Efficacy and Safety of Ibrutinib Plus Venetoclax in Patients With Mantle Cell Lymphoma and *TP53* Mutations in the SYMPATICO Study

Michael Wang, MD[1], Wojciech Jurczak, MD, PhD[2], Marek Trneny, MD[3], David Belada, MD[4], Tomasz Wrobel, MD, PhD[5], Nilanjan Ghosh, MD, PhD[6], Mary-Margaret Keating, MD[7], Tom van Meerten, MD, PhD[8], Ruben Fernandez Alvarez, MD[9], Gottfried von Keudell, MD, PhD[10], Catherine Thieblemont, MD, PhD[11], Frederic Peyrade, MD[12], Marc Andre, MD[13], Marc Hoffmann, MD[14], Maoko Naganuma, MSc[15], Edith Szafer-Glusman, PhD[15], Jennifer Lin, MS, MA[15], James P. Dean, MD, PhD[15], Jutta K. Neuenburg, MD, PhD[15], Constantine S. Tam, MD, MBBS[16]

[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland; [3]General University Hospital in Prague, Prague, Czech Republic; [4]4th Department of Internal Medicine - Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [5]Wrocław Medical University, Wrocław, Poland; [6]Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [7]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [8]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [9]Hospital Universitario de Cabueñes, Asturias, Spain; [10]Beth Israel Deaconess Medical Center, Boston, MA, USA; [11]Université de Paris, Assistance Publique-Hôpitaux de Paris, Hôpital Saint-Louis, service d'hémato-oncologie, Paris, France; [12]Centre Antoine Lacassagne, Nice, France; [13]CHU UCL Namur Mont-Godinne, Yvoir, Belgium; [14]University of Kansas Cancer Center, Westwood, KS, USA; [15]AbbVie, North Chicago, IL, USA; [16]Peter MacCallum Cancer Centre, Alfred Health and Monash University, Melbourne, Victoria, Australia

Presented by M Wang at the 2024 ASCO Annual Meeting; May 31-June 4, 2024; Chicago, IL, USA

Ibrutinib and Venetoclax Work Synergistically Through Distinct and Complementary Modes of Action

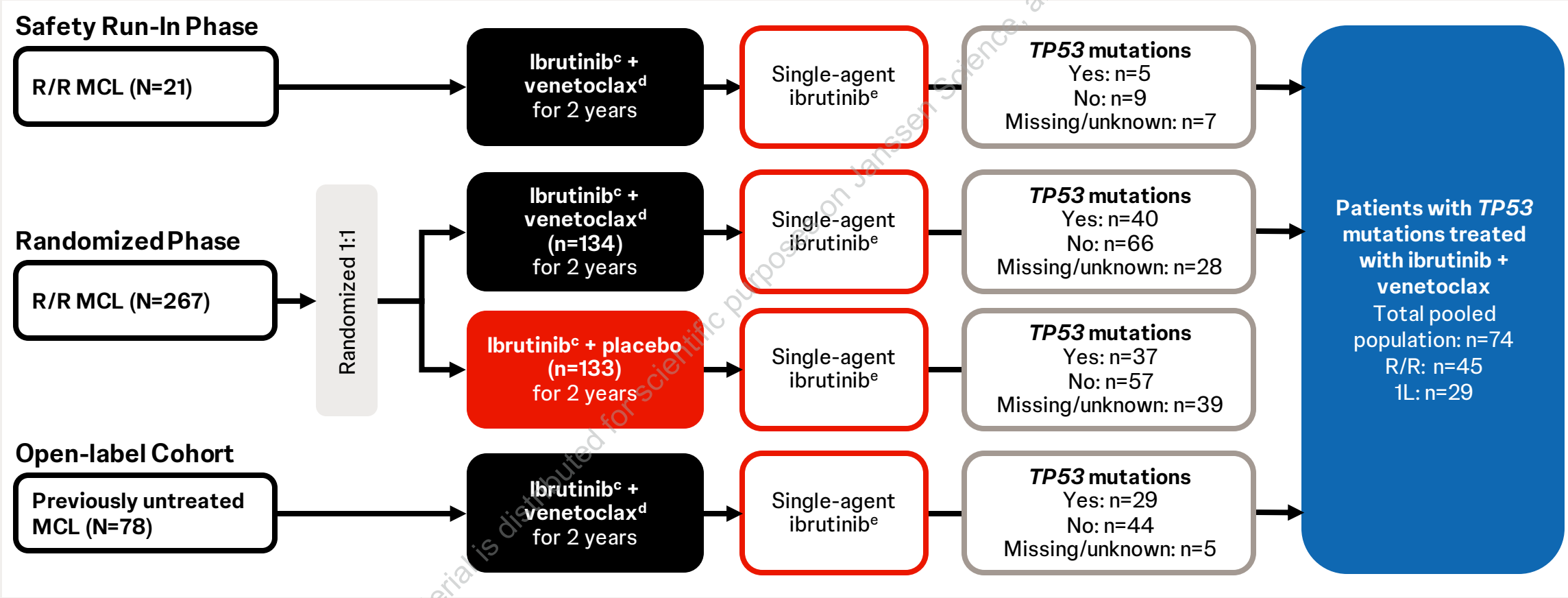
- MCL is a subtype of non-Hodgkin lymphoma that has an aggressive clinical course and a poor prognosis[1]
- The combination of ibrutinib, a once-daily oral BTK inhibitor, and venetoclax, a once-daily oral BCL-2 inhibitor, leverages complementary modes of action and has demonstrated synergistic antitumor activity in preclinical models of MCL[2,3]
- *TP53* mutations occur in 15-20% of patients with MCL[4,5] and confer high risk of early progressive disease (PD) and poor outcomes with standard chemoimmunotherapy[6]
  - To date, data on novel treatment options for these patients are limited to small single-arm analyses[6]
- The phase 3 SYMPATICO study is evaluating ibrutinib + venetoclax in 3 cohorts of patients with MCL
  - Primary analysis of the randomized phase showed superior PFS with ibrutinib + venetoclax compared with ibrutinib + placebo in patients with R/R MCL[7]
- Here, we report efficacy and safety of ibrutinib + venetoclax in 74 patients with *TP53* mutations across cohorts in the SYMPATICO study which demonstrates:
  - Ibrutinib + venetoclax demonstrated promising efficacy with high CR rates and durable remissions in patients with MCL and *TP53* mutations
  - The safety profile of ibrutinib + venetoclax in patients with *TP53* mutations was consistent with the safety profile in the overall study and with the known safety profile of each agent

