Ibrutinib plus venetoclax in relapsed or refractory mantle cell lymphoma (SYMPATICO): a multicentre, randomised, double-blind, placebo-controlled, phase 3 study

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See **Comment** page 150

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Summary

Background The combination of ibrutinib and venetoclax leverages complementary mechanisms of action and has shown promising clinical activity in mantle cell lymphoma (MCL). This study evaluated the efficacy and safety of ibrutinib–venetoclax compared with ibrutinib–placebo in patients with relapsed or refractory MCL.

Methods SYMPATICO is a multicentre, randomised, double-blind, placebo-controlled, phase 3 study performed at 84 hospitals in Europe, North America, and Asia–Pacific. Eligible patients were adults (aged ≥18 years) with pathologically confirmed relapsed or refractory MCL after one to five previous lines of therapy and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were randomly assigned (1:1) to receive oral ibrutinib 560 mg once daily concurrently with oral venetoclax (5-week ramp-up to 400 mg once daily) or placebo for 2 years, then single-agent ibrutinib 560 mg once daily until disease progression or unacceptable toxicity. Randomisation and treatment assignment occurred via interactive response technology using a stratified permuted block scheme (block sizes of 2 and 4) with stratification by ECOG performance status, previous lines of therapy, and tumour lysis syndrome risk category. Patients and investigators were masked to treatment assignment. The primary endpoint was investigator-assessed progression-free survival in the intention-to-treat population. Safety was assessed in all patients who received at least one dose of study treatment. This study is registered with ClinicalTrials.gov, NCT03112174, and is closed to enrolment.

Findings Between April 26, 2018, and Aug 28, 2019, 267 patients were enrolled and randomly assigned; 134 to the ibrutinib–venetoclax group and 133 to the ibrutinib–placebo group. 211 (79%) of 267 patients were male and 56 (21%) were female. With a median follow-up of 51·2 months (IQR 48·2–55·3), median progression-free survival was 31·9 months (95% CI 22·8–47·0) in the ibrutinib–venetoclax group and 22·1 months (16·5–29·5) in the ibrutinib–placebo group (hazard ratio 0·65 [95% CI 0·47–0·88]; p=0·0052). The most common grade 3–4 adverse events were neutropenia (42 [31%] of 134 patients in the ibrutinib–venetoclax group *vs* 14 [11%] of 132 patients in the ibrutinib–placebo group), thrombocytopenia (17 [13%] *vs* ten [8%]), and pneumonia (16 [12%] *vs* 14 [11%]). Serious adverse events occurred in 81 (60%) of 134 patients in the ibrutinib–venetoclax group and in 79 (60%) of 132 patients in the ibrutinib–placebo group. Treatment-related deaths occurred in three (2%) of 134 patients in the ibrutinib–venetoclax group (n=1 COVID-19 infection, n=1 cardiac arrest, and n=1 respiratory failure) and in two (2%) of 132 patients in the ibrutinib–placebo group (n=1 cardiac failure and n=1 COVID-19-related pneumonia).

Interpretation The combination of ibrutinib–venetoclax significantly improved progression-free survival compared with ibrutinib–placebo in patients with relapsed or refractory MCL. The safety profile was consistent with known safety profiles of the individual drugs. These findings suggest a positive benefit–risk profile for ibrutinib–venetoclax treatment.

Funding Pharmacyclics (an AbbVie Company) and Janssen Research and Development.

