Efficacy and Safety of First-Line Ibrutinib Plus Venetoclax in Patients With Mantle Cell Lymphoma Who Were Older or Had *TP53* Mutations in the SYMPATICO Study

Michael Wang, MD,[1] Marc Hoffmann, MD,[2] Tomasz Wrobel, MD, PhD,[3] Marek Trneny, MD,[4] David Belada, MD,[5] Fatih Demirkan, MD,[6] Panayiotis Panayiotidis, MD, PhD,[7] Wojciech Jurczak, MD, PhD,[8] Pier Luigi Zinzani, MD, PhD,[9] Mary-Margaret Keating, MD,[10] Sung-Soo Yoon, MD, PhD,[11] Miklós Egyed, MD, PhD,[12] Constantine S. Tam, MD, MBBS,[13] Nathalie A. Johnson, MD, PhD,[14] Edith Szafer-Glusman, PhD,[15] Jennifer Lin, MS, MA,[15] James P. Dean, MD, PhD,[15] Jutta K. Neuenburg, MD, PhD,[15] Gottfried von Keudell, MD, PhD[16]

[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]University of Kansas Cancer Center, Westwood, KS, USA; [3]Wrocław Medical University, Wrocław, Poland; [4]General University Hospital in Prague, Prague, Czech Republic; [5]4th Department of Internal Medicine - Haematology, Charles University, Hospital and Faculty of Medicine, Hradec Králové, Czech Republic; [6]Dokuz Eylul University, Izmir, Turkey; [7]General Hospital of Athens Laiko, Athens, Greece; [8]Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland; [9]University of Bologna, Bologna, Italy; [10]Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada; [11]Seoul National University Hospital, Seoul, South Korea; [12]Somogy County Mór Kaposi General Hospital, Kaposvár, Hungary; [13]Peter MacCallum Cancer Centre, Alfred Health and Monash University, Melbourne, Victoria, Australia; [14]Jewish General Hospital, Montreal, Quebec, Canada; [15]AbbVie, North Chicago, IL, USA; [16]Beth Israel Deaconess Medical Center, Boston, MA, USA

Presented by M Wang at the 2025 ASCO Annual Meeting; May 29–June 2, 2025; Chicago, IL

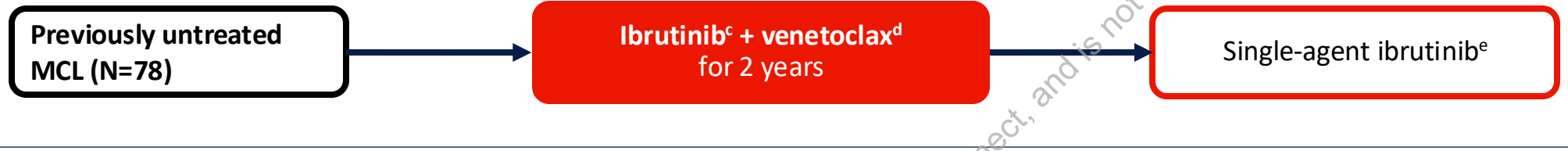
Ibrutinib + Venetoclax Is Effective as First-Line Treatment for MCL With and Without *TP53* Mutations, and in Older Patients (≥65 Years)

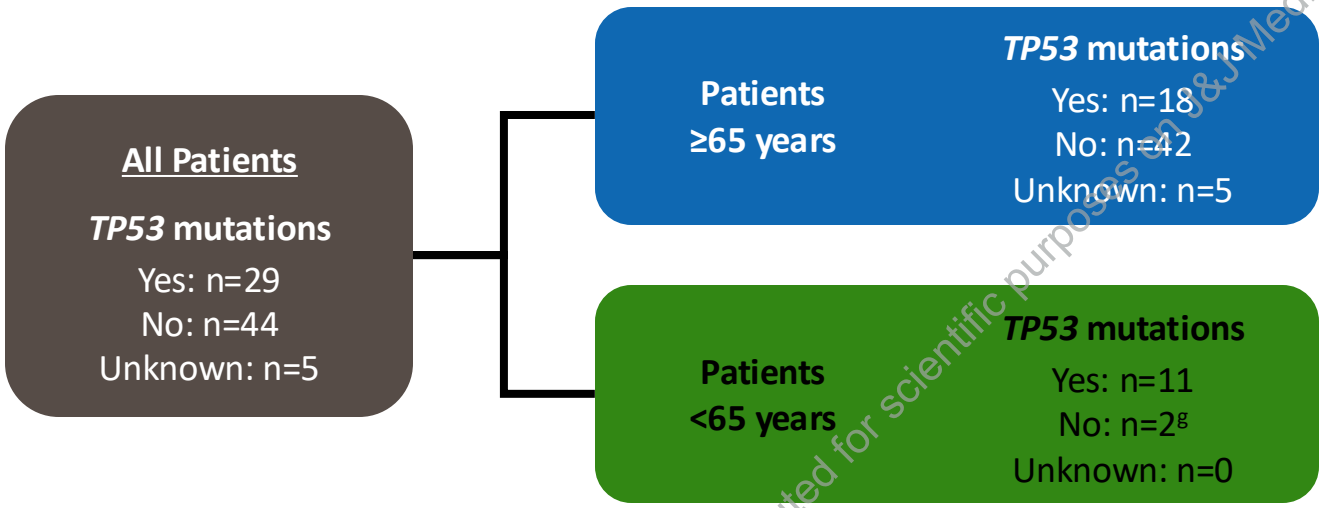
- The combination of ibrutinib, a once-daily oral BTK inhibitor, and venetoclax, a once-daily oral BCL-2 inhibitor, leverages complementary modes of action and has demonstrated synergistic antitumor activity in preclinical models of MCL[1,2]
- *TP53* mutations occur in 15%–20% of patients with MCL[3,4] and confer a high risk of early PD and poor outcomes with chemoimmunotherapy,[5] especially in older patients who are less tolerant of aggressive chemoimmunotherapy
- The phase 3 SYMPATICO study (NCT03112174) evaluated ibrutinib + venetoclax in 2 cohorts of patients with MCL after completion of the open-label safety run-in cohort[6]:
  - Randomization phase primary analysis showed superior PFS with ibrutinib + venetoclax compared with ibrutinib + placebo in patients with R/R MCL (median PFS, 31.9 vs 22.1 months, HR, 0.65)[7]
  - Here, open-label TN cohort efficacy and safety of ibrutinib + venetoclax are reported, including in patients ≥65 years of age and in patients 18–65 years of age with a *TP53* mutation
    - First-line ibrutinib + venetoclax showed promising efficacy, with high CR rates and durable remissions in younger and older patients with TN MCL, including those with and without *TP53* mutations
    - The safety of ibrutinib + venetoclax in patients with TN MCL was consistent with known safety profiles of the individual agents, with lower AE rates in patients <65 years
    - Ibrutinib + venetoclax may be an option for TN MCL patients ≥65 years of age or patients of any age with a *TP53* mutation