BCL-2, B cell lymphoma 2; BTK, Bruton tyrosine kinase; MCL, mantle cell lymphoma; PFS, progression-free survival; R/R, relapsed/refractory.

[1]Armitage JO and Longo DL. *N Engl J Med*. 2022;386:2495-2506. [2]Zhao X et al. *Br J Haematol*. 2015;168:757-768. [3]Portell CA et al. *Blood*. 2014;124:509. [4]Xu-Monette ZY et al. *Blood*. 2012;119:3668-3683. [5]Cheung K-JJ et al. *Br J Haematol*. 2009;146:257-269. [6]Lew TE et al. *Lancet Haematol*. 2023;10:e142-e154. [7]Wang M et al. Presented at: 65th ASH Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA, USA.

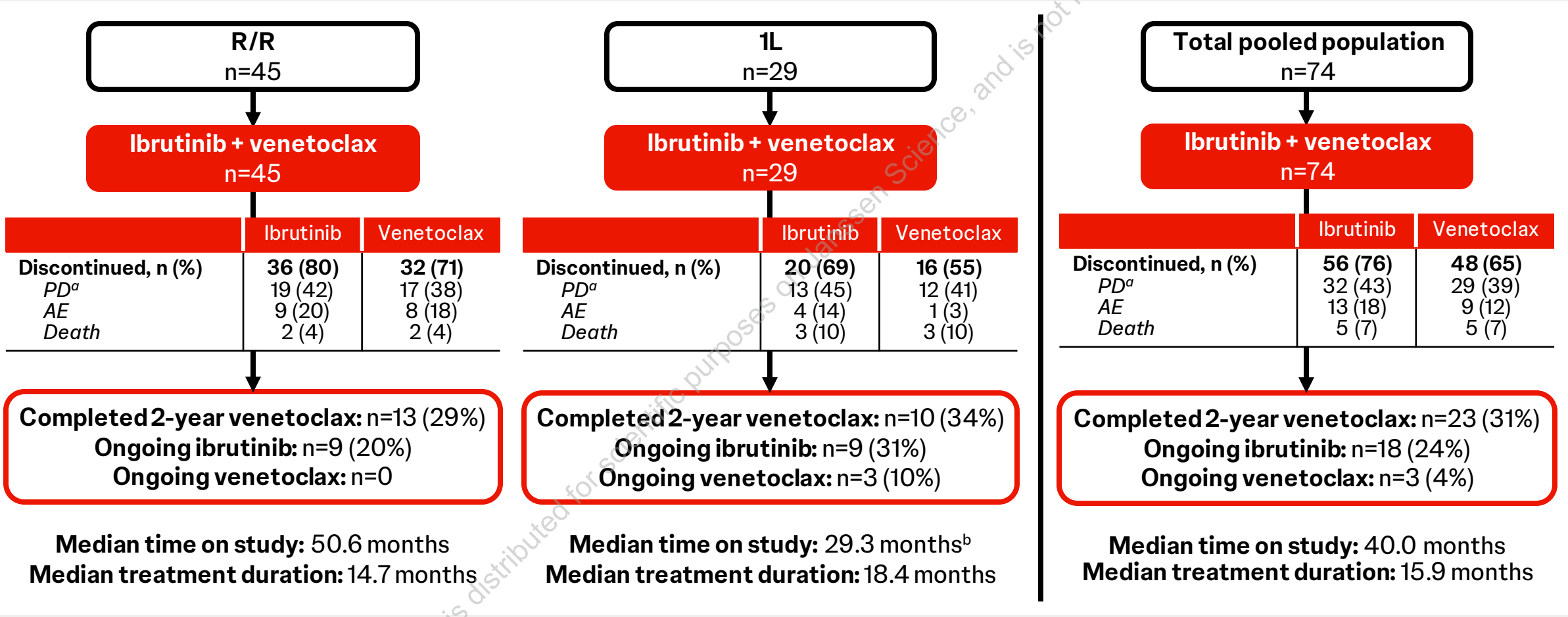
SYMPATICO Study Design

- SYMPATICO[a] is a multinational, randomized, double-blind, placebo-controlled, Phase 3 study
- Data were pooled (3 cohorts) for patients with *TP53* mutations (no deletions)[b] treated with ibrutinib + venetoclax



1L, first-line.
[a]NCT03112174. [b]Somatic mutations in exons 1–11 of *TP53* were evaluated by next-generation sequencing with a variant allele fraction cutoff of 2%. [c]560 mg once daily. [d]5-week ramp-up to 400 mg once daily. [e]560 mg once daily until PD or unacceptable toxicity.

