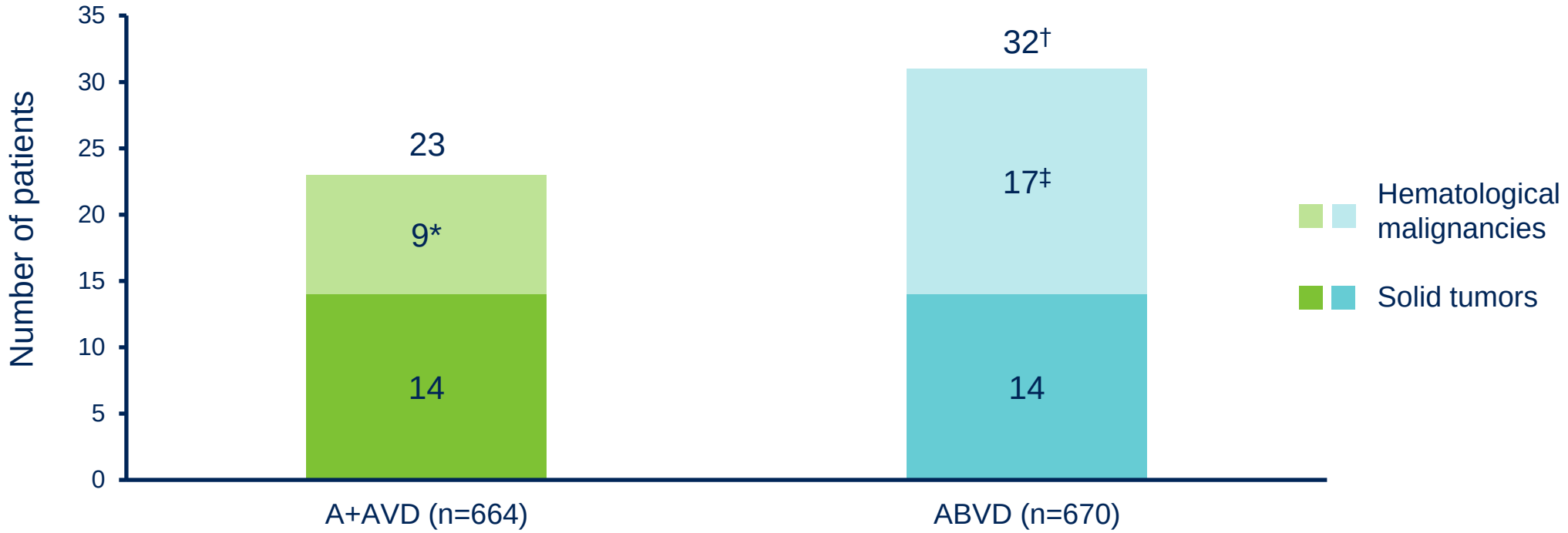
- Among those who died:
  - A+AVD: 19 patients had prior disease progression (not always the cause of death); 18 received subsequent therapy
  - ABVD: 28 patients had prior disease progression, 25 received a subsequent therapy (13 received brentuximab vedotin)

Use of subsequent therapy was less common with A+AVD versus ABVD (safety population)

	A+AVD n=662	ABVD n=659	Total N=1,321
Patients with ≥1 subsequent anticancer therapy, n (%)	135 (20)	157 (24)	292 (22)
Type of therapy, n (%)			
Brentuximab vedotin or chemotherapy regimens	78 (12)	108 (16)	186 (14)
Brentuximab vedotin monotherapy	8 (1)	49 (7)	57 (4)
Brentuximab vedotin + chemotherapy	2 (<1)	20 (3)	22 (2)
Radiation	54 (8)	54 (8)	108 (8)
Chemotherapy + radiation	1 (<1)	4 (<1)	5 (<1)
High-dose chemotherapy + transplant	44 (7)	59 (9)	103 (8)
Allogeneic transplant	4 (<1)	12 (2)	16 (1)
Immunotherapy*	18 (3)	24 (4)	42 (3)
Brentuximab vedotin + nivolumab	0 (0)	4 (<1)	4 (<1)
Nivolumab	15 (2)	18 (3)	33 (2)
Pembrolizumab	2 (<1)	6 (<1)	8 (<1)
Nivolumab combinations	1 (<1)	1 (<1)	2 (<1)
Other	0 (0)	1 (<1)	1 (<1)

*Immunotherapy was based predominantly on anti-PD-1 agents.

Fewer second malignancies were reported in the A+AVD vs ABVD arm, consistent with prior reports[1]



*Includes 2 cases of acute myeloid leukemia and 6 cases of B- or T-cell lymphomas; †Includes 1 unknown malignancy; ‡Includes 1 case each of acute myeloid leukemia, acute promyelocytic leukemia, and myelodysplastic syndrome, and 13 cases of B- or T-cell lymphomas.

- Among patients with second malignancies:
  - Two patients on each arm received transplant
  - Three patients on the ABVD arm received prior radiation (none with A+AVD)

1. Straus DJ, et al. Lancet Haematol 2021;8:e410–21.

Pregnancy and peripheral neuropathy data consistent with prior reports

Pregnancies

- Fertility was not formally assessed
- A total of 191 pregnancies were reported among patients and their partners (A+AVD: 113; ABVD: 78)
  - Among female patients with A+AVD and ABVD:
    - Pregnancies: 49 and 28
    - Live births*: 56 and 23
  - Among partners of male patients with A+AVD and ABVD:
    - Pregnancies: 33 and 33
    - Live births*: 40 and 36
  - No still births were reported in either arm

Peripheral neuropathy

- Incidence of PN at 2 years of follow-up was greater with A+AVD (67%) vs ABVD (43%)[1]
- In patients with PN in the A+AVD and ABVD arms, after 6 years follow-up:
  - Treatment-emergent PN either resolved or continued to improve† in 86% and 87%
  - Median time to resolution was 16 and 10 weeks

Safety population	A+AVD (n=662)	ABVD (n=659)
Patients with ongoing PN at last follow-up, n (%)	125 (19)	59 (9)
Grade 1	71 (11)	39 (6)
Grade 2	38 (6)	16 (2)
Grade 3‡	15 (2)	4 (<1)
Grade 4‡	1 (<1)	0

*Some female patients (13 on the A+AVD arm and 3 on the ABVD arm)/partners of male patients (8 on the A+AVD arm and 7 on the ABVD arm) recorded more than one live birth; †Resolution was defined as resolved/recovered with or without sequelae or return to baseline or lower severity as of the latest assessment for pre-existing events. Improvement was defined as resolution or a decrease by at least 1 grade from the worst grade with no higher grade thereafter; ‡Patients who were lost to follow-up or died prior to resolution or improvement were not censored (11/16 patients [including the 1 patient with Grade 4 PN] on the A+AVD arm; 4/4 on the ABVD arm).