BCL-2, B cell lymphoma 2; BTK, Bruton tyrosine kinase; CR, complete response; HR, hazard ratio; MCL, mantle cell lymphoma; PD, progressive disease; PFS, progression-free survival; R/R, relapsed/refractory; TN, treatment-naive.

[1]Zhao X et al. *Br J Haematol*. 2015;168:757–768. [2]Portell CA et al. *Blood*. 2014;124:509. [3]Xu-Monette ZY et al. *Blood*. 2012;119:3668–3683. [4]Cheung K-JJ et al. *Br J Haematol*. 2009;146:257–269.
[5]Lew TE et al. *Lancet Haematol*. 2023;10:e142–e154. [6]Wang M et al. *J Hematol Oncol*. 2021;14:179. [7]Wang M et al. *Lancet Oncol*. 2025;26:200–213.

SYMPATICO[a] Included an Open-Label, Single-Arm Cohort for Patients With TN MCL Who Were Older and/or Had *TP53* Mutations[b]





Treatment Disposition, n (%)	Ibrutinib	Venetoclax
Discontinued	**52 (67)**	**39 (50)**
PD[f]	18 (23)	17 (22)
AE	15 (19)	11 (14)
Ongoing single-agent	**26 (33)**	**0**

- **Median time on study:** 40.5 months (range, 0.6+ to 46.9)
- **Median treatment duration:** 24.0 months (range, 0.3–46.9)

[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. [f]PD per protocol criteria or clinical PD. [g]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.

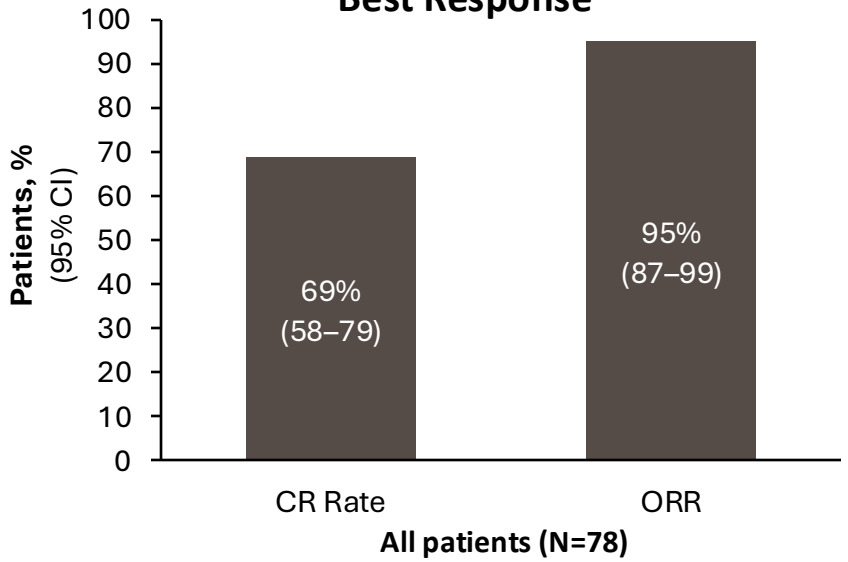
Baseline Characteristics of Patients With TN MCL Treated With Ibrutinib + Venetoclax

Characteristic	All Patients N=78
Age	
Median (range), years	70 (41–86)
≥65 years, n (%)	65 (83)
Sex, n (%)	
Male	53 (68)
Female	25 (32)
MCL histology, n (%)	
Typical	53 (68)
Blastoid	1 (1)
Pleomorphic	6 (8)
Other	18 (23)
sMIPI score, n (%)	
Low risk	6 (8)
Intermediate risk	37 (47)
High risk	35 (45)
Bulky disease, n (%)	
≥5 cm	24 (31)
≥10 cm	5 (6)
Extranodal disease, n (%)	39 (50)
BM involvement, n (%)	61 (78)
Splenomegaly, n (%)	36 (46)
***TP53* mutated, n (%)**	29 (37)