Disposition of Patients With *TP53* Mutations Treated With Ibrutinib + Venetoclax



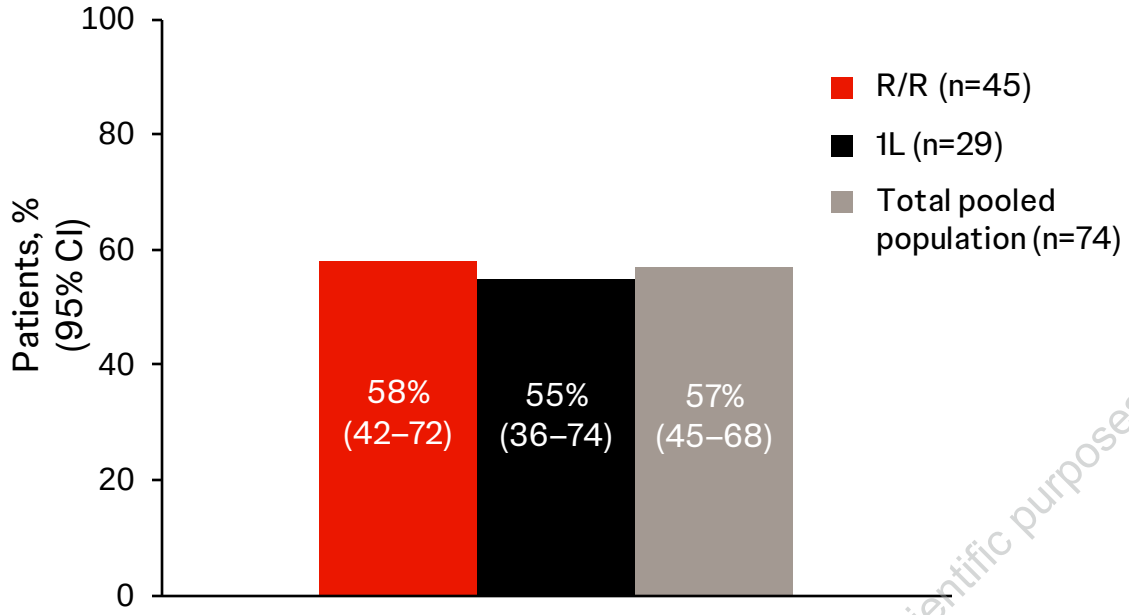
AE, adverse event. [a]PD per protocol criteria or clinical PD. [b]Enrollment in the 1L open-label cohort began after completion of enrollment in the safety run-in and randomization phases.

Baseline Characteristics of Patients With *TP53* Mutations Treated With Ibrutinib + Venetoclax

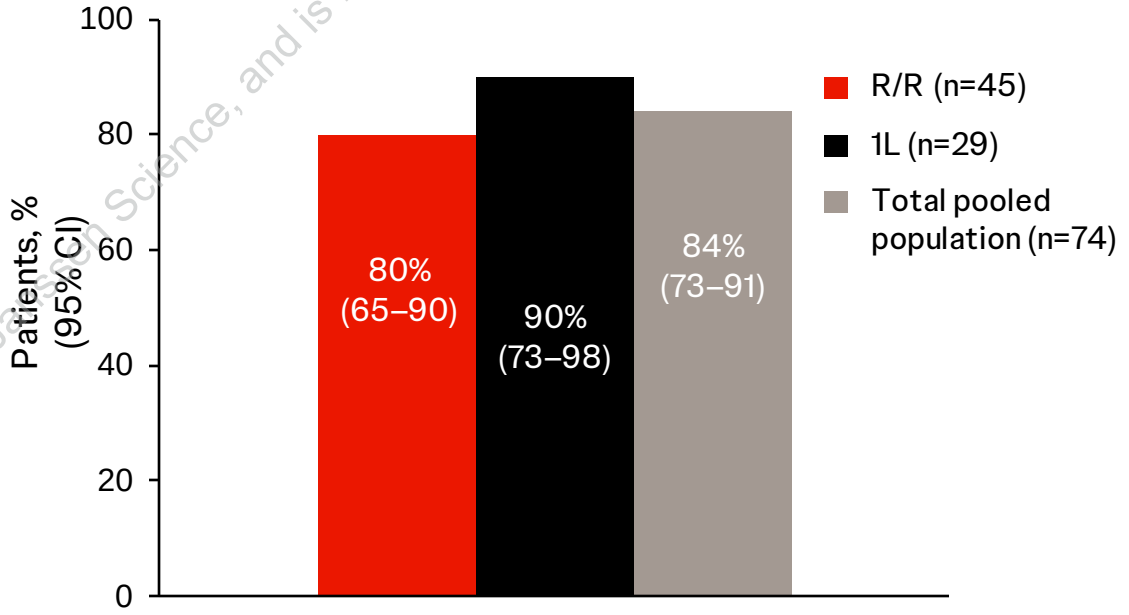
Characteristic	R/R n=45	1L n=29	Total pooled population n=74
Age			
Median (range), years	67 (44–82)	66 (41–79)	67 (41–82)
≥65 years, n (%)	28 (62)	18 (62)	46 (62)
ECOG PS, n (%)			
0	25 (56)	15 (52)	40 (54)
1–2	20 (44)	14 (48)	34 (46)
MCL histology, n (%)			
Typical	29 (64)	18 (62)	47 (64)
Blastoid	8 (18)	0	8 (11)
Pleomorphic	3 (7)	5 (17)	8 (11)
Other	5 (11)	6 (21)	11 (15)
Simplified MIPI score, n (%)			
Low risk	7 (16)	5 (17)	12 (16)
Intermediate risk	15 (33)	13 (45)	28 (38)
High risk	21 (47)	11 (38)	32 (43)
Missing	2 (4)	0	2 (3)
Bulky disease, n (%)			
≥5 cm	18 (40)	9 (31)	27 (36)
≥10 cm	3 (7)	3 (10)	6 (8)
Extranodal disease, n (%)	24 (53)	13 (45)	37 (50)
BM involvement, n (%)	22 (49)	25 (86)	47 (64)
Splenomegaly, n (%)	16 (36)	13 (45)	29 (39)

BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group performance status; MIPI, MCL International Prognostic Index.