Introduction

Targeted therapy has transformed the treatment landscape for patients with relapsed or refractory mantle cell lymphoma (MCL), but relapse is inevitable.[1] Additionally, patients with MCL and high-risk factors, such as blastoid or pleomorphic histology or *TP53* mutations, have poor responses and survival outcomes with chemoimmunotherapy, and thus have unmet needs for improved and novel treatment strategies.[1] Ibrutinib is a once-daily oral Bruton tyrosine kinase (BTK) inhibitor approved in multiple regions of the world for patients with relapsed or refractory MCL and other B-cell malignancies. In patients with relapsed or refractory MCL, single-agent ibrutinib provided complete response

Research in context

Evidence before this study

Bruton's tyrosine kinase (BTK) inhibitors are the standard of care second-line treatment for patients with relapsed or refractory mantle cell lymphoma (MCL). However, relapse remains inevitable and improved and novel treatment strategies are needed. We searched PubMed for clinical trials published from database inception to April 18, 2024, using the terms "mantle cell lymphoma" AND ("relapsed" OR "refractory"), with no language restrictions. The search found one randomised phase 3 trial that demonstrated superior progression-free survival with ibrutinib compared with temsirolimus. High response rates have also been reported with single-agent venetoclax in patients with relapsed or refractory MCL in early-phase studies and real-world data, but progression-free survival was short among patients previously treated with a BTK inhibitor. Two early studies of the ibrutinib–venetoclax combination reported complete response rates appearing substantially higher than those found in studies of either agent alone.

Added value of this study

Results from this phase 3 SYMPATICO study showed that the combination of ibrutinib plus venetoclax confers superior efficacy compared with single-agent ibrutinib in patients with relapsed or refractory MCL, which is consistent with previous findings of preclinical synergistic antitumour activity with ibrutinib and venetoclax. Improvements in progression-free survival were generally robust across prespecified subgroups, including in the subgroup of patients with a *TP53* mutation who have unmet medical needs. To our knowledge, this analysis represents the largest single-study cohort of patients with MCL and *TP53* mutations reported to date and is the first randomised trial to demonstrate improved progression-free survival in patients with relapsed or refractory MCL and *TP53* mutations. The safety profile of ibrutinib–venetoclax was consistent with known adverse events for each single agent, with no new observed safety signals.

Implications of all the available evidence

The combination of ibrutinib–venetoclax might improve outcomes compared with BTK inhibitors alone and provide a favourable benefit–risk profile in patients with relapsed or refractory MCL. These data have the potential to change current practice for the treatment of patients with relapsed or refractory MCL.

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rates of 19–28% and median progression-free survival of 12·5–15·6 months.[2,3] Venetoclax is a once-daily oral BCL-2 inhibitor approved in multiple world regions for patients with chronic lymphocytic leukaemia and previously untreated acute myeloid leukaemia. Single-agent venetoclax provided complete response rates of 18–21% in patients with relapsed or refractory MCL,[4,5] with median progression-free survival of 2·8–3·2 months in patients previously treated with BTK inhibitors.[5,6]

The combination of ibrutinib–venetoclax leverages complementary mechanisms of action and has demonstrated synergistic antitumour activity in preclinical models of MCL.[7,8] Promising clinical activity was observed with ibrutinib–venetoclax in early-phase studies in patients with relapsed or refractory MCL, with complete response rates of 62–71% and with a median progression-free survival of 28–35 months.[9,10]

This phase 3 SYMPATICO study evaluated the efficacy and safety of ibrutinib–venetoclax in three cohorts of patients with MCL: an open-label safety run-in phase to evaluate concurrent initiation of ibrutinib and venetoclax in relapsed or refractory MCL; a double-blind, randomisation phase to evaluate ibrutinib–venetoclax compared with ibrutinib–placebo in relapsed or refractory MCL; and an open-label cohort to evaluate first-line ibrutinib–venetoclax in previously untreated MCL. The open-label safety run-in phase was completed before the randomisation phase and demonstrated that concurrent initiation of ibrutinib and venetoclax was safe.[9] Results of the primary analysis of the randomisation phase of SYMPATICO are presented here. Results for the open-label cohort in patients with previously untreated MCL will be reported separately.

Methods

Study design and participants

SYMPATICO was a multicentre, randomised, double-blind, placebo-controlled, phase 3 study done in 84 hospitals in 17 countries across Europe, North America, and the Asia–Pacific region (appendix pp 2–3). The study was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and provisions of the Declaration of Helsinki. The protocol and amendments were approved by independent ethics committees at each site (appendix pp 4–6). The study protocol and statistical analysis plan are available in the appendix.