1. Connors JM, et al. N Engl J Med 2018;378:331–44.

Conclusions

- A+AVD is the first regimen to show an improvement in OS versus classic ABVD in patients with previously untreated advanced cHL
- A+AVD improved OS versus ABVD despite the wide availability and use of active salvage therapies, including substantial use of subsequent brentuximab vedotin in the ABVD arm
- The OS benefit with A+AVD was coupled with fewer second malignancies vs ABVD
- The observed OS benefit with A+AVD, fewer disease-related deaths, and a concomitant reduction in disease progression, suggests that A+AVD has potentially cured more patients of their disease
- Based on these data, A+AVD should be considered a preferred first-line treatment option for patients with previously untreated stage III or IV cHL

Discussion points : ECHELON-1 Study

1. Subsequent treatments
2. Causes of death
3. Practice changing?

Fixed-duration (FD) ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma: 3-year follow-up from the FD cohort of the phase 2 CAPTIVATE study

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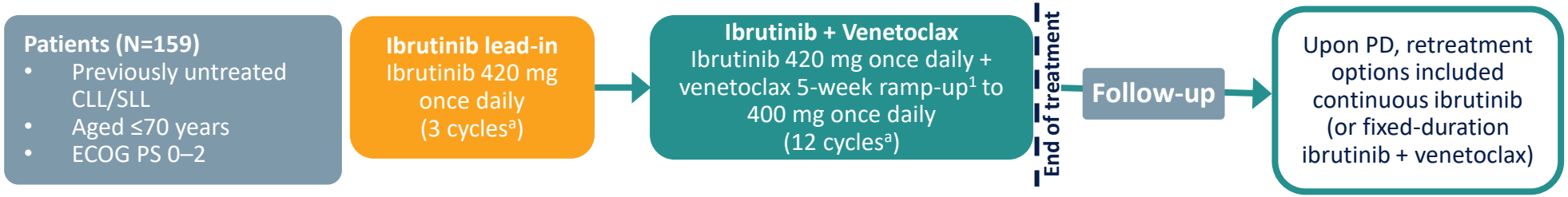
CAPTIVATE FD Cohort Study Design and Disposition

- 3-year follow up data from the FD cohort of CAPTIVATE are presented. CAPTIVATE is an international, multicenter phase 2 study evaluating first-line treatment with 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax



- **Median time on study: 38.7 months (range, 0.8–41.4)**
  - 92% completed planned 12 cycles of combined ibrutinib + venetoclax[2]
  - Median treatment duration: 13.8 months (range, 0.5–24.9), equivalent to fifteen 28-day cycles[2]
- **Median of 25 months follow-up after completion of FD therapy**
- Baseline characteristics have been previously published[2]

Key Characteristics[2]	All treated patients N=159
Median age, years (range)	60 (33–71)
High-risk features, n (%)	
Unmutated IGHV	89 (56)
del(17p)/*TP53* mutation	27 (17)
del(17p)	20 (13)
del(11q)[b]	28 (18)
Complex karyotype[c]	31 (19)
Lymph node diameter ≥5 cm, n (%)	48 (30)
Median ALC × 10^9/L (range)	70 (1–503)
ALC ≥25 × 10^9/L, n (%)	120 (75)

ALC, absolute lymphocyte count; ECOG PS, Eastern Cooperative Oncology Group performance status; FD, fixed-duration; PD, progressive disease; SLL, small lymphocytic lymphoma.

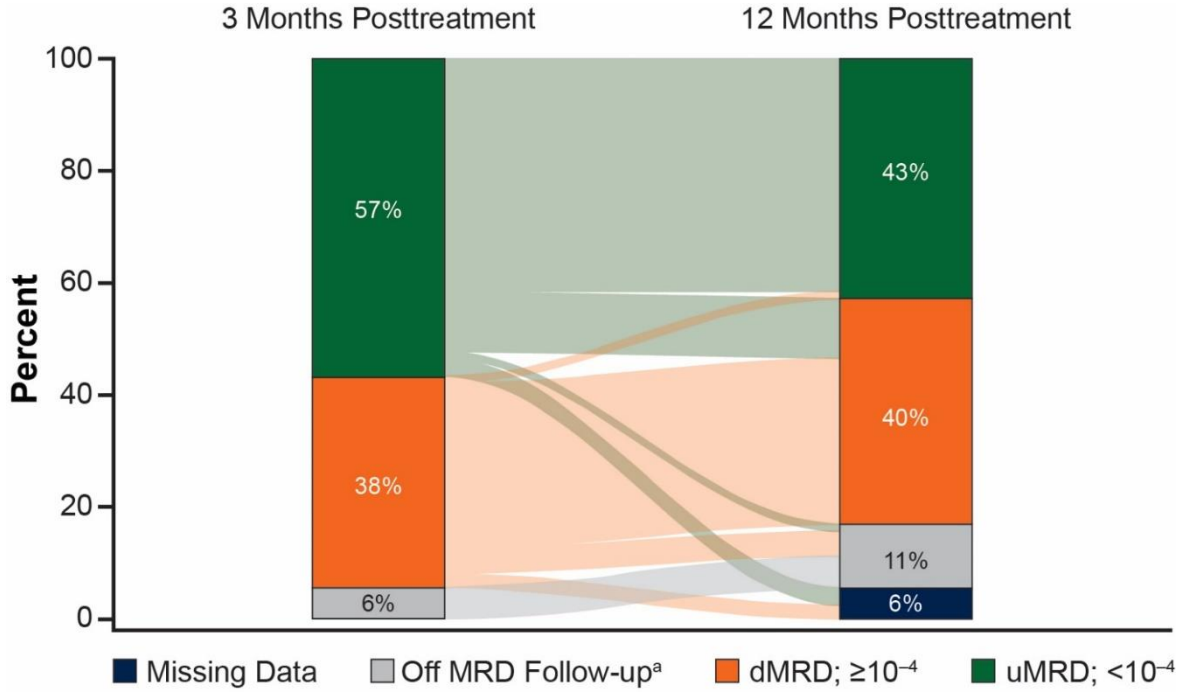
[a]1 cycle = 28 days; [b]Without del(17p) per Dohner hierarchy; [c]Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics.

1. VENCLEXTA (venetoclax tablets) for oral use [package insert]. South San Francisco, CA: Genentech USA Inc; 2021. 2. Tam CS et al. Blood. 2022; doi: 10.1182/blood.2021014488.

With An Additional Year of Off-treatment Follow-up Since the Primary Analysis, Rates of CR and Undetectable MRD Remained High

- The CR rate in all treated patients increased from 55% (95% CI, 48–63) at primary analysis to 57% (95% CI, 50–65) with an additional year of follow-up off treatment
- 79% of patients (125/159) had a best response of uMRD in PB and/or BM