Ibrutinib + Venetoclax Provided High CR Rates and Durable Remissions in Patients with *TP53* Mutations



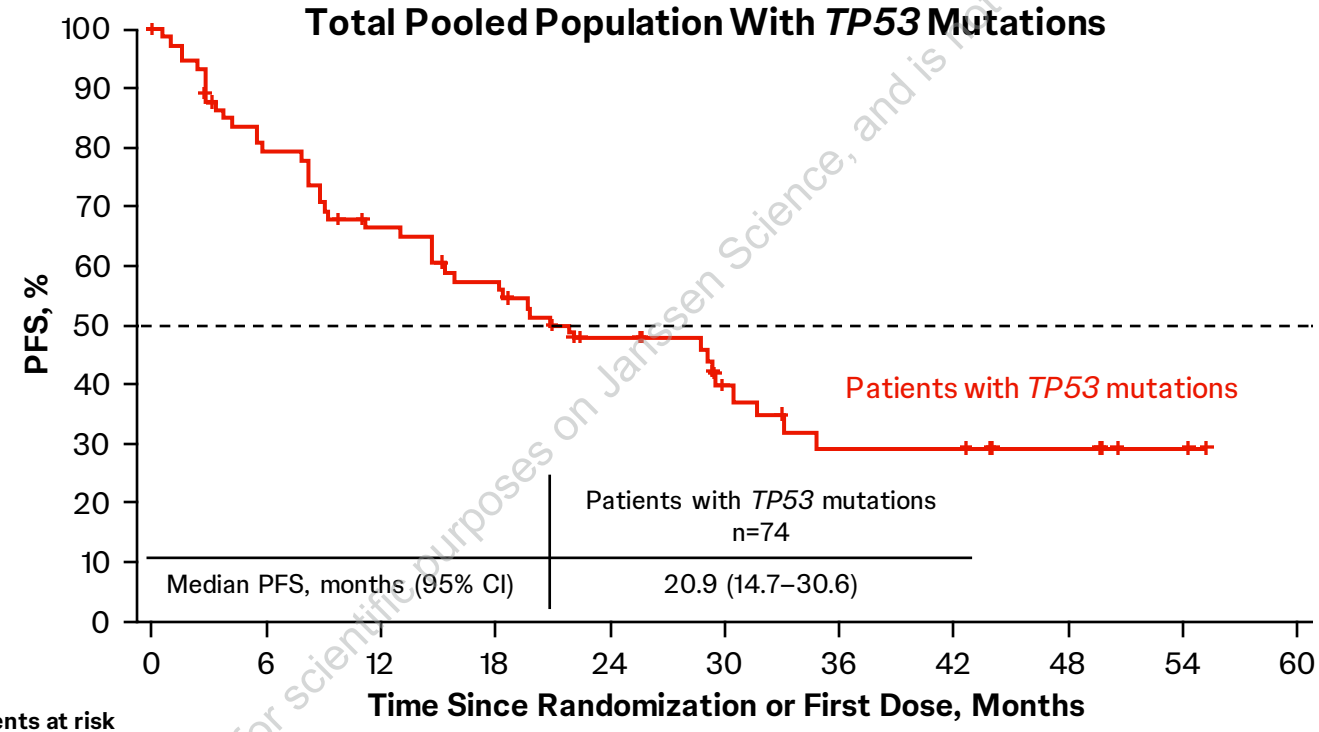
	R/R n=26	1L n=16	Total n=42
Median DOCR, months (95% CI)	NR (18.7–NE)	20.5 (5.4–NE)	32.2 (18.7–NE)



	R/R n=36	1L n=26	Total n=62
Median DOR, months (95% CI)	26.5 (16.8–NE)	20.5 (12.0–NE)	26.0 (16.8–32.2)

CR, complete response; DOCR, duration of complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate.

Ibrutinib + Venetoclax Provided Encouraging PFS in Patients With *TP53* Mutations