See **Online** for appendix

Eligible patients were adults (aged ≥18 years) with pathologically confirmed MCL, relapsed or refractory disease (did not have at least partial response with, or had documented disease progression after, the most recent treatment regimen), one to five previous lines of therapy (including ≥1 rituximab or anti-CD20-containing regimen), at least one measurable disease site on cross-sectional imaging by CT, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate haematological and end-organ function. Excluded previous anticancer treatments and comorbid conditions are described in the appendix (p 7). Full inclusion and exclusion criteria are provided in the study

protocol (appendix). Sex and ethnicity were determined by the investigators. All patients provided written informed consent.

This study is registered with ClinicalTrials.gov, NCT03112174.

Randomisation and masking

Patients were randomly assigned (1:1) to receive ibrutinib–venetoclax or ibrutinib–placebo using permuted blocks (sizes of 2 and 4) via interactive response technology (IRT) and stratified according to ECOG performance status (0–1 *vs* 2), previous lines of therapy (1–2 *vs* ≥3), and risk categories of tumour lysis syndrome (low *vs* increased risk; appendix p 7). The randomisation list and code were generated by and maintained within the IRT system to prevent knowledge of the next treatment in the sequence. However, the IRT system enabled masking to be broken for an individual patient if necessary. Patients were enrolled by investigators and assigned to treatment groups by the IRT system. All patients, investigators, and representatives of the study sponsor were masked to treatment assignment in a double-blind manner. Masking was maintained using identical tablets and packaging for venetoclax and placebo.

Procedures

Patients received oral ibrutinib 560 mg once daily concurrently with oral venetoclax (5-week ramp-up to 400 mg once daily) or matching placebo for 2 years, followed by single-agent ibrutinib 560 mg once daily until disease progression or unacceptable toxicity. Dose modification, including treatment interruption and dose reduction, was allowed for the management of adverse events as described in the protocol. Use of supportive medications for the management of adverse events was permitted in accordance with standard practice (appendix p 7). Patients were withdrawn from the study (including all follow-up) in the event of consent withdrawal for follow-up, loss to follow-up, study termination, or death.

Response and progression were assessed using CT (with contrast, unless contraindicated) of the neck, chest, abdomen, and pelvis, and any other disease sites at baseline, every 12 weeks in year 1, every 16 weeks in years 2 and 3, and every 24 weeks thereafter until disease progression or as clinically indicated. MRI could be used for lesions not well visualised by CT. PET was required at baseline and was mandatory to confirm a complete response in patients with a positive baseline CT scan. Overall disease assessments were performed by investigators per protocol; a central independent review committee (IRC) was implemented to perform supplementary overall disease assessments.

Minimal residual disease (MRD) was assessed in bone marrow aspirate obtained at baseline and at documented complete response and in peripheral blood samples obtained at baseline, documented complete response, and each response assessment thereafter. Pharmacokinetic samples were obtained on day 1 of week 6 at 30 min pre-dose and at 1, 2, 4, 6, and 8 h post-dose.

Safety was assessed by patient-reported symptoms, physical examination, laboratory tests (haematology and serum chemistry), and vital signs at each study visit during and up to 30 days after the last dose of study treatment. Adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. Laboratory and clinical tumour lysis syndrome were assessed per Howard criteria;[11] clinical tumour lysis syndrome further required an increase in serum creatinine concentrations greater than 1·0 mg/dL from baseline.