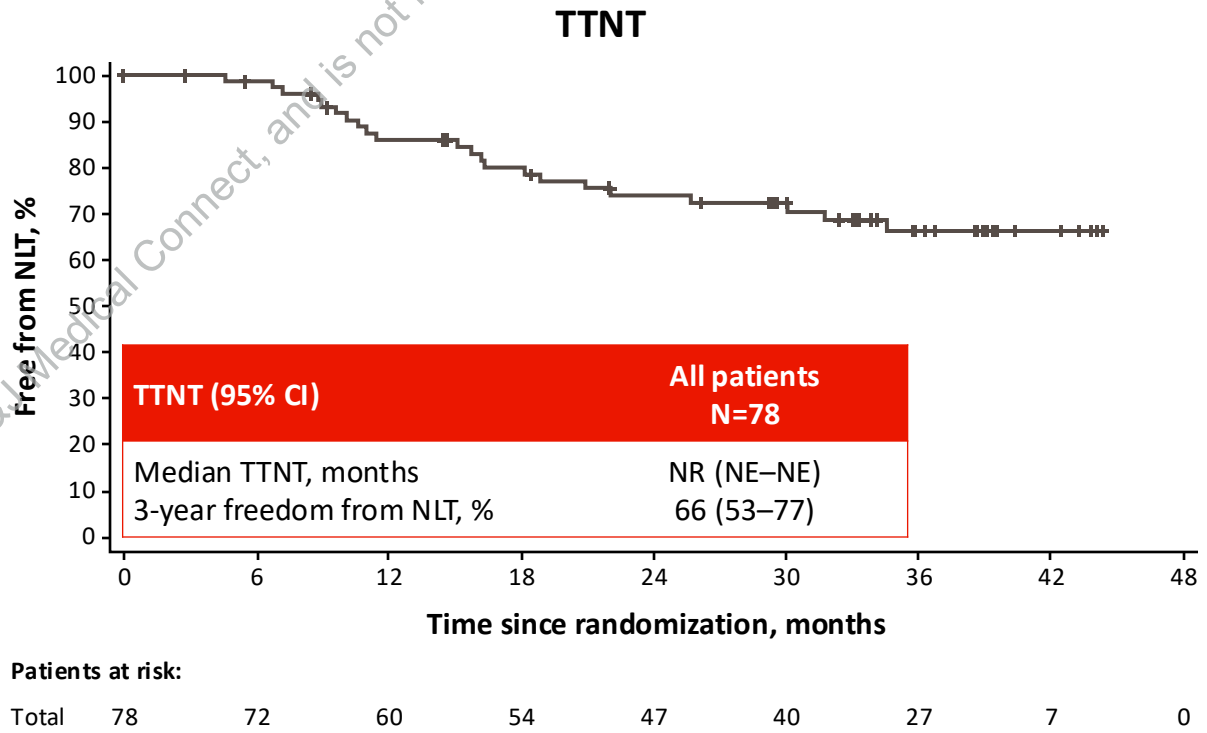
- Most patients (83%) were ≥65 years of age
- A substantial proportion of patients had poor prognostic features, including:
  - *TP53* mutated, 37%
  - High risk by sMIPI, 45%
  - Bulky disease ≥5 cm, 31%
  - Extranodal disease, 50%

BM, bone marrow; sMIPI, simplified MCL International Prognostic Index.

Ibrutinib + Venetoclax Met the Primary Endpoint for CR Rate and Showed Promising ORR and TTNT in Patients With TN MCL



Outcome (95% CI)	DOCR n=54	DOR n=74
Median, months	37.1 (34.0–NE)	37.1 (30.3–NE)



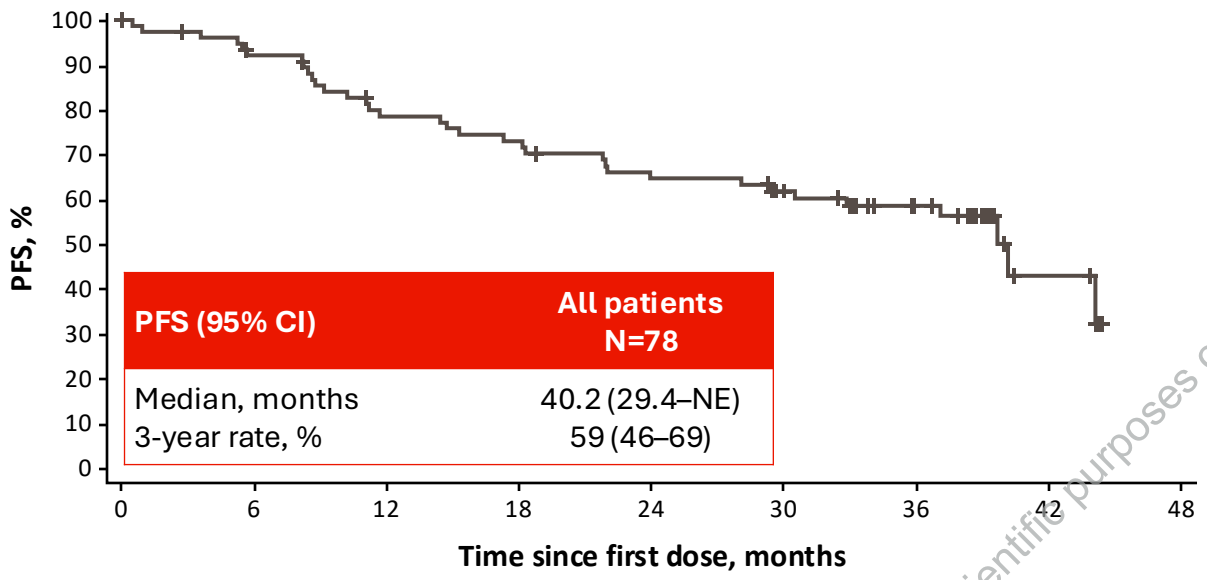
TTNT (95% CI)	All patients N=78
Median TTNT, months	NR (NE–NE)
3-year freedom from NLT, %	66 (53–77)

- Among patients with CR, MRD-negative remission[a] was achieved in:
  - 13 of 22 evaluable patients (59%) in bone marrow
  - 26 of 34 evaluable patients (76%) in peripheral blood

CR, complete response; DOCR, duration of complete response; DOR, duration of response; MRD, minimal residual disease; NE, not estimable; NLT, next line treatment; NR, not reached; ORR, overall response rate; TTNT, time to next treatment.
[a]MCL cells <0.05% by 8-color flow cytometry.