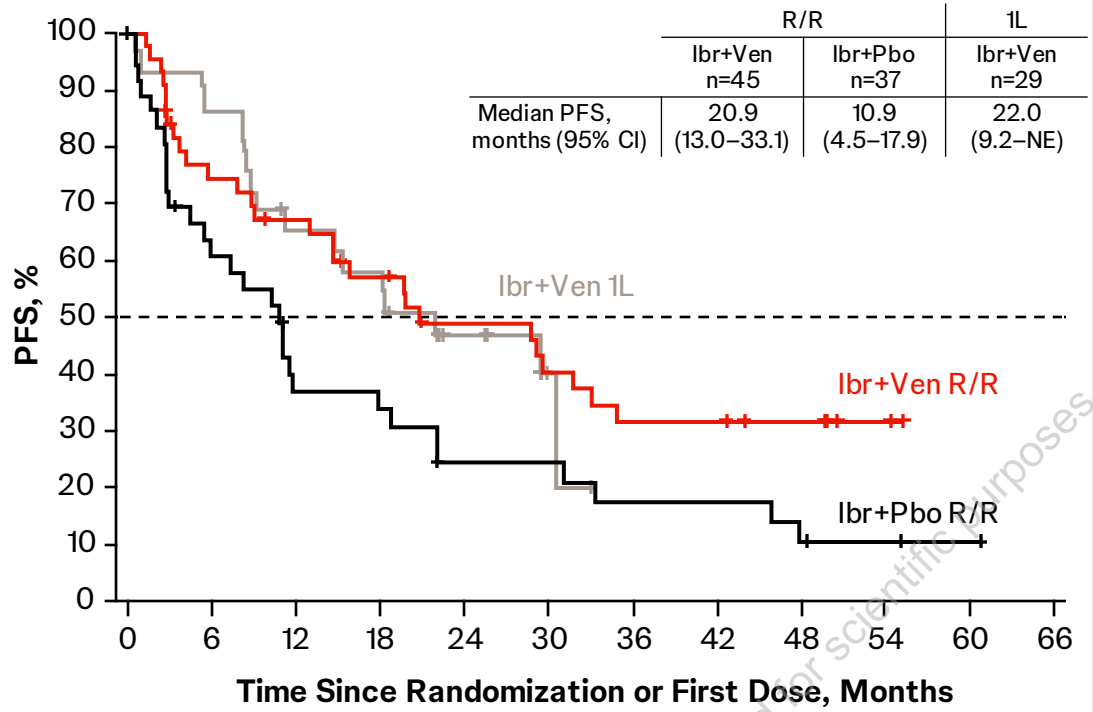


Setting	Regimen	n	PFS
R/R	Ibrutinib + zilovertamab[1] Ibrutinib + venetoclax[2] Venetoclax[3]	7 11 NA	Median 17.3 months Median 5 months Median 3.2 months
1L	Zanubrutinib + venetoclax + obinutuzumab[4]	25	16-month rate: 75%

[1]Lee HJ, et al. *Blood*. 2023; 142(Suppl 1):566-568. [2]Handunnetti SM, et al. *Blood*. 2024:blood.2023023388. [3]Eyre T et al. *Haematologica*. 2019;104:e68-e71. [4]Kumar A et al. *Blood*. 2023; 142 (Suppl 1):738-738.

PFS Benefit Was Observed With Ibrutinib + Venetoclax in Patients With and Without *TP53* Mutations

Patients With *TP53* Mutations

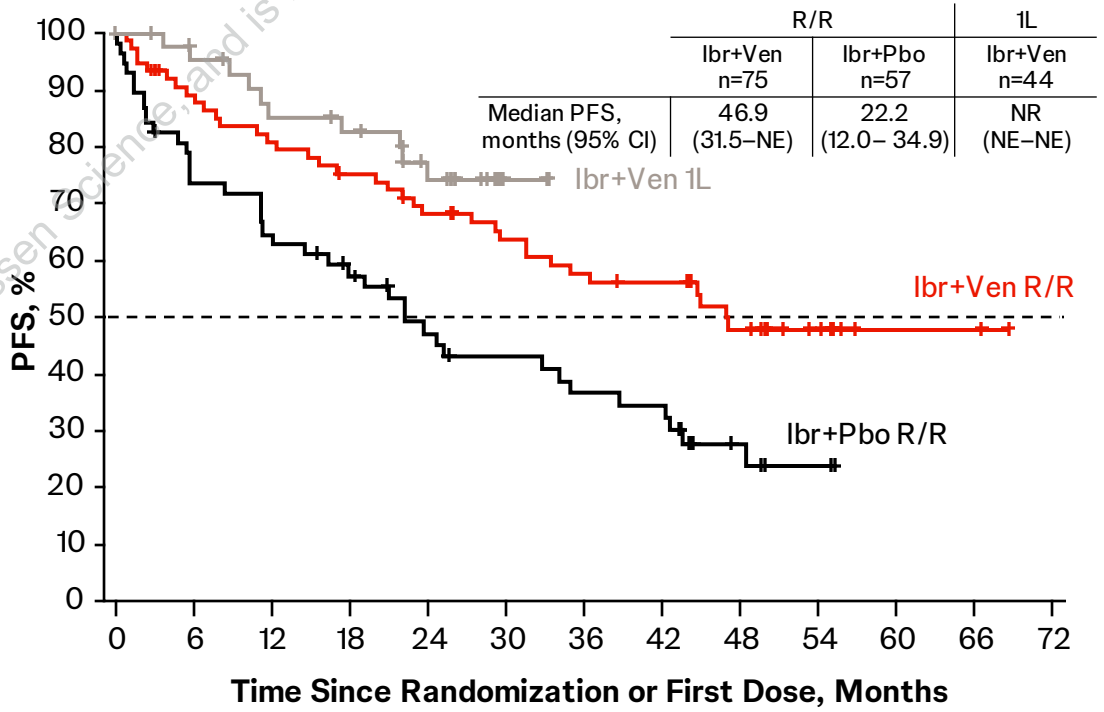


	R/R		1L
	Ibr+Ven n=45	Ibr+Pbo n=37	Ibr+Ven n=29
Median PFS, months (95% CI)	20.9 (13.0–33.1)	10.9 (4.5–17.9)	22.0 (9.2–NE)

Patients at risk

Ibr+Ven R/R	45	31	27	22	17	14	11	11	7	2	0	0
Ibr+Pbo R/R	37	21	12	11	7	7	5	5	3	2	1	0
Ibr+Ven 1L	29	25	18	16	9	2	0	0	0	0	0	0

