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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

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OBJECTIVE

To report the safety and efficacy of ibrutinib + venetoclax treatment in patients with treatment-naive (TN) mantle cell lymphoma (MCL) in the SYMPATICO study

CONCLUSIONS

Unmet needs persist in patients with MCL, especially in those with
- *TP53* mutations, due to high risk of early progressive disease and poor outcomes with chemoimmunotherapy
- Older age, due to less tolerance of highly efficacious chemoimmunotherapy

First-line ibrutinib + venetoclax showed promising efficacy, with high complete response 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 adverse event rates in patients aged <65 years

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

https://www.congresshub.com/EHA2025/Oncology/Ibrutinib/Keudell

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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 Pharmacyclics LLC, an AbbVie Company.

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. **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, Bristol Myers Squibb, 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, Celltrion, 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. **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, Newbridge 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 from Acerta 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.

Presented at the European Hematology Association (EHA) Hybrid Congress; June 12–15, 2025; Milan, Italy

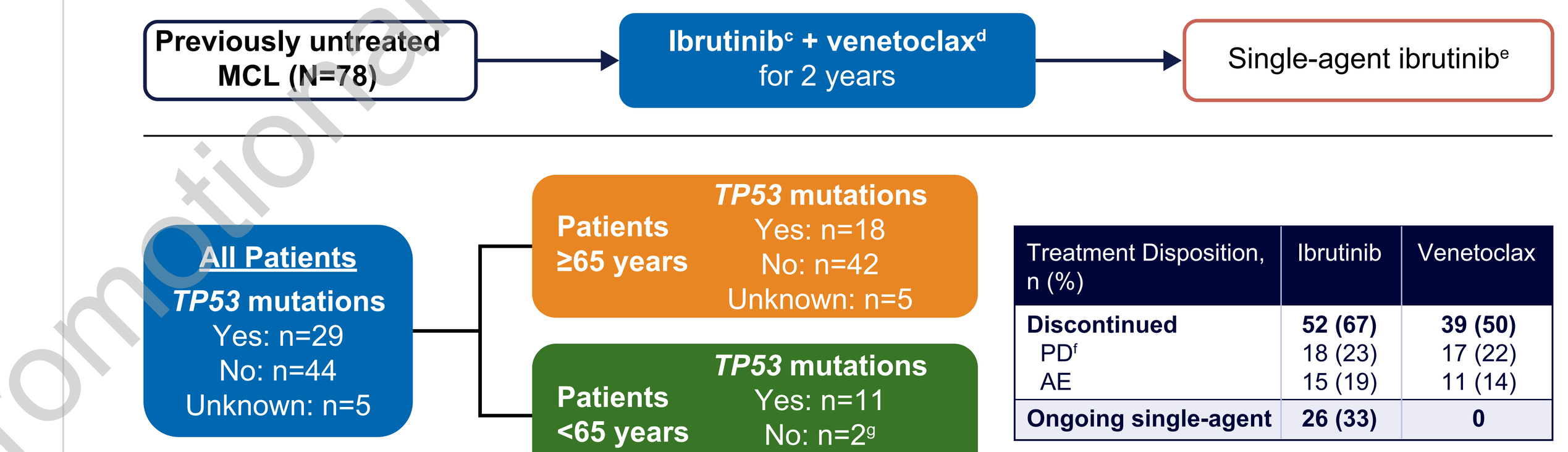
INTRODUCTION

- The combination of ibrutinib, a once-daily oral Bruton tyrosine kinase (BTK) inhibitor, and venetoclax, a once-daily oral B-cell lymphoma-2 protein (BCL-2) inhibitor, leverages complementary modes of action and has demonstrated synergistic antitumor activity in preclinical models of mantle cell lymphoma (MCL)[1,2]
- *TP53* mutations occur in 15%–20% of patients with MCL[3,4] and confer a high risk of early progressive disease (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 progression-free survival (PFS) with ibrutinib + venetoclax compared with ibrutinib + placebo in patients with relapsed or refractory MCL (median PFS, 31.9 vs 22.1 months, hazard ratio, 0.65)[7]
  - Here, open-label treatment-naive (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

METHODS

- SYMPATICO (NCT03112174) is a multinational, randomized, double-blind, placebo-controlled, phase 3 study

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.