Encouraging PFS and OS were Observed With Ibrutinib + Venetoclax in Patients With TN MCL

PFS

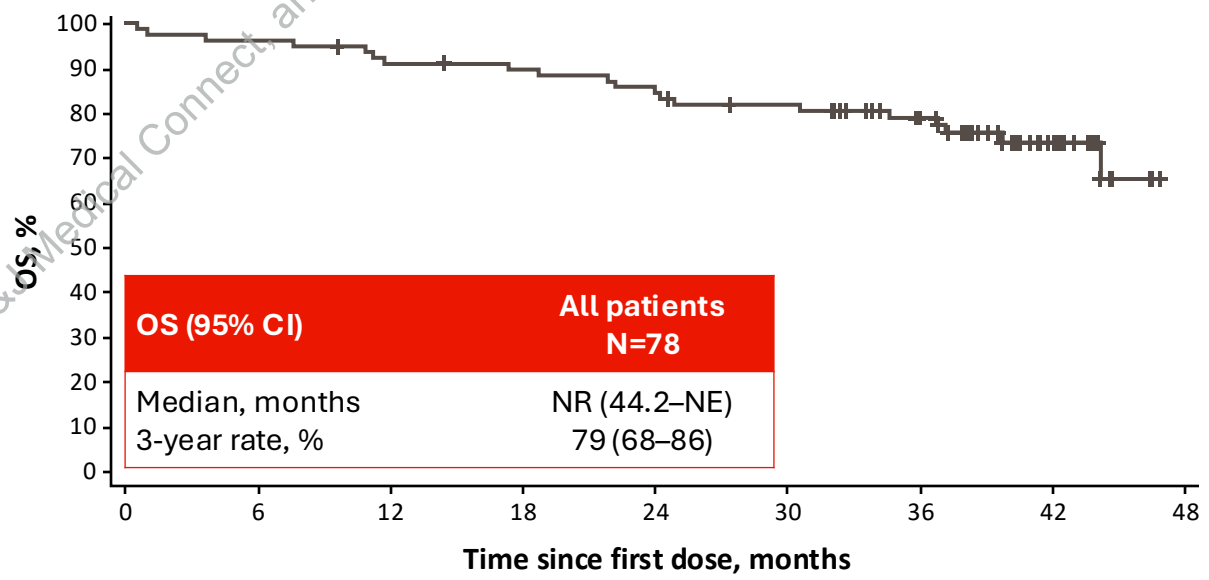


PFS (95% CI)	All patients N=78
Median, months	40.2 (29.4–NE)
3-year rate, %	59 (46–69)

Patients at risk:

Total	78	69	57	53	47	40	27	5	0

OS

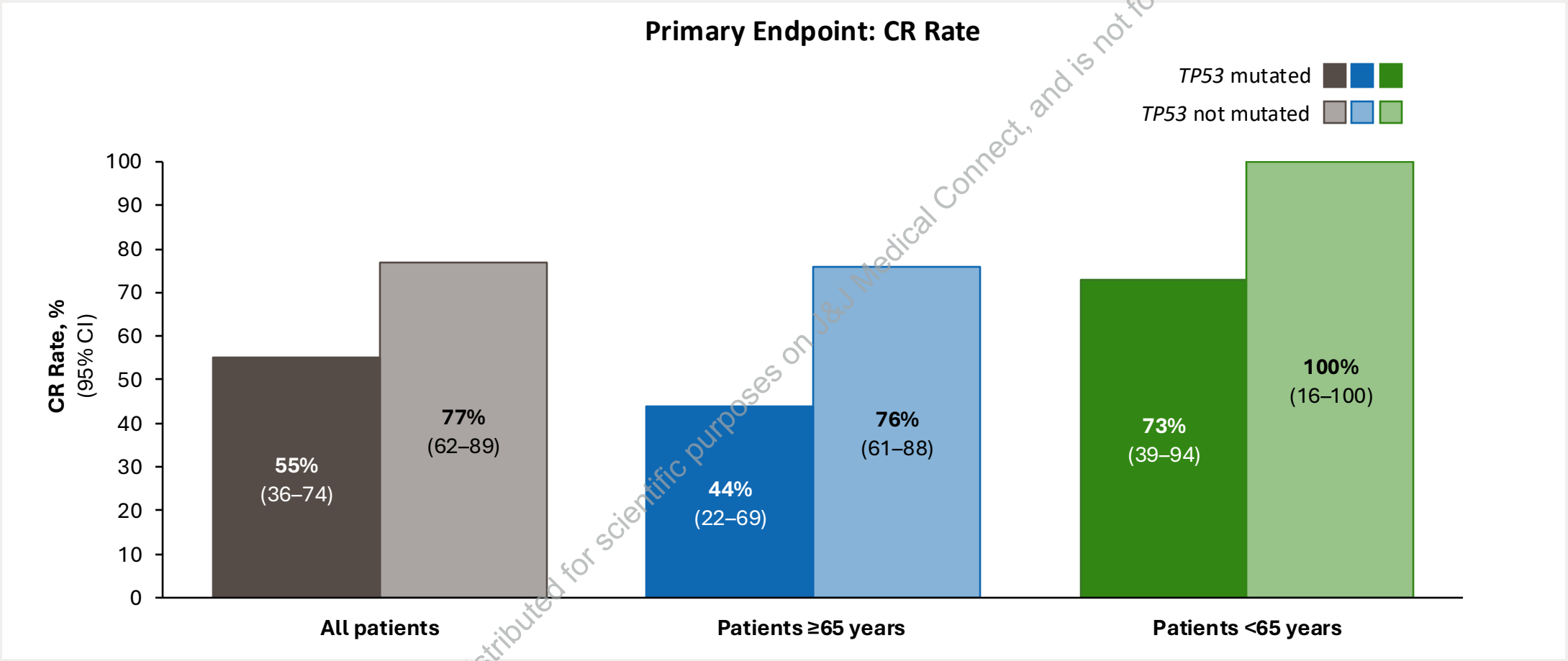


OS (95% CI)	All patients N=78
Median, months	NR (44.2–NE)
3-year rate, %	79 (68–86)