Patients Without *TP53* Mutations

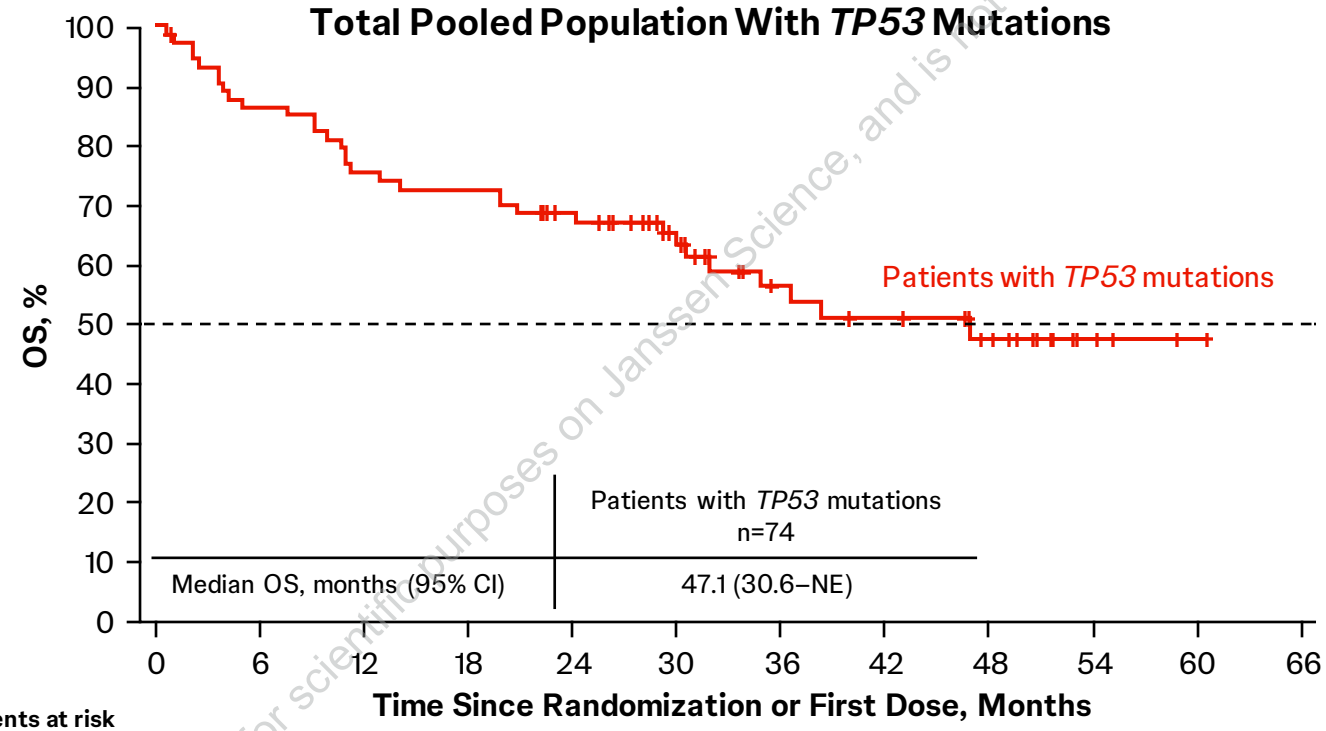


	R/R		1L
	Ibr+Ven n=75	Ibr+Pbo n=57	Ibr+Ven n=44
Median PFS, months (95% CI)	46.9 (31.5–NE)	22.2 (12.0– 34.9)	NR (NE–NE)

Ibr+Ven R/R	75	64	58	53	47	42	38	36	23	11	2	2	0
Ibr+Pbo R/R	57	41	36	30	23	20	17	16	7	3	0	0	0
Ibr+Ven 1L	44	39	34	32	26	5	0	0	0	0	0	0	0

Ibr, ibrutinib; NR, not reached; Pbo, placebo; Ven, venetoclax.

Ibrutinib + Venetoclax Provided Encouraging OS in Patients With *TP53* Mutations



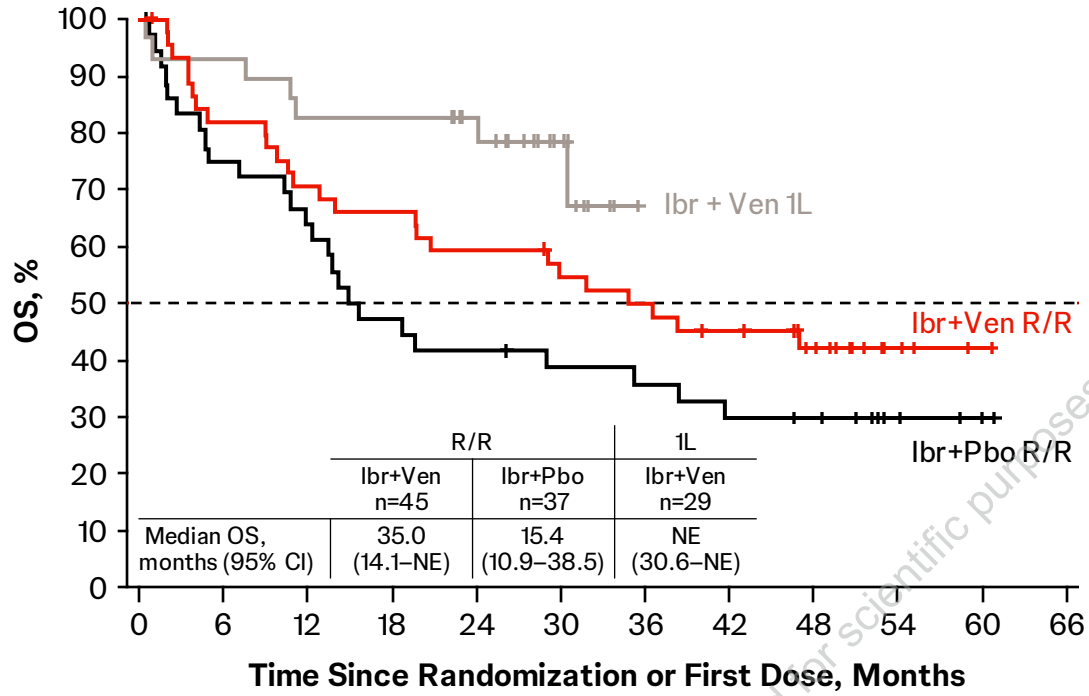
Setting	Regimen	n	OS
R/R	Ibrutinib + venetoclax[1] Venetoclax[2]	11 NA	Median 1.28 years Median 9.4 months
1L	Zanubrutinib + venetoclax + obinutuzumab[3]	25	16-month rate: 87%

NA, not available; OS, overall survival.