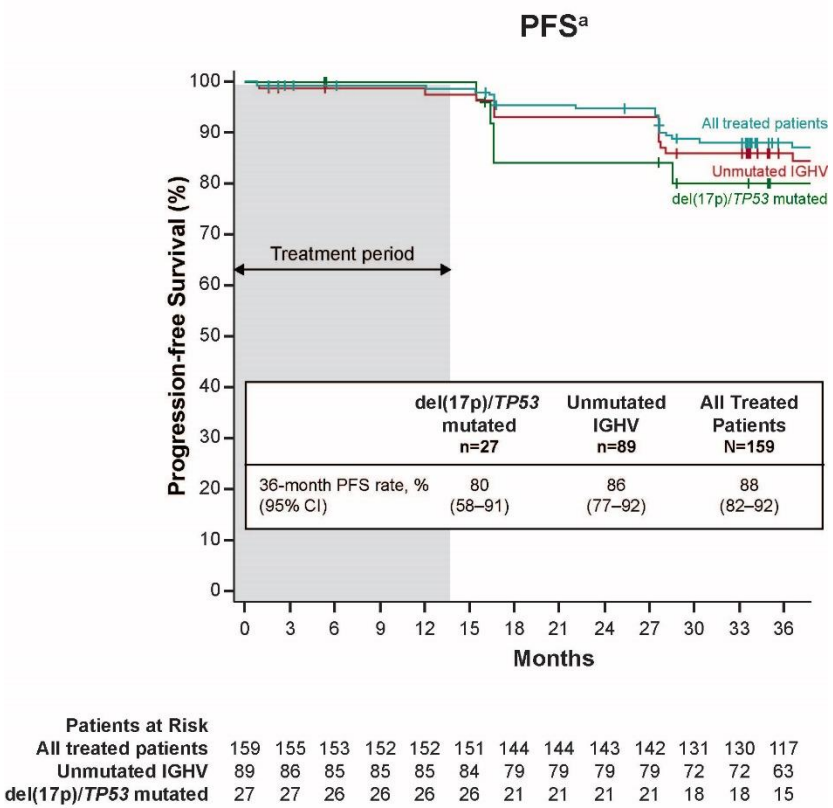
- Of patients with uMRD in PB at 3 months posttreatment, 78% (66/85) of evaluable patients maintained uMRD through 12 months posttreatment



[a]Off MRD Follow-up included patients who met any one of the criteria: progressive disease, initiation of subsequent therapy, death, or withdrawal from study.
BM, bone marrow; dMRD, detectable minimal residual disease; MRD, minimal residual disease; PB, peripheral blood; uMRD, undetectable minimal residual disease.

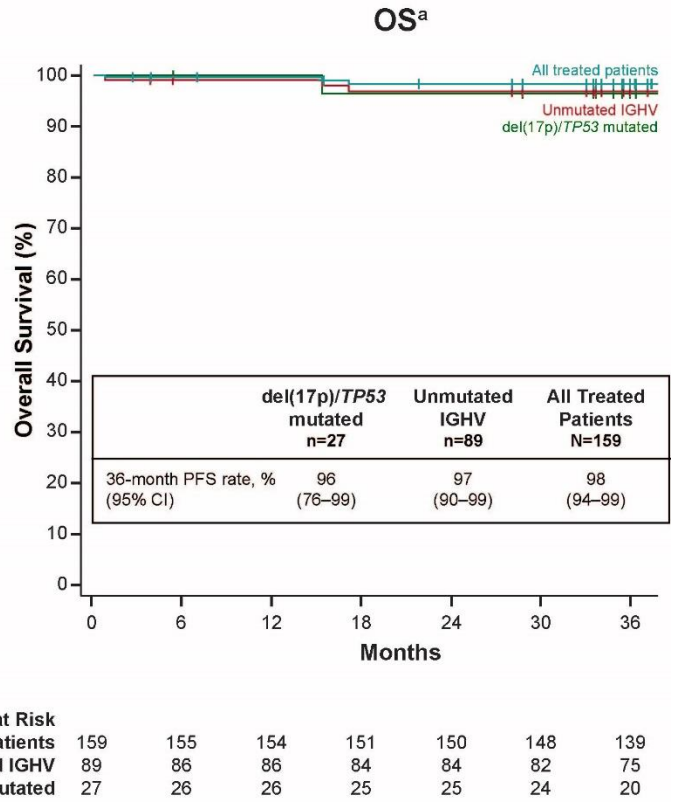
ASCO 2022, PCYC-1142 FD CAPTIVATE; Wierda et al.

With An Additional Year of Off-treatment Follow-up Since the Primary Analysis, Ibrutinib + Venetoclax Continued to Provide High Rates of PFS and OS



	del(17p)/*TP53* mutated n=27	Unmutated IGHV n=89	All Treated Patients N=159
36-month PFS rate, % (95% CI)	80 (58–91)	86 (77–92)	88 (82–92)

Patients at Risk													
All treated patients	159	155	153	152	152	151	144	144	143	142	131	130	117
Unmutated IGHV	89	86	85	85	85	84	79	79	79	79	72	72	63
del(17p)/*TP53* mutated	27	27	26	26	26	26	21	21	21	21	18	18	15



	del(17p)/*TP53* mutated n=27	Unmutated IGHV n=89	All Treated Patients N=159
36-month PFS rate, % (95% CI)	96 (76–99)	97 (90–99)	98 (94–99)

Patients at Risk							
All treated patients	159	155	154	151	150	148	139
Unmutated IGHV	89	86	86	84	84	82	75
del(17p)/*TP53* mutated	27	26	26	25	25	24	20

- The estimated 36-mo PFS rate was 88%
  - Similar rates in patients with del(17p)/*TP53* mutated (80%) or unmutated IGHV (86%)
- The estimated 36-mo OS rate was 98%
  - Similar rates in patients with del(17p)/*TP53* mutated (96%) or unmutated IGHV (97%)

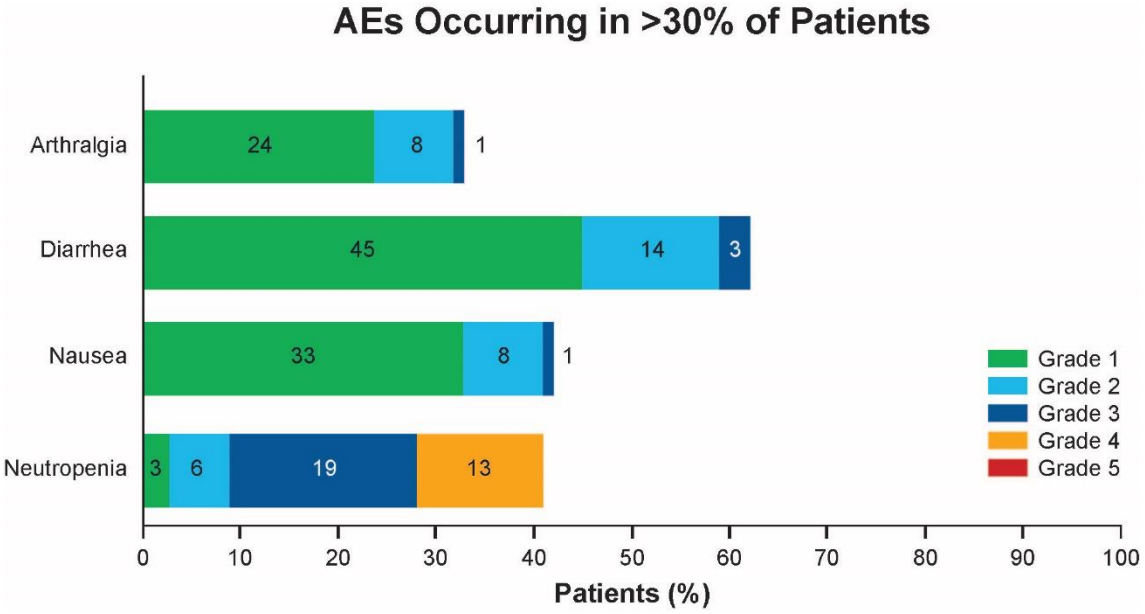
[a]Due to rapid enrollment in the study, the number of patients at risk drops substantially between 36 and 39 months. The Kaplan-Meier curves have therefore been truncated at 38 months due to instability of the curves.

CR, complete response; FD, fixed duration; OS, overall survival; PFS, progression-free survival.

ASCO 2022, PCYC-1142 FD CAPTIVATE; Wierda et al.

