MCL-058

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

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OBJECTIVE

To report efficacy and safety of ibrutinib + venetoclax in patients with *TP53* mutations across cohorts in the SYMPATICO study

CONCLUSIONS

This study represents the largest single-study cohort of patients with mantle cell lymphoma (MCL) and *TP53* mutations reported to date (n=74; relapsed/refractory, n=45; first-line, n=29)

Ibrutinib + venetoclax demonstrated promising efficacy with high complete response 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

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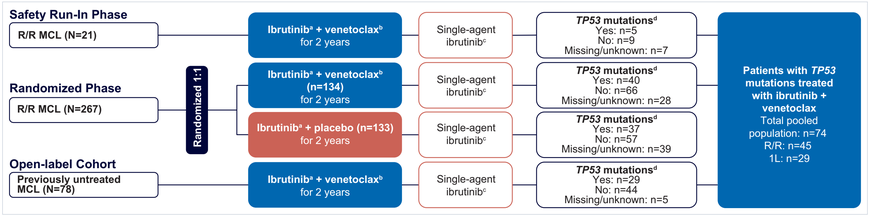
INTRODUCTION

- Mantle cell lymphoma (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 Bruton tyrosine kinase (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% to 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 progression-free survival (PFS) with ibrutinib + venetoclax compared with ibrutinib + placebo in patients with relapsed/refractory (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

METHODS

- SYMPATICO (NCT03112174) is a multinational, randomized, double-blind, placebo-controlled, phase 3 study
- Data were pooled across cohorts for patients with *TP53* mutations treated with ibrutinib + venetoclax

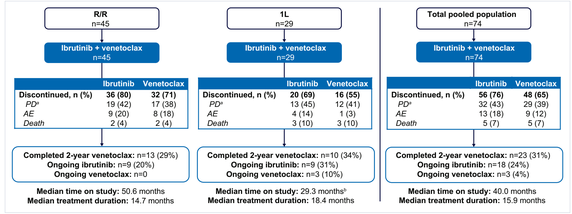
SYMPATICO Study Design



1L, first-line.
[a]560 mg once daily. [b]5-week ramp-up to 400 mg once daily. [c]560 mg once daily until PD or unacceptable toxicity. [d]Somatic mutations in exons 1–11 of *TP53* were evaluated by next-generation sequencing with a variant allele fraction cutoff of 2%; deletions were not assessed.

RESULTS

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



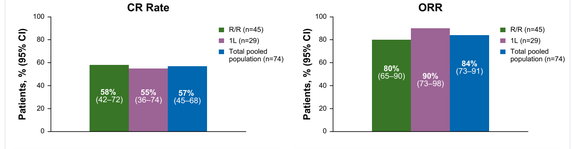
AE, adverse event.
[a]PD per protocol criteria or clinical PD.
[b]Enrollment in the 1L open-label cohort began after completion of enrollment in the safety run-in and randomization phases.

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

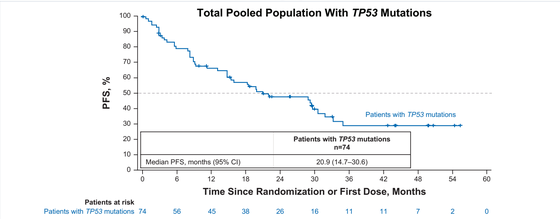


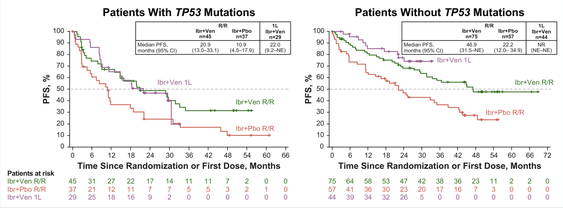
	R/R n=26	1L n=16	Total n=42
Median DOCR, months (95% CI)	NR (18.7–NE)	20.5 (5.4–NE)	32.2 (18.7–NE)

	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; NR, not reached; ORR, overall response rate.

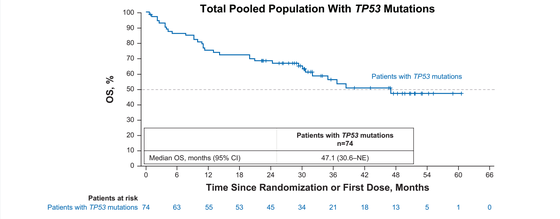
Ibrutinib + Venetoclax Provided Encouraging PFS in Patients With *TP53* Mutations

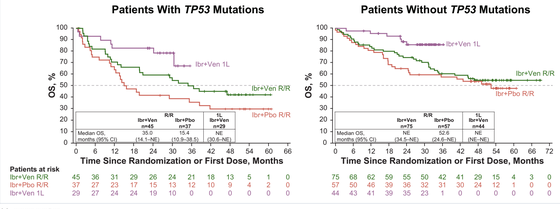




Ibr, ibrutinib; Pbo, placebo; Ven, venetoclax.

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

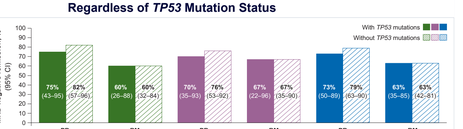




OS, overall survival.

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

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



Ibrutinib + venetoclax-treated patients who achieved CR	R/R (n=65)		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, %[a]	9 (75) / 14 (82)	6 (60) / 9 (60)	7 (70) / 16 (76)	4 (67) / 8 (67)	16 (73) / 30 (79)	10 (63) / 17 (63)

1L, first-line; BM, bone marrow; CR, complete response; MCL, mantle cell lymphoma; MRD, minimal residual disease; PB, peripheral blood; R/R, relapsed/refractory.
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

Characteristic	R/R n=45	1L n=29	Total Pooled Population 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
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.

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