RESULTS

- In the open-label TN cohort, 78 patients received ibrutinib + venetoclax treatment
- Median time on study was 40.5 months (range, 0.6+ to 46.9), and median treatment duration was 24.0 months (range, 0.3–46.9)

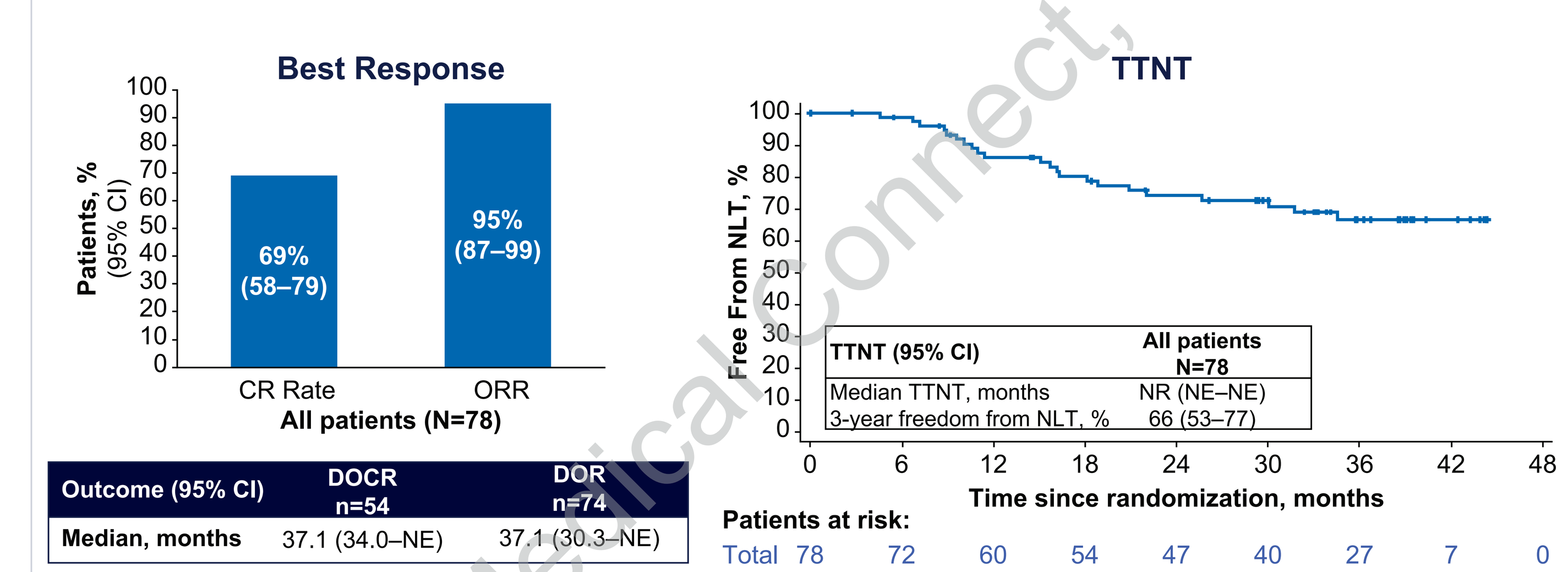
Baseline Characteristics of Patients With TN MCL Treated With Ibrutinib + Venetoclax

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)
Bone marrow involvement, n (%)	61 (78)
Splenomegaly, n (%)	36 (46)
TP53 mutated, n (%)	29 (37)

sMIPI, simplified MCL International Prognostic Index.

- Most patients (83%) were aged ≥65 years
- 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%

Ibrutinib + Venetoclax Met the Primary Endpoint for Complete Response (CR) Rate and Showed Promising Overall Response Rate (ORR) and Time to Next Treatment (TTNT) in Patients With TN MCL