Retreatment With Single-Agent Ibrutinib Elicits Promising Responses; Onset and Resolution of Frequently Occurring AEs

- **Retreatment: 12 patients who progressed after FD treatment with ibrutinib + venetoclax have been retreated with single-agent ibrutinib, with duration of retreatment ranging from 6–32 months**
  - 11/12 patients were evaluable for response, with 9 achieving PR, 1 PR-L and 1 achieving SD
- **Most frequently occurring AEs (>30% of patients) were grade 1-2, occurred within 4 months of treatment initiation, and resolved**



AE (occurring in >30% of patients)	Median time to first onset (range), days	Median time from onset to resolution or improvement (range), days	Resolution rate (%)
Arthralgia	30 (1-449)	42.5 (1-1187)	87
Diarrhea	102 (1-475)	16.5 (1-587)	95
Nausea	100 (1-412)	40.5 (1-676)	96
Neutropenia	127 (21-338)	17 (1-757)	100

AE, adverse event.

ASCO 2022, PCYC-1142 FD CAPTIVATE; Wierda et al.

Conclusions

- FD ibrutinib + venetoclax continues to demonstrate deep, durable responses and clinically meaningful PFS rate of 88% at 3 years, including PFS rates ≥80% in patients with del(17p)/*TP53* mutated or unmutated IGHV
- With an additional year of follow-up, no additional OS events occurred
- The safety profile is manageable and unchanged from that previously reported. Most frequently occurring AEs were low-grade, had onset within 4 months of treatment start, and high rates of improvement or resolution
- Early data suggest that patients who progress after FD treatment with ibrutinib + venetoclax can be successfully retreated with single-agent ibrutinib
- Ibrutinib + venetoclax represents an efficacious, all-oral, once-daily, chemotherapy-free FD regimen for previously untreated patients with CLL/SLL

CLL, chronic lymphocytic lymphoma; FD, fixed duration; OS, overall survival; PFS, progression-free survival; SLL, small lymphocytic lymphoma.

ASCO 2022, PCYC-1142 FD CAPTIVATE; Wierda et al.

Discussion points : CAPTIVATE FD

1. Practice changing?

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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*Professors Le Gouill and Dreyling contributed equally.

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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]

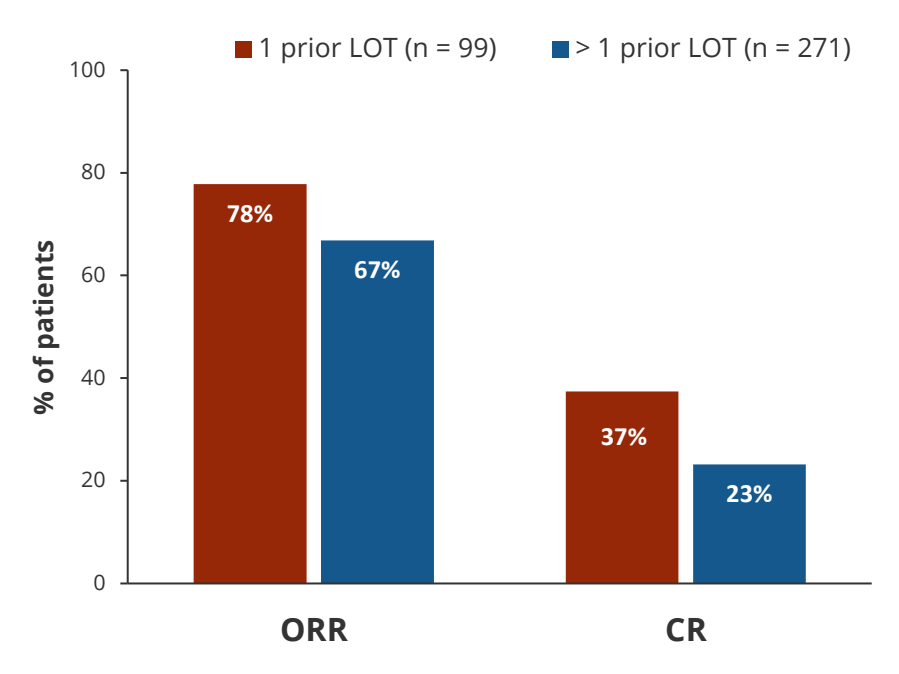
- BR with rituximab maintenance:
  - Significantly improved PFS compared with BR alone in 2 independent real world studies[5,8]

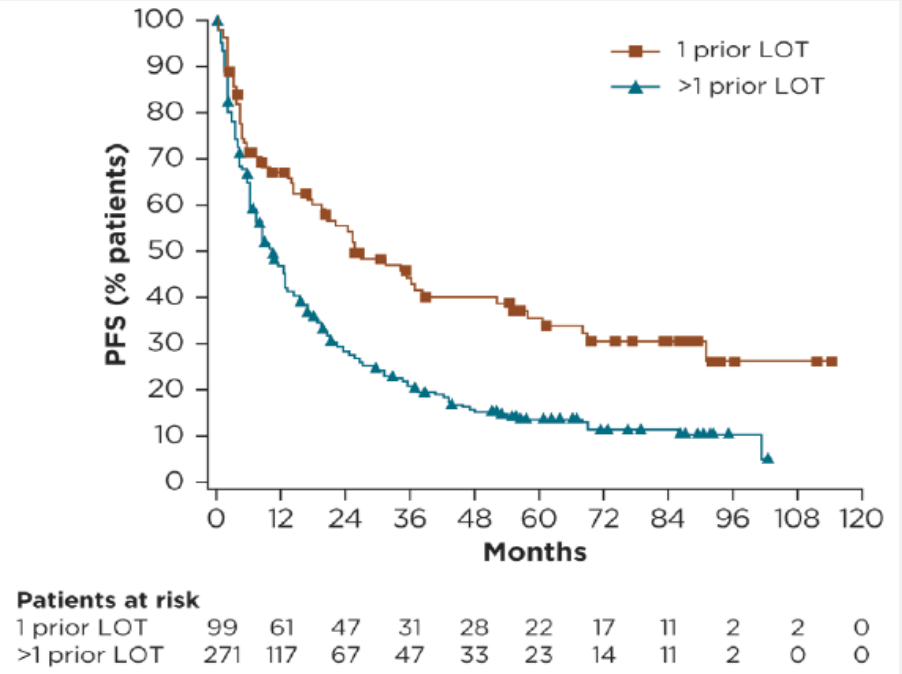
R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