Outcomes

The primary endpoint was progression-free survival, defined as the time from randomisation until disease progression or death from any cause, whichever occurred first. Disease progression and responses were assessed by investigators per Revised Response Criteria for Malignant Lymphoma (Lugano criteria).[12] Secondary endpoints were complete response rate and overall response rate (complete or partial response), time to next treatment (time from randomisation to start of subsequent anti-lymphoma treatment), overall survival (time from randomisation to death), duration of response (time from first documentation of response to disease progression or death, whichever occurs first), MRD-negative rate (<0·05% MCL cells by 8-colour flow cytometry, assessed in bone marrow and peripheral blood) of patients with complete response and evaluable MRD (positive at baseline and post-baseline sample available), safety, steady-state pharmacokinetics of ibrutinib and venetoclax, and time to worsening in the Functional Assessment of Cancer Therapy Lymphoma (FACT-Lym) subscale. Quality of life was assessed as an exploratory endpoint using the EQ-5D-5L.

Statistical analysis

The sample size was calculated based on the primary endpoint of progression-free survival. Enrolment of 260 patients was estimated to be necessary to accrue 134 progression-free survival events, which would provide approximately 80% power to detect a hazard ratio (HR) of 0·61 at a one-sided significance level of 0·025, assuming a median progression-free survival of 14 months for ibrutinib–placebo.[13] In alignment with US Food and Drug Administration (FDA) guidance, follow-up was extended to accrue 150 progression-free survival events to mitigate the potential effect of deaths due to COVID-19 and account for additional censoring per US FDA censoring rules. For primary analysis using global censoring rules, patients without disease progression or death were censored at the last adequate disease assessment. Sensitivity analyses of progression-free survival were performed by IRC

assessment using global censoring rules and by investigator and IRC assessment using US FDA censoring rules, with additional censoring at the last adequate disease assessment before either of the following events (whichever occurred first): initiation of subsequent anticancer therapy; and missing two or more consecutive assessments before progression or death. Sensitivity analyses were also performed to explore the effect of COVID-19-related deaths. For progression-free survival, patients who died due to COVID-19 without disease progression were censored at the last adequate overall disease assessment before death; for overall survival, patients who died due to COVID-19 were censored one day before death.

To control the overall type I error at a two-sided α of 0·05, endpoints were tested hierarchically in the following order: progression-free survival, complete response rate, time to next treatment, overall survival, and overall response rate. If the previous endpoint was significant at a two-sided α of 0·05, the α of 0·05 could be passed down to the next endpoint. Interim analysis of overall survival was prespecified to occur at the primary analysis of progression-free survival with an α spend of 0·001 (two-sided); the remaining α would be spent at the final overall survival analysis, planned after 170 deaths. To maintain a one-sided overall significance level of 0·025 for the final overall survival analysis, the α spend was based on Lan-DeMets spending function with Haybittle-Peto boundary (instead of O'Brien-Fleming boundary as specified in the protocol).

Time-to-event endpoints were estimated using Kaplan–Meier methodology; HRs were estimated using stratified Cox regression modelling with treatment as the only covariate, and p values were calculated by stratified log-rank test. Landmark analysis of 24-month progression-free survival and overall survival rates was done post hoc. Proportional hazard assumption for progression-free survival was evaluated by visual inspection of a plot in which the y-axis is log(–log[survival function]) and the x-axis is log(time); the plot showed two generally parallel lines (one for each treatment group) with no crossing, indicating the assumption was reasonably met. Due to a small number of patients with an ECOG performance status of 2, stratified testing was based on two randomisation stratification factors: previous lines of therapy (1–2 *vs* ≥3) and tumour lysis syndrome risk category (low *vs* increased risk); sensitivity analysis of progression-free survival was performed with stratified testing based on all three protocol-specified randomisation stratification factors. Response rates were compared by rate ratios (rather than proportion difference as specified in the protocol) using a stratified Cochran–Mantel–Haenszel test; due to small sample size, MRD-negative rates were compared using Fisher exact test instead of the protocol-specified Cochran–Mantel–Haenszel test.