Patients at risk:

Total	78	75	70	68	65	60	50	20	0

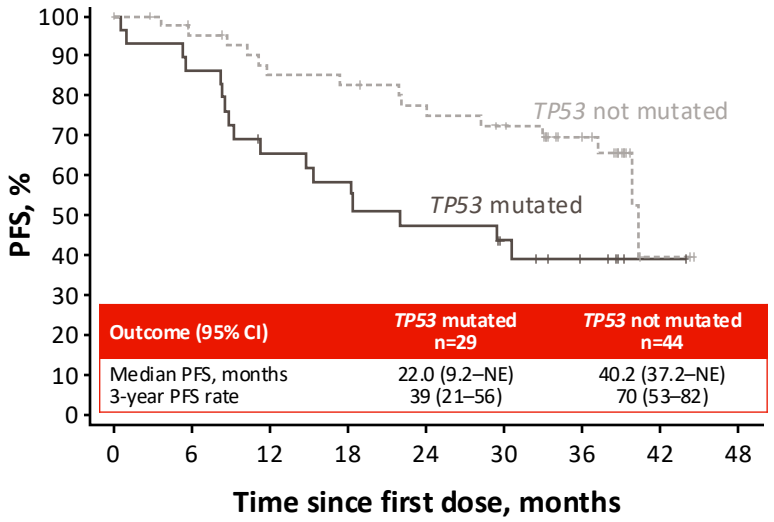
Ibrutinib + Venetoclax Also Improved Response Rates in Patients With *TP53* Mutations Overall and Across Subgroups by Age



[a]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.

Encouraging PFS and OS with Ibrutinib + Venetoclax in Patients With and Without *TP53* Mutations Across Age Subgroups

All Patients

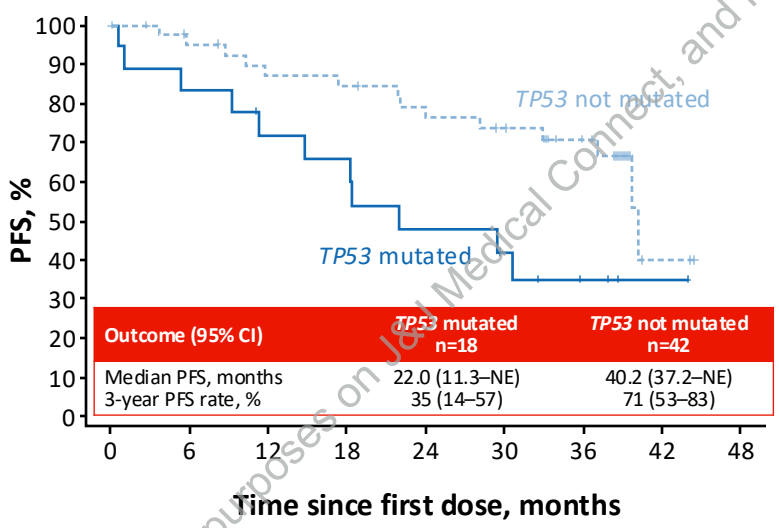


Outcome (95% CI)	*TP53* mutated n=29	*TP53* not mutated n=44
Median PFS, months	22.0 (9.2–NE)	40.2 (37.2–NE)
3-year PFS rate	39 (21–56)	70 (53–82)

Number of patients at risk:

TP53 mutated	29	25	18	16	13	9	5	1	0
TP53 not mutated	44	39	34	33	30	27	18	2	0

Patients ≥65 years

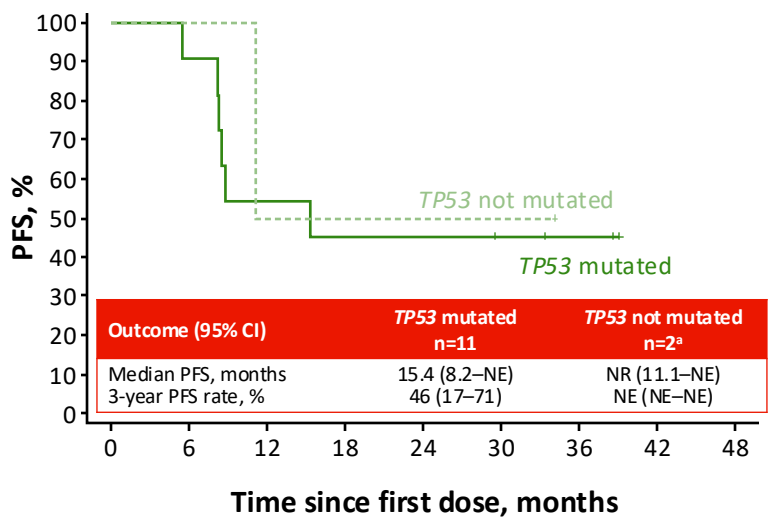


Outcome (95% CI)	*TP53* mutated n=18	*TP53* not mutated n=42
Median PFS, months	22.0 (11.3–NE)	40.2 (37.2–NE)
3-year PFS rate, %	35 (14–57)	71 (53–83)

Number of patients at risk:

TP53 mutated	18	15	12	11	8	6	3	1	0
TP53 not mutated	42	37	33	32	29	26	18	2	0

Patients <65 years



Outcome (95% CI)	*TP53* mutated n=11	*TP53* not mutated n=2[a]
Median PFS, months	15.4 (8.2–NE)	NR (11.1–NE)
3-year PFS rate, %	46 (17–71)	NE (NE–NE)

Number of patients at risk:

TP53 mutated	11	10	6	5	5	3	2	0	0
TP53 not mutated	2	2	1	1	1	1	0	0	0

- 3-year OS rates (95% CI) in all patients
  - *TP53* mutated: 68% (47–82)
  - *TP53* not mutated: 86% (71–93)

- 3-year OS rates (95% CI) in patients ≥65 years
  - *TP53* mutated: 66% (39–83)
  - *TP53* not mutated: 85% (70–93)

- 3-year OS rates (95% CI) in patients <65 years
  - *TP53* mutated: 73% (37–90)
  - *TP53* not mutated: 100% (100–100)

[a]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.

Safety in Patients With TN MCL Was Consistent With Known Safety Profiles of the Individual Agents

AEs, n (%)	All Patients N=78	Patients ≥65 Years n=65	Patients <65 Years n=13
Any TEAE	78 (100)	65 (100)	13 (100)
Grade ≥3 AEs	67 (86)	57 (88)	10 (77)
Serious AEs	46 (59)	40 (62)	6 (46)
AEs leading to death	7 (9)	7 (11)	0
Most frequent any-grade AEs[a]			
Diarrhea	38 (49)	31 (48)	7 (54)
Fatigue	29 (37)	26 (40)	3 (23)
Neutropenia	27 (35)	23 (35)	4 (31)
COVID-19	25 (32)	22 (34)	3 (23)
Nausea	23 (29)	17 (26)	6 (46)
Pyrexia	19 (24)	15 (23)	4 (31)
Anemia	17 (22)	14 (22)	3 (23)
Dizziness	17 (22)	15 (23)	2 (15)
Increased tendency to bruise	17 (22)	16 (25)	1 (8)
Dyspnea	16 (21)	13 (20)	3 (23)
Hypomagnesemia	16 (21)	12 (18)	4 (31)
Hypertension	16 (21)	13 (20)	3 (23)
Myalgia	16 (21)	13 (20)	3 (23)
Vomiting	16 (21)	11 (17)	5 (38)

- Atrial fibrillation occurred in 13 patients (17%), with grade 3/4 events in 4 patients (5%) and no grade 5 events
- Laboratory TLS was reported as a TEAE in 5 patients (6%), all of whom were ≥65 years
- No clinical TLS was observed

TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome.
[a]Occurring in ≥20% of patients in the total population.

Conclusions

Unmet needs persist in patients with MCL, especially in those with

- *TP53* mutations, due to high risk of early PD and poor outcomes with chemoimmunotherapy
- Older age, due to less tolerance of highly efficacious chemoimmunotherapy

First-line ibrutinib + venetoclax showed promising efficacy, with high CR rates and durable remissions in younger and older patients with TN MCL, including those with and without *TP53* mutations

The safety of ibrutinib + venetoclax in patients with TN MCL was consistent with known safety profiles of the individual agents, with lower AE rates in patients <65 years

Ibrutinib + venetoclax may be an option for TN MCL patients ≥65 years of age or patients of any age with a *TP53* mutation

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.

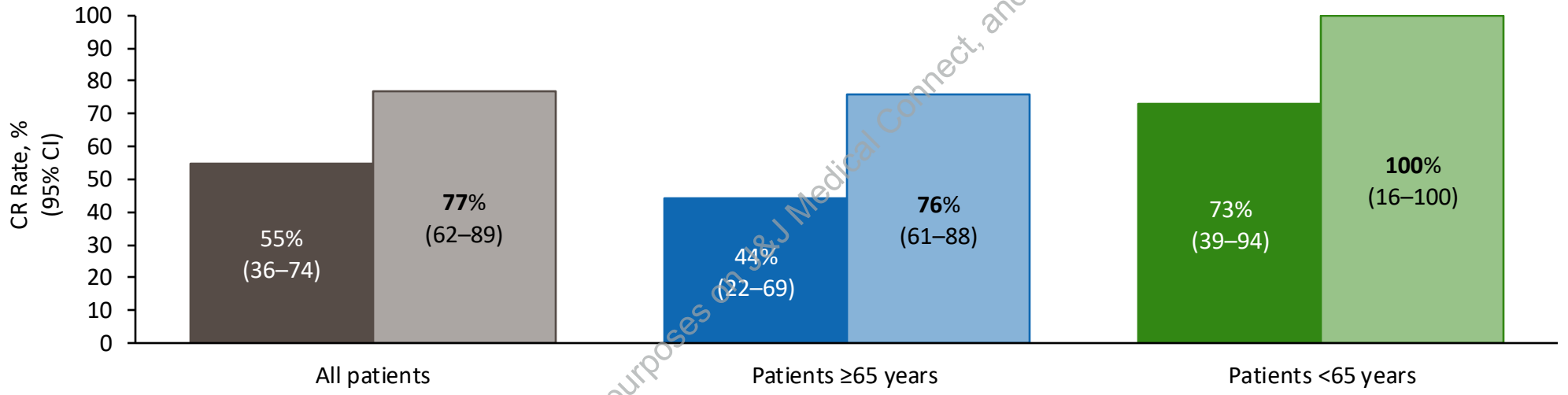
Medical writing support was provided by Melanie Sweetlove, MSc, and funded by AbbVie.