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

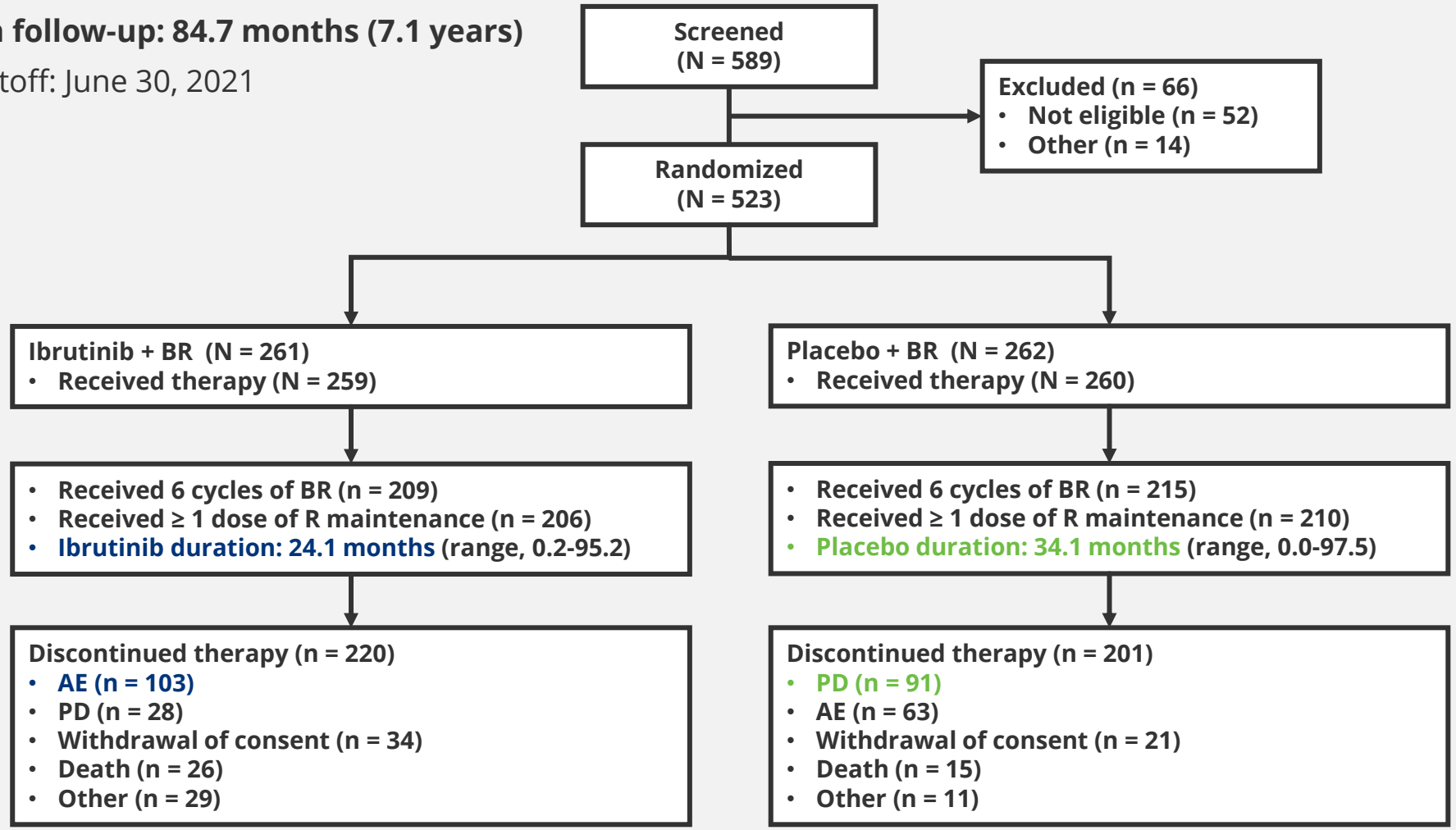
Induction: **B**endamustine 90 mg/m2 Days 1 and 2, **R**ituximab 375 mg/m2 Day 1, Q4W. A cycle is defined as 28 days.

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



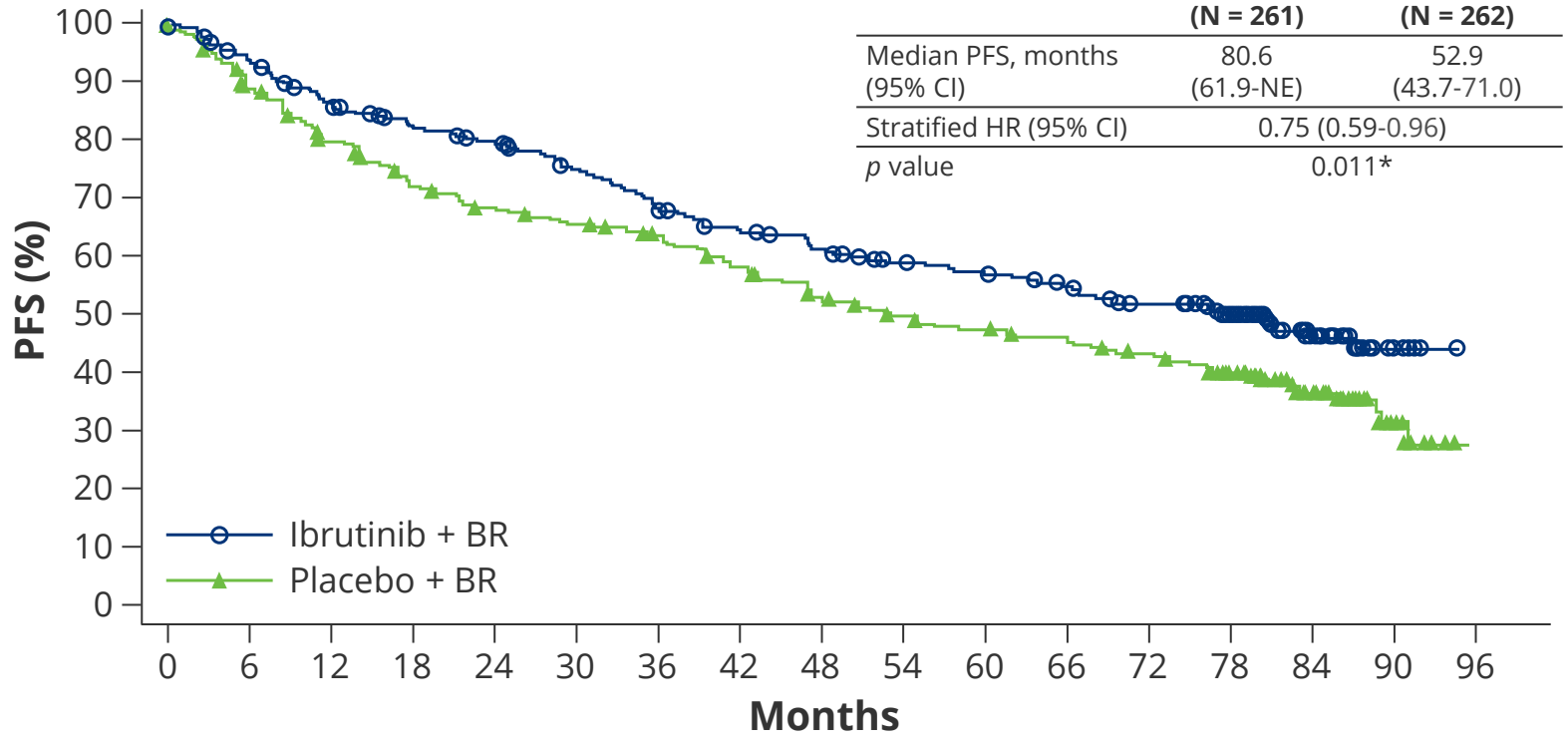
AE, adverse event; PD, progressive disease.