Baseline characteristics, pharmacokinetics, EQ-5D-5L scores, and safety were summarised descriptively. Efficacy was assessed in all randomly assigned patients (intention-to-treat population). Patients without post-baseline disease assessment were considered non-responders and were included in the denominator for response analysis. Prespecified subgroup analyses of progression-free survival were performed according to age (<65 years *vs* ≥65 years), sex (male *vs* female), race (White *vs* other), geographical region (North America, Europe, or Asia–Pacific), number of previous lines of therapy (1–2 *vs* ≥3), ECOG performance status (0 *vs* 1–2), tumour lysis syndrome risk category (low *vs* increased risk), simplified MCL International Prognostic Index score (low, intermediate, or high risk), bulky disease (largest diameter <5 cm *vs* ≥5 cm), splenomegaly (yes *vs* no), extranodal disease (present *vs* absent), blastoid variant (yes *vs* no), blastoid or pleomorphic variant, or both (yes *vs* no), *TP53* mutation status (mutated, not mutated, or not performed or missing), and previous stem cell transplantation (yes *vs* no). Subgroup analyses of progression-free survival by baseline lactate dehydrogenase level (≤185 U/L *vs* >185 U/L) and overall

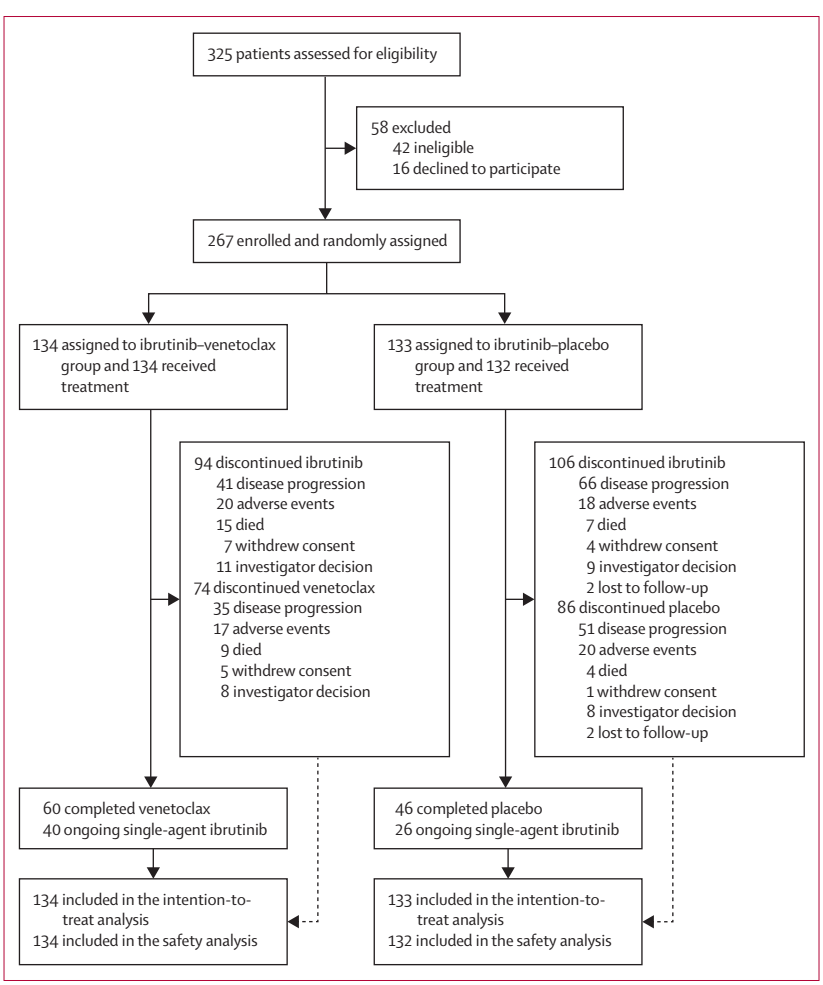


Figure 1: **Trial profile**

	Ibrutinib–venetoclax (n=134)	Ibrutinib–placebo (n=133)
Age, years	69 (62–74)	67 (60–73)
<65	41 (31%)	47 (35%)
≥65	93 (69%)	86 (65%)
Sex		
Female	31 (23%)	25 (19%)
Male	103 (77%)	108 (81%)
Race		
White	116 (87%)	115 (86%)
Asian	2 (1%)	3 (2%)
Black	1 (1%)	1 (1%)
Not reported	15 (11%)	14 (11%)
Ethnicity		
Hispanic, Latino, Latina, or Latinx	8 (6%)	7 (5%)
Other	112 (84%)	110 (83%)
Not reported	14 (10%)	16 (12%)
ECOG performance status		
0	74 (55%)	74 (56%)
1 or 2	60 (45%)	59 (44%)
Previous lines of therapy	1 (1–2)	1 (1–2)
1	80 (60%)	79 (59%)
2	32 (24%)	31 (23%)
≥3	22 (16%)	23 (17%)
Previous SCT	39 (29%)	50 (38%)
TLS risk category		
Low risk	105 (78%)	104 (78%)
Increased risk	29 (22%)	29 (22%)
Simplified MIPI score		
Low risk	18 (13%)	23 (17%)
Intermediate risk	63 (47%)	68 (51%)
High risk	51 (38%)	41 (31%)
MCL histology		
Typical	88 (66%)	95 (71%)
Blastoid	19 (14%)	17 (13%)
Pleomorphic	8 (6%)	6 (5%)
Round cell (CLL-like)	1 (1%)	0
Other	18 (13%)	15 (11%)