Disclosures

MW: honoraria from Acerta Pharma, Anticancer Association, AstraZeneca, BeiGene, BGICS, BioInvent, CAHON, Chinese Medical Association, Clinical Care Options, Dava Oncology, Eastern Virginia Medical School, Epizyme, Hebei Cancer Prevention Federation, Imedex, Janssen, Kite Pharma LLC, TS Oncology, Miltenyi Biomedicine GmbH, Moffitt Cancer Center, Mumbai Hematology Group, Newsbridge Pharmaceuticals, OMI, OncLive, Physicians Education Resources (PER), Practice Point Communications (PPC), Scripps, The First Afflicted Hospital of Zhejiang University, and Pharmacyclics LLC, an AbbVie Company; consulting/advisory role for AstraZeneca, Bayer Healthcare, BeiGene, BioInvent, CStone, DTRM Biopharma (Cayman) Limited, Epizyme, Genentech, InnoCare, Janssen, Juno Therapeutics, Kite Pharma, Loxo Oncology, Miltenyi Biomedicine GmbH, Oncternal, VelosBio, and Pharmacyclics LLC, an AbbVie Company; research funding fromAcerta Pharma, AstraZeneca, BeiGene, BioInvent, Celgene, Genentech, InnoCare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Molecular Templates, Oncternal, VelosBio, and Pharmacyclics LLC, an AbbVie Company; travel/accommodations/expenses from Physician Education Resources (PER), Kite, Janssen, AstraZeneca, Acerta Pharma, Juno Therapeutics, Celgene, Loxo Oncology, VelosBio, Verastem, Molecular Templates, BioInvent, Oncternal, and Pharmacyclics LLC, an AbbVie Company. MH: honoraria from and consulting/advisory role for AstraZeneca,BeiGene, Janssen, Kite, Novartis, TG Therapeutics, and Pharmacyclics LLC, an AbbVie Company. TW: honoraria from Roche, Takeda, Novartis, Bristol Myers Squibb, Celgene, Janssen-Cilag, BeiGene, Gilead, and Sanofi; consulting/advisory role for Roche, Novartis, Takeda, Celgene, Bristol Myers Squibb, Janssen-Cilag, BeiGene, Pfizer, Gilead, Sanofi, and GlaxoSmithKline; research funding from Roche; speakers bureau for Roche, Novartis, Takeda, Celgene, BMS, Janssen-Cilag, BeiGene, and Sanofi; travel/accommodations/expenses from Gilead, Roche, and Takeda. MT: honoraria from Janssen, Gilead Sciences, Takeda, BMS, Amgen, AbbVie, Roche, MorphoSys, Novartis, SOBI, Swixx BioPharma; consulting/advisory role for Takeda, Bristol Myers Squibb, Incyte, AbbVie, Amgen, Roche, Gilead, Janssen, MorphoSys, Novartis, Genmab, SOBI, Autolus, and Caribou Biosciences; travel/accommodations/expenses from Gilead, Takeda, Bristol Myers Squibb, Roche, Janssen, AbbVie, and SOBI. DB: consulting/advisory role for Roche, Takeda, Janssen-Cilag, Gilead, and Novartis; research funding from Roche, Janssen-Cilag, Genma, and MorphoSys; travel/ accommodations/expenses from Roche, Takeda, and Gilead. FD: nothing to disclose. PP: honoraria from AbbVie, Janssen, Novartis, Gilead, and Genesis Pharma; research funding from AbbVie, Roche, Novartis, and Genesis Pharma. WJ: consulting/advisory role for AstraZeneca, BeiGene, Janssen, Loxo Oncology, Sandoz, and Roche; research funding from AbbVie, AstraZeneca, Bayer, BeiGene, Celtrion, Celgene, Debiopharm, Epizyme, Incyte, Janssen, Loxo Oncology, Merck, Mei Pharma, MorphoSys, Novo Nordisk, Roche, Sandoz, Takeda, and TG Therapeutics. PLZ: consulting/advisory role for ADC Therapeutics, AstraZeneca, BeiGene, BMS, Incyte, Janssen, Kite-Gilead, Kyowa Kirin, MSD, Novartis, Recordati, Roche, Secura Bio, Servier, Sobi, and Takeda; speakers bureau for AstraZeneca, BeiGene, BMS, Incyte, Janssen, Kite-Gilead, Kyowa Kirin, MSD, Novartis, Recordati, Roche, Servier, Sobi, and Takeda. MMK: consulting/advisory role for AbbVie, AstraZeneca, BeiGene, Eli Lilly, and Roche. SSY: honoraria from Novartis, Celgene, and Janssen; consulting/advisory role for Amgen, Antengene, Novartis, Janssen, Regeneron, Takeda, and Sanofi; research funding from Roche/Genentech, Kyowa Kirin, Yuhan, JW Pharmaceutical Corporation, and Chong Kun Dang Pharmaceutical Corp. ME: nothing to disclose. CST: honoraria from Janssen, AbbVie, LOXO, and BeiGene; research funding from Janssen, AbbVie, and BeiGene. NAJ: consulting/advisory role for Roche/Genentech, AbbVie, Gilead, AstraZeneca, BeiGene, Incyte, and Lilly;
honoraria from AbbVie, Incyte, and AstraZeneca; research funding from Gilead, Incyte, and Roche. ESG, JL, JPD, and JKN: employment and stock with AbbVie. GvK: honoraria from and consulting/advisory role for AbbVie, Incyte, Merck, and Pharmacyclics LLC, an AbbVie Company; research funding from AbbVie, Merck, Janssen, Syndax, and TG Therapeutics.