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

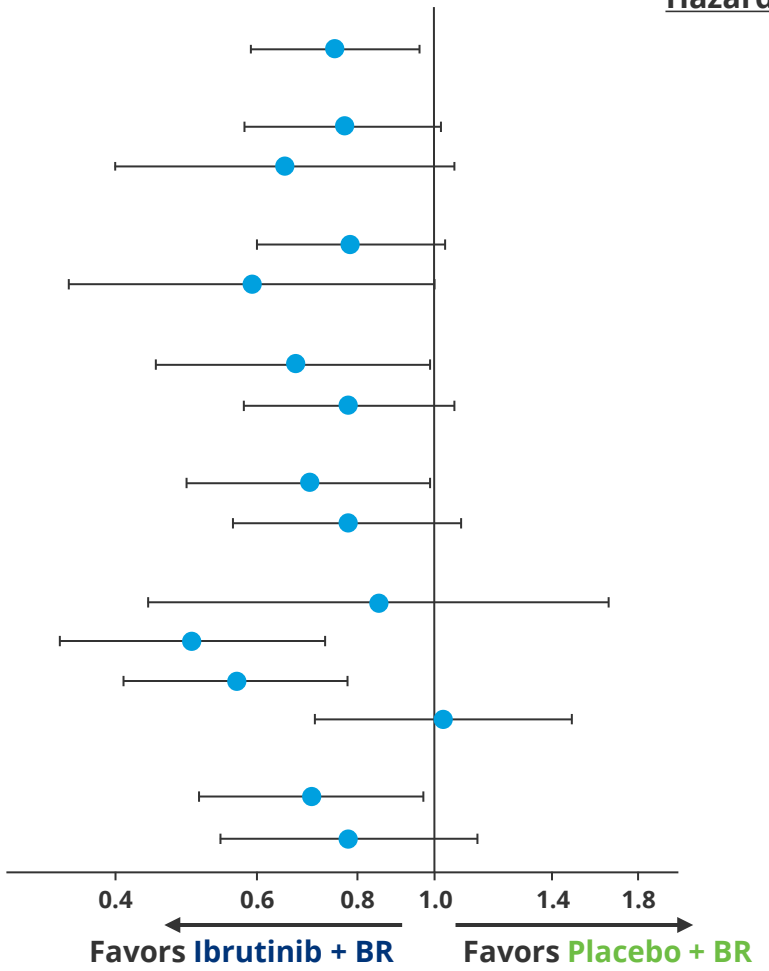
Ibrutinib + BR and R maintenance achieved:

- **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

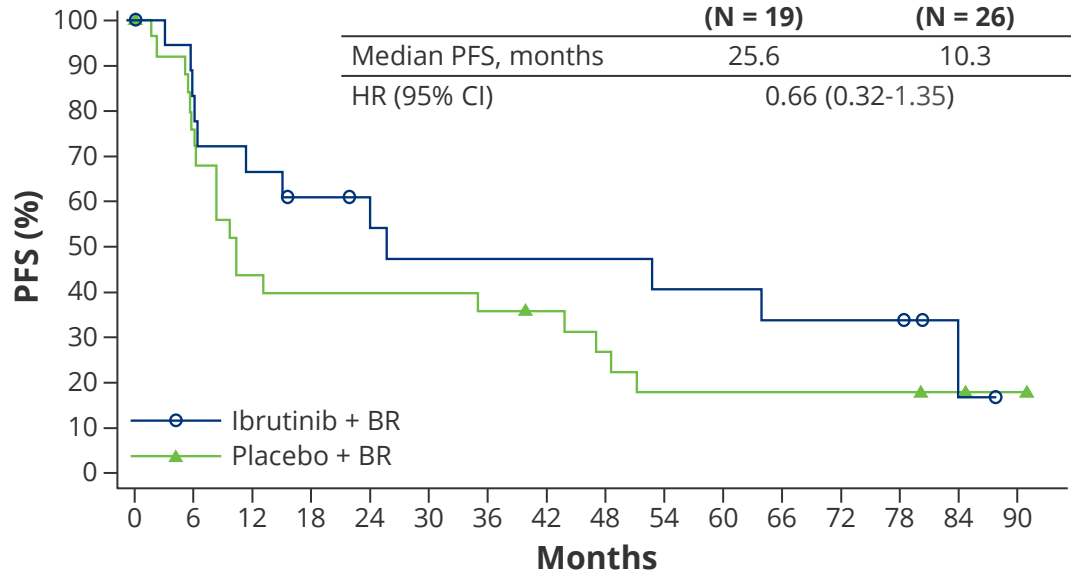
Characteristic, n/N	Ibrutinib + BR	Placebo + BR	Hazard Ratio (HR)	95% CI
All patients	116/261	152/262	**0.75**	0.59-0.96
Sex				
Male	88/178	111/186	**0.77**	0.58-1.02
Female	28/83	41/76	**0.65**	0.40-1.06
Race				
White	92/199	118/206	**0.78**	0.60-1.03
Non-white	24/62	34/56	**0.59**	0.35-1.00
Age				
< 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

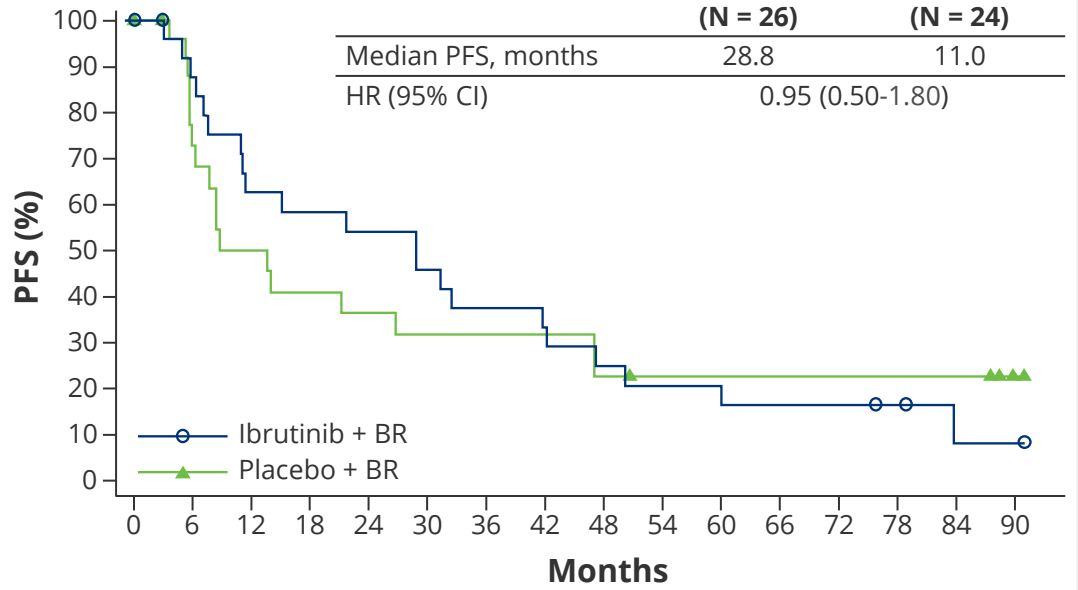


	Ibrutinib + BR (N = 19)	Placebo + BR (N = 26)
Median PFS, months	25.6	10.3
HR (95% CI)	0.66 (0.32-1.35)	