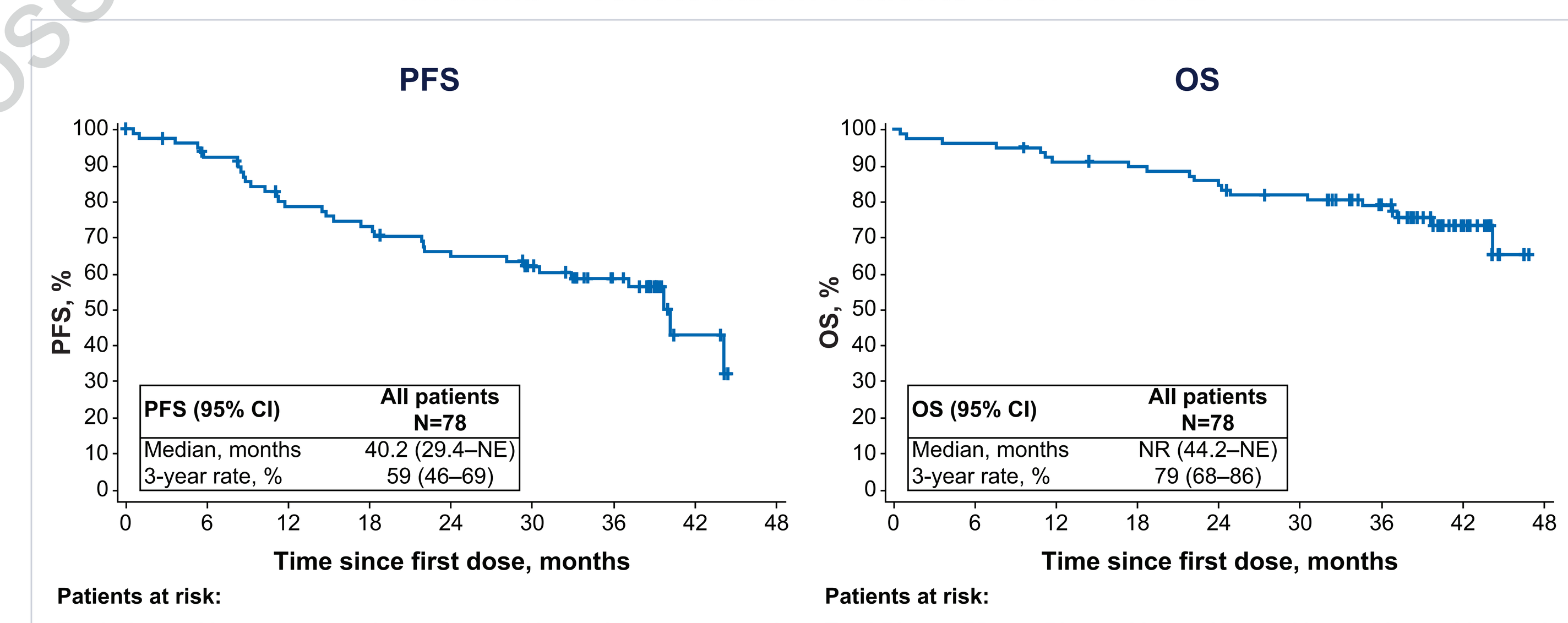


Outcome (95% CI)	DOCR n=54	DOR n=74
Median, months	37.1 (34.0–NE)	37.1 (30.3–NE)