[1]Handunnetti SM (personal communication, May 21, 2024). [2]Eyre T et al. *Haematologica*. 2019;104:e68-e71. [3]Kumar A et al. *Blood*. 2023; 142(Suppl 1):738-738.

OS Benefit With Ibrutinib + Venetoclax in Patients With and Without *TP53* Mutations

Patients With *TP53* Mutations

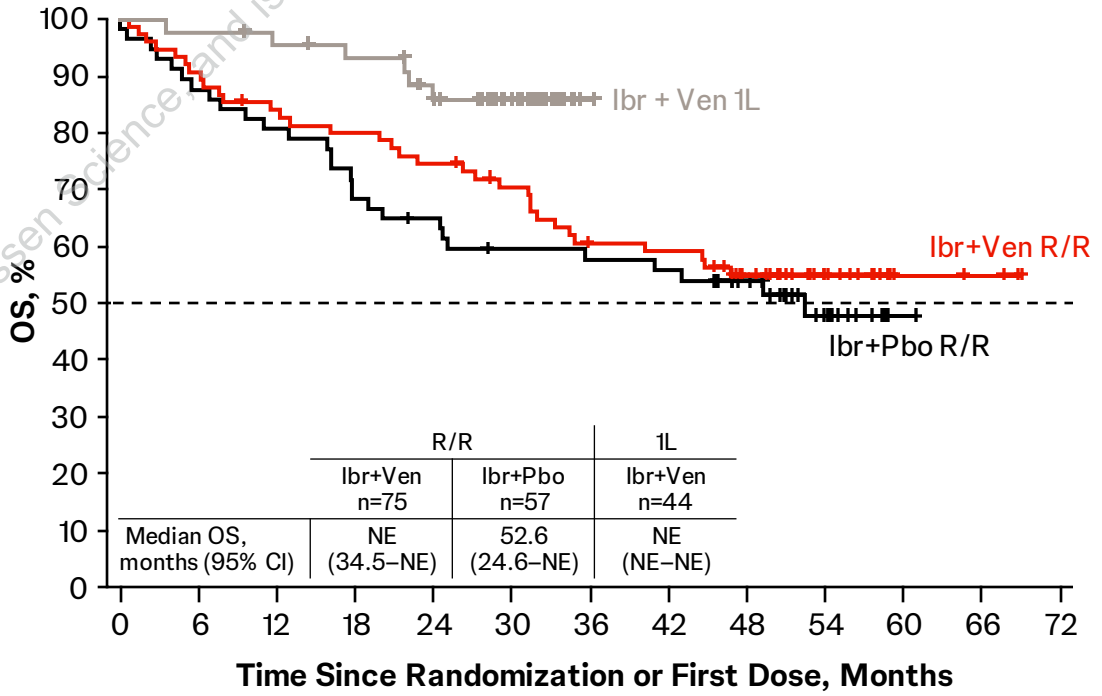


	R/R		1L
	Ibr+Ven n=45	Ibr+Pbo n=37	Ibr+Ven n=29
Median OS, months (95% CI)	35.0 (14.1–NE)	15.4 (10.9–38.5)	NE (30.6–NE)

Patients at risk

Ibr+Ven R/R	45	36	31	29	26	24	21	18	13	5	1	0
Ibr+Pbo R/R	37	27	23	17	15	13	12	10	9	4	2	0
Ibr+Ven 1L	29	27	24	24	19	10	0	0	0	0	0	0

Patients Without *TP53* Mutations

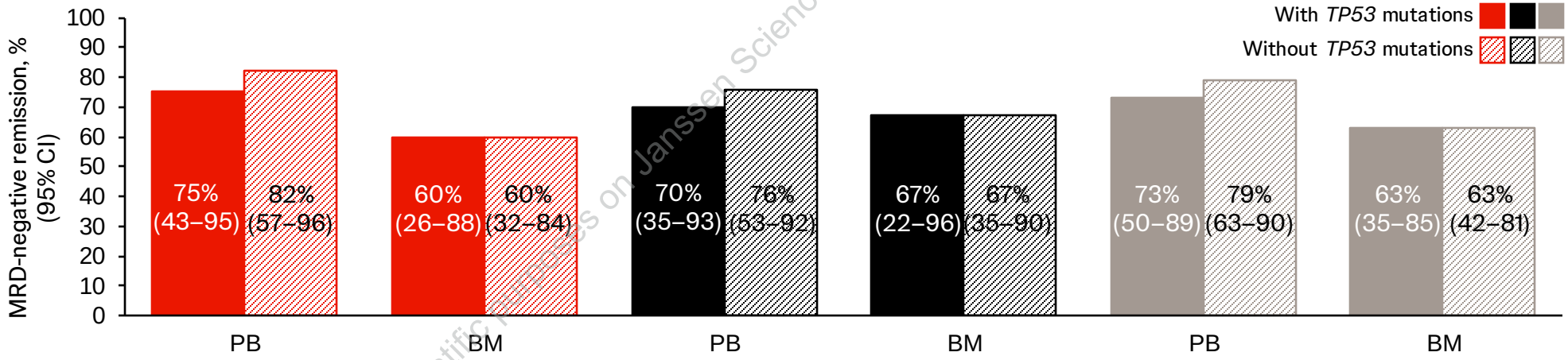


	R/R		1L
	Ibr+Ven n=75	Ibr+Pbo n=57	Ibr+Ven n=44
Median OS, months (95% CI)	NE (34.5–NE)	52.6 (24.6–NE)	NE (NE–NE)