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



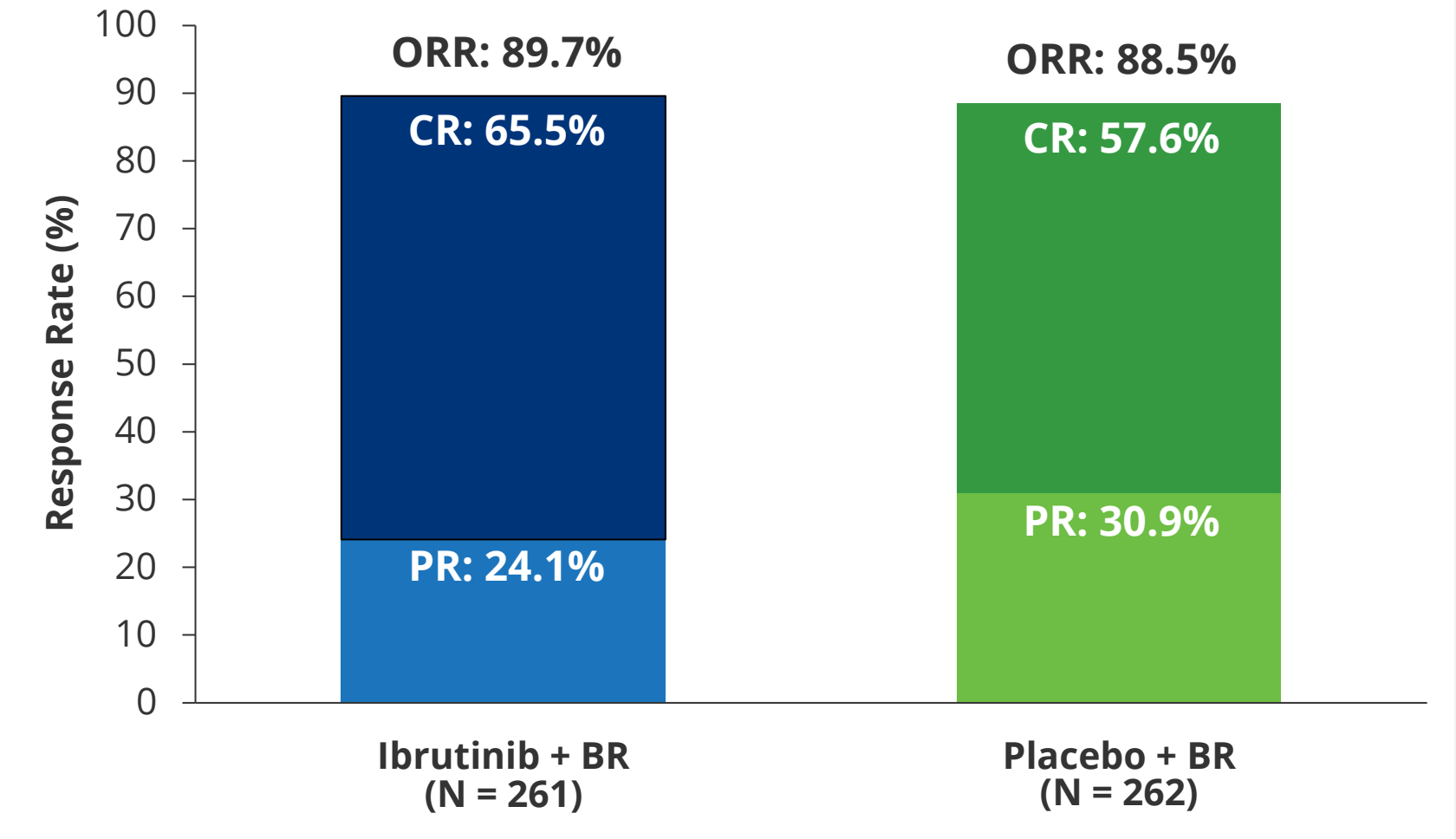
	Ibrutinib + BR (N = 26)	Placebo + BR (N = 24)
Median PFS, months	28.8	11.0
HR (95% CI)	0.95 (0.50-1.80)	