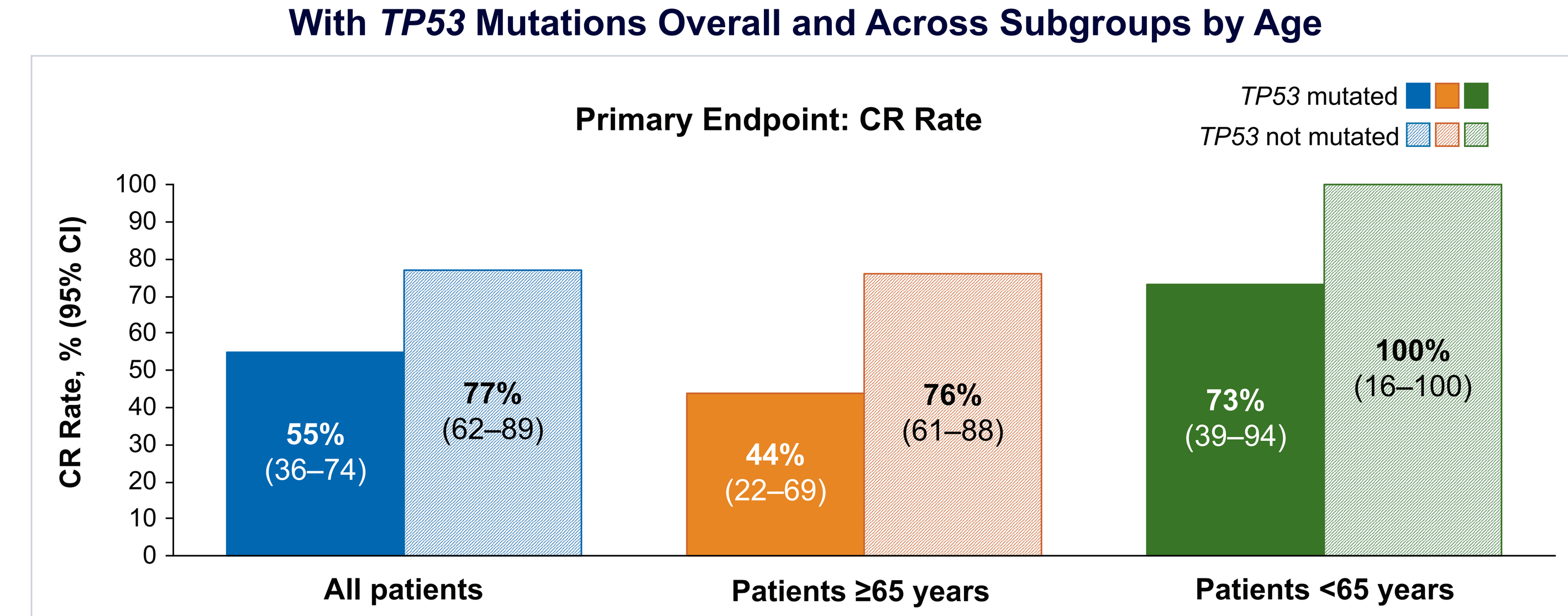
DOCR, duration of complete response; DOR, duration of response; MRD, minimal residual disease; NE, not estimable; NLT, next-line treatment; NR, not reached.

- Among patients with CR, MRD-negative remission (MCL cells <0.05% by 8-color flow cytometry) was achieved in:
  - 13 of 22 evaluable patients (59%) in bone marrow
  - 26 of 34 evaluable patients (76%) in peripheral blood

Encouraging PFS and Overall Survival (OS) Were Observed With Ibrutinib + Venetoclax in Patients With TN MCL

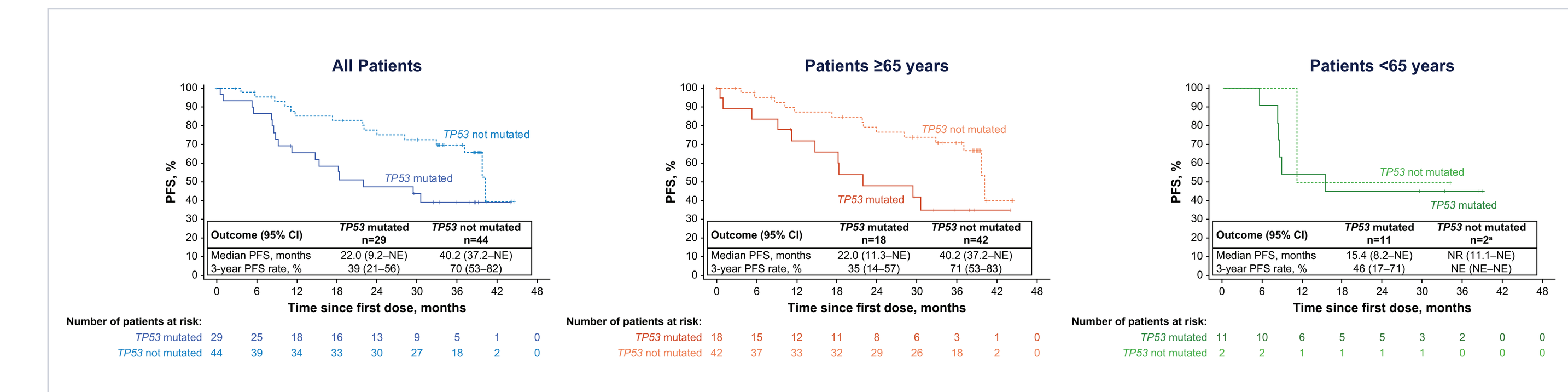


Ibrutinib + Venetoclax Also Improved Response Rates in Patients With *TP53* Mutations Overall and Across Subgroups by Age