Supplementary Information

Ibrutinib + Venetoclax Improved Response Rates in Patients With *TP53* Mutations Overall and Across Subgroups by Age

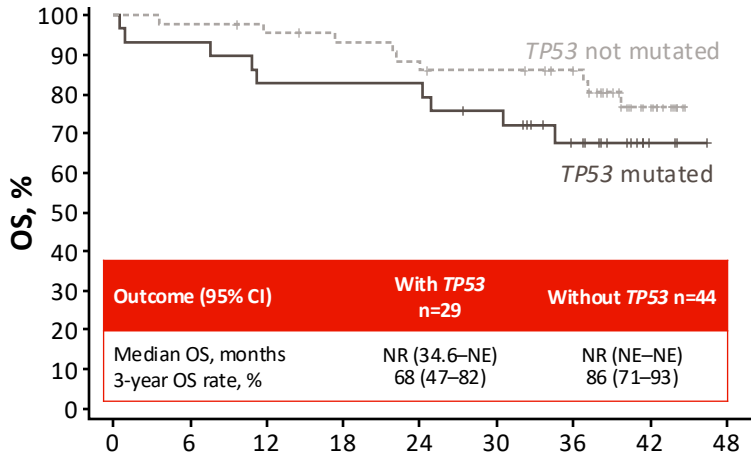


Outcome (95% CI)	All Patients		Patients ≥65 Years		Patients <65 Years	
	TP53 Mutated n=29	*TP53* Not Mutated n=44	*TP53* Mutated n=18	*TP53* Not Mutated n=42	*TP53* Mutated n=11	*TP53* Not Mutated n=2[a]
Median DOCR, months	NR (5.4–NE)	NR (34.0–NE)	NR (11.1–NE)	NR (34.0–NE)	NR (2.8–NE)	NR (8.2–NE)
ORR, %	90 (73–98)	98 (88–100)	89 (65–99)	98 (87–100)	91 (59–100)	100 (16–100)
Median DOR, months	20.5 (12.0–NE)	37.1 (34.2–NE)	20.5 (12.0–NE)	37.1 (34.2–NE)	NR (5.3–NE)	NR (8.2–NE)

[a]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.

Encouraging OS with Ibrutinib + Venetoclax in Patients With and Without *TP53* Mutations Across Age Subgroups

All Patients

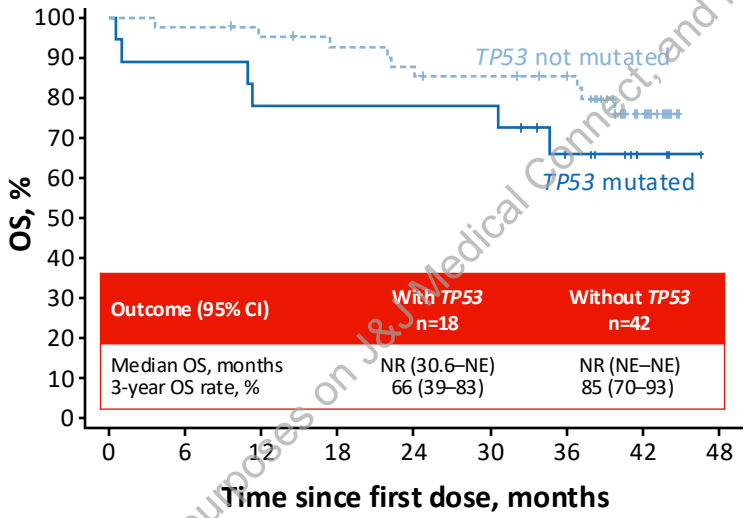


Outcome (95% CI)	With *TP53* n=29	Without *TP53* n=44
Median OS, months	NR (34.6–NE)	NR (NE–NE)
3-year OS rate, %	68 (47–82)	86 (71–93)

Patients at risk:

TP53 mutated	29	27	24	24	24	21	14	3	0
TP53 not mutated	44	43	41	39	37	35	32	13	0

Patients ≥65 years

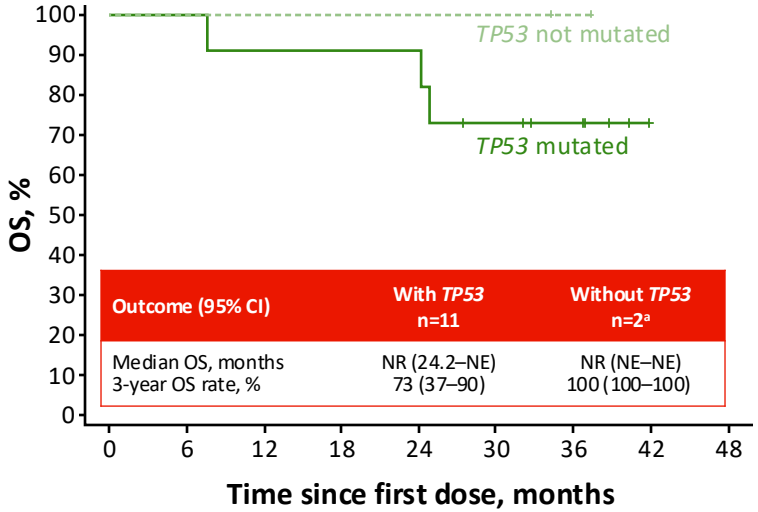


Outcome (95% CI)	With *TP53* n=18	Without *TP53* n=42
Median OS, months	NR (30.6–NE)	NR (NE–NE)
3-year OS rate, %	66 (39–83)	85 (70–93)

Patients at risk:

TP53 mutated	18	16	14	14	14	14	9	3	0
TP53 not mutated	42	41	39	37	35	33	31	13	0

Patients <65 years



Outcome (95% CI)	With *TP53* n=11	Without *TP53* n=2[a]
Median OS, months	NR (24.2–NE)	NR (NE–NE)
3-year OS rate, %	73 (37–90)	100 (100–100)

Patients at risk:

TP53 mutated	11	11	10	10	10	7	5	0	0
TP53 not mutated	2	2	2	2	2	2	1	0	0

[a]2 patients <65 years had *TP53* mutations per local laboratory, but not per central laboratory.