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

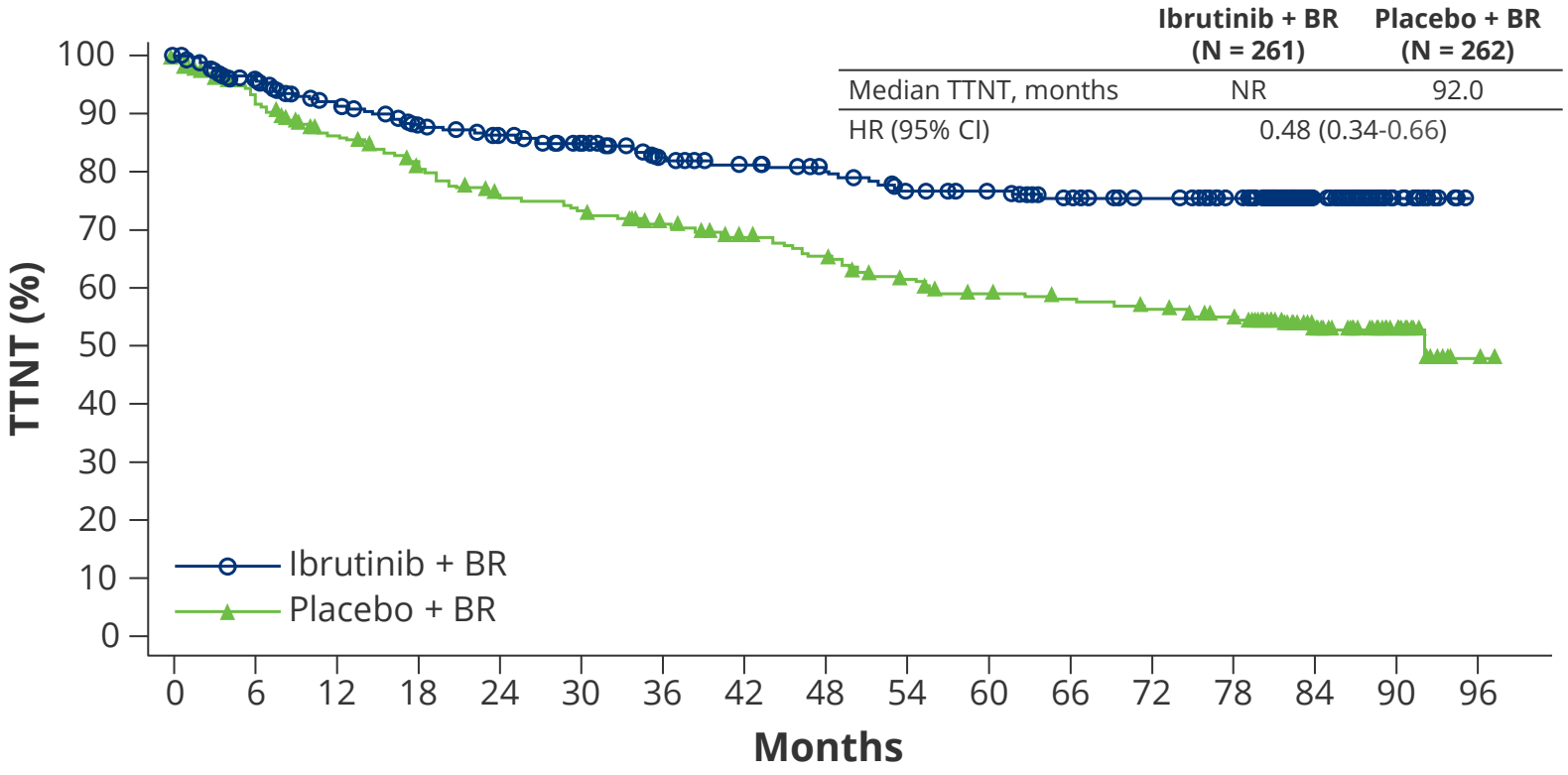
Response Rate



- 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



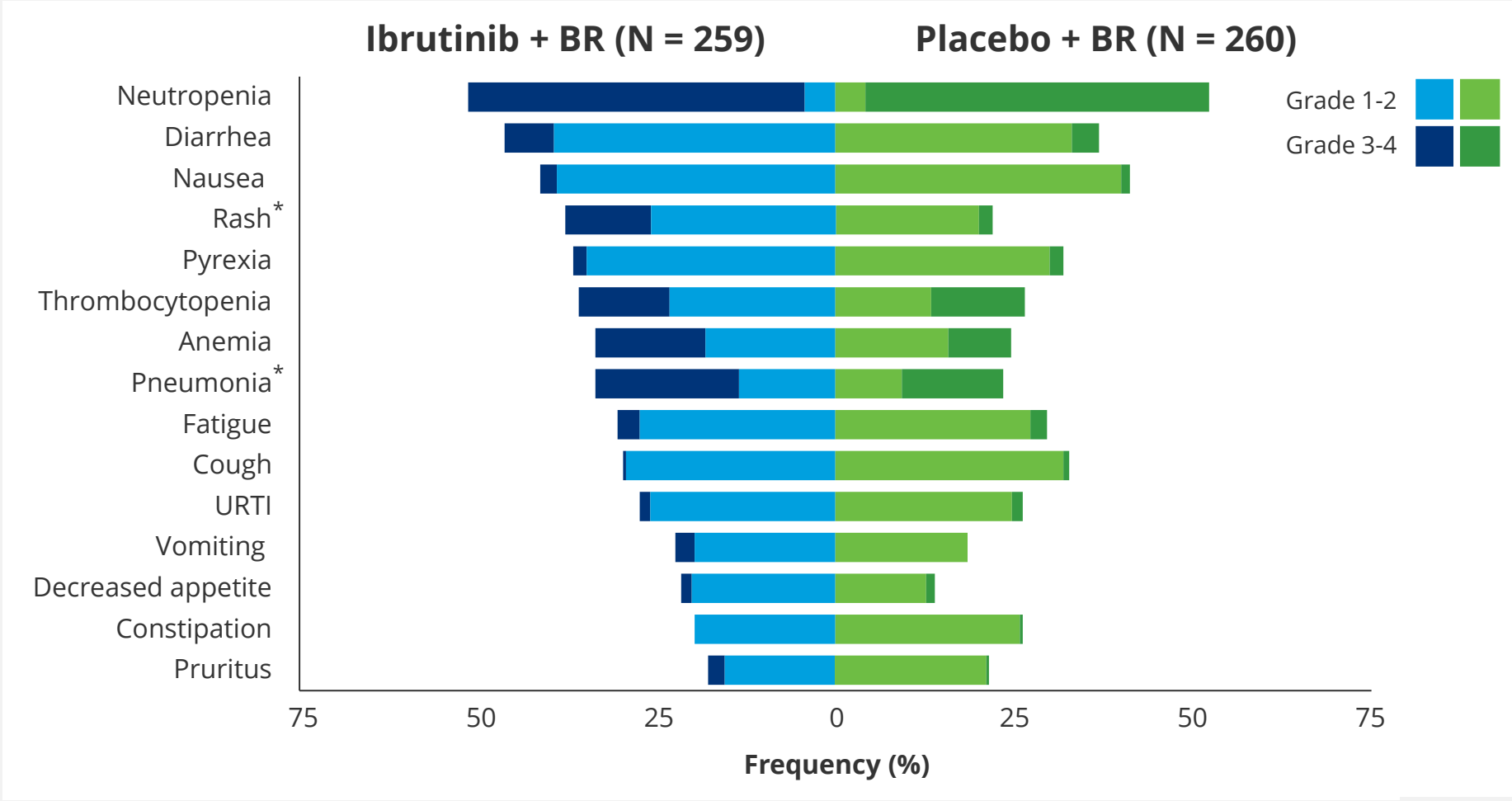
Patients at Risk

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.

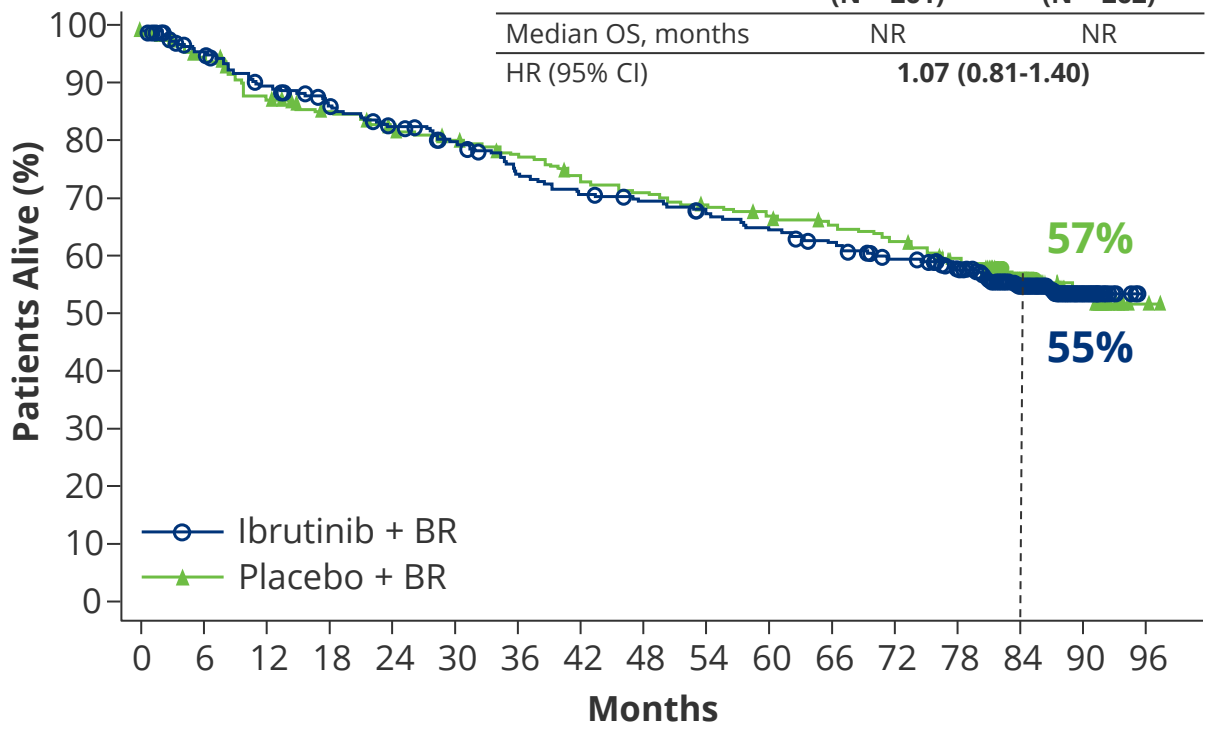
TEAEs of Clinical Interest With BTKis

	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.

Discussion points : SHINE

1. Practice changing?

Thank You!

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