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

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



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

3-Year OS Rates With Ibrutinib + Venetoclax in Patients With and Without *TP53* Mutations Across Age Subgroups

Patients	3-Year OS Rate (95% CI), %	
	TP53 mutated	*TP53* not mutated
All patients	68 (47–82)	86 (71–93)
Patients aged ≥65 years	66 (39–83)	85 (70–93)
Patients aged <65 years	73 (37–90)	100 (100–100)

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 treatment-emergent AE	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)

AE, adverse event.
[a]Occurring in ≥20% of patients in the total population.

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

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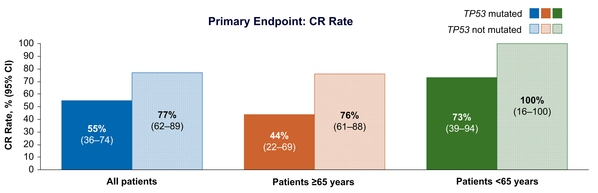
SUPPLEMENTAL RESULTS

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



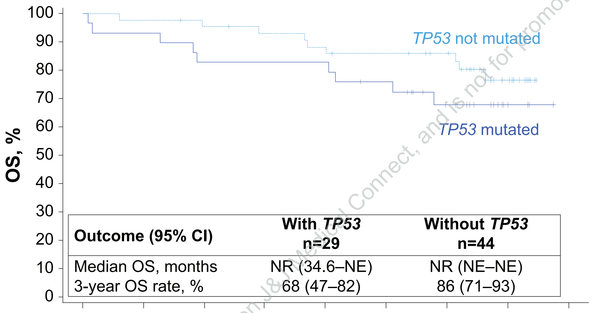
Outcome (95% CI)	All Patients		Patients ≥65 Years		Patients <65 Years	
	TP53 Mutated n=29	*TP53* Not Mutated n=44	*TP53* Mutated n=18	*TP53* Not Mutated n=42	*TP53* Mutated n=11	*TP53* Not Mutated n=2[a]
Median DOCR, months	NR (5.4–NE)	NR (34.0–NE)	NR (11.1–NE)	NR (34.0–NE)	NR (2.8–NE)	NR (8.2–NE)
ORR, %	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)

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

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

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

All Patients

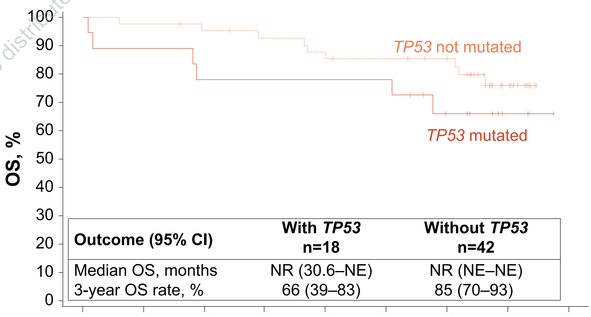


Outcome (95% CI)	With *TP53* n=29	Without *TP53* n=44
Median OS, months	NR (34.6–NE)	NR (NE–NE)
3-year OS rate, %	68 (47–82)	86 (71–93)

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 aged ≥65 years

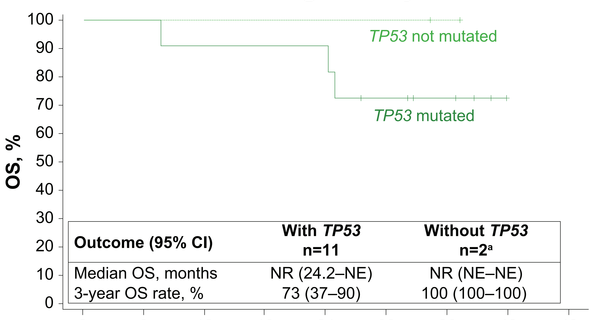


Outcome (95% CI)	With *TP53* n=18	Without *TP53* n=42
Median OS, months	NR (30.6–NE)	NR (NE–NE)
3-year OS rate, %	66 (39–83)	85 (70–93)

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 aged <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 aged <65 years had *TP53* mutations per local laboratory, but not per central laboratory.