	75	68	62	59	55	50	42	41	29	15	4	3	0
	57	50	46	39	36	32	31	30	24	12	1	0	0
	44	43	41	39	35	23	1	0	0	0	0	0	0

Ibrutinib + Venetoclax Provided High MRD-Negative Remission Rates in Patients With CR Regardless of *TP53* Mutation Status

- At baseline, ~50% had detectable MCL cells in peripheral blood or bone marrow by 8-color flow cytometry
- Among MRD-evaluable patients[a] who achieved a CR, MRD-negative remission rates[b] with ibrutinib + venetoclax were similar for patients with and without *TP53* mutations



Ibrutinib + venetoclax-treated patients who achieved CR	R/R (n=85)				1L (n=54)				Total pooled population (n=139)			
MRD evaluable	PB (n=38)		BM (n=31)		PB (n=34)		BM (n=22)		PB (n=72)		BM (n=53)	
TP53 mutations	With	Without	With	Without	With	Without	With	Without	With	Without	With	Without
MRD evaluable, n[a]	12	17	10	15	10	21	6	12	22	38	16	27
MRD-negative remission, %[b]	9 (75)	14 (82)	6 (60)	9 (60)	7 (70)	16 (76)	4 (67)	8 (67)	16 (73)	30 (79)	10 (63)	17 (63)

BM, bone marrow; MRD, minimal residual disease; PB, peripheral blood. Threshold for MRD negativity of <0.05% MCL cells.
[a]Positive at baseline and post-baseline sample available. [b]MRD-negative remission was defined as MRD negative at documented CR and at confirmatory sample collected 12 weeks later.

Safety in Patients With *TP53* Mutations was Consistent With Known Safety Profiles of Ibrutinib and Venetoclax

AE, n (%)	R/R n=45	1L n=29	Total n=74
Grade ≥3 AEs	37 (82)	22 (76)	59 (80)
Serious AEs	26 (58)	15 (52)	41 (55)
AEs leading to discontinuation	15 (33)	7 (24)	22 (30)
Ibrutinib only	4 (9)	3 (10)	7 (9)
Venetoclax only	2 (4)	0	2 (3)
Both	9 (20)	4 (14)	13 (18)
AEs leading to dose reduction	20 (44)	14 (48)	34 (46)
Ibrutinib only	9 (20)	5 (17)	14 (19)
Venetoclax only	6 (13)	3 (10)	9 (12)
Both	5 (11)	6 (21)	11 (15)
AEs leading to death	6 (13)	5 (17)	11 (15)
Ibrutinib related[a]	1 (2)	0	1 (1)
Venetoclax related[a]	0	0	0

AE, n (%)	R/R n=45	1L n=29	Total n=74
Most frequent any-grade AEs[b]			
Diarrhea	34 (76)	15 (52)	49 (66)
Neutropenia	18 (40)	9 (31)	27 (36)
Fatigue	13 (29)	12 (41)	25 (34)
Nausea	16 (36)	9 (31)	25 (34)
Thrombocytopenia	15 (33)	7 (24)	22 (30)
Anemia	13 (29)	8 (28)	21 (28)
COVID-19	7 (16)	11 (38)	18 (24)
Vomiting	9 (20)	8 (28)	17 (23)
Hypomagnesemia	6 (13)	9 (31)	15 (20)
Pyrexia	6 (13)	9 (31)	15 (20)
Most frequent grade ≥3 AEs[c]			
Neutropenia	17 (38)	7 (24)	24 (32)
Anemia	8 (18)	3 (10)	11 (15)
Thrombocytopenia	9 (20)	2 (7)	11 (15)
Tumor lysis syndrome			
Laboratory	2 (4)	3 (10)	5 (7)
Clinical	0	0	0

[a]Per investigator opinion. [b]Occurring in ≥20% of patients in the total population. [c]Occurring in ≥10% of patients in the total population.

Conclusions

- This study represents the largest single-study cohort of patients with MCL and *TP53* mutations reported to date (n=74; R/R, n=45; 1L, n=29)
- Ibrutinib + venetoclax demonstrated promising efficacy with high CR rates and durable remissions in patients with MCL and *TP53* mutations
- The safety profile of ibrutinib + venetoclax in patients with *TP53* mutations was consistent with the safety profile in the overall study and with the known safety profile of each agent
- These results are encouraging in light of the poor responses and shorter survival outcomes with standard chemoimmunotherapy in patients with MCL and *TP53* mutations

https://www.congresshub.com/Oncology/AM2024/Ibrutinib/Wang

AbbVie and the authors thank the patients who participated in the study and their supportive families, as well as the investigators, study coordinators, study team, and nurses who cared for the patients.

AbbVie funded this study and participated in the study design, research, analysis, data collection, interpretation of data, and the review and approval of the publication. All authors had access to relevant data and participated in the drafting, review, and approval of this publication. No honoraria or payments were made for authorship.

Medical writing support was provided by Melanie Sweetlove, MSc, and funded by AbbVie.