TP53 status*		
Mutated	40 (30%)	37 (28%)
Not mutated	66 (49%)	57 (43%)
Missing	28 (21%)	39 (29%)
Bulky disease		
≥5 cm	62 (46%)	53 (40%)
≥10 cm	13 (10%)	10 (8%)
Extranodal disease	64 (48%)	61 (46%)
Bone marrow involvement	62 (46%)	54 (41%)
Splenomegaly	42 (31%)	33 (25%)

Data are n (%) or median (IQR). CLL=chronic lymphocytic leukaemia. ECOG=Eastern Cooperative Oncology Group. MCL=mantle cell lymphoma. MIPI=MCL International Prognostic Index. SCT=stem cell transplantation. TLS=tumour lysis syndrome. *Somatic mutations in exons 1–11 of *TP53* were evaluated by next-generation sequencing with a variant allele fraction cutoff of 2%.

Table 1: **Baseline demographics and clinical characteristics**

survival by *TP53* mutation status (mutated *vs* not mutated) were post hoc. Safety was assessed in all patients who received one or more dose of study treatment (safety population). An independent data monitoring committee performed regular assessments of unblinded safety data.

The full statistical analysis plan is provided in the protocol (appendix). Statistical analyses were completed using SAS (version 9.4).

Role of the funding source

The funders were involved in study design, data analysis, data interpretation, and writing of the report.

Results

Between April 26, 2018, and Aug 28, 2019, 267 patients were enrolled and randomly assigned; 134 to the ibrutinib–venetoclax group and 133 to the ibrutinib–placebo group (figure 1). Overall, age and sex distribution of the study population was consistent with published estimates for patients with MCL in the USA; Black and Asian patients might be under-represented (appendix p 14). The median age of patients was 68 years (IQR 61–74). 56 (21%) of 267 patients were female and 211 (79%) of 267 patients were male. Baseline characteristics were generally well balanced (table 1) between groups. The median number of previous regimens was one (IQR 1–2) in both groups.

At data cutoff (July 5, 2023), median follow-up was 51·2 months (IQR 48·2–55·3). Ibrutinib had been discontinued in 94 (70%) of 134 patients in the ibrutinib–venetoclax group and 106 (80%) of 133 patients in the ibrutinib–placebo group; venetoclax had been discontinued in 74 (55%) patients and placebo had been discontinued in 86 (65%) patients, respectively. The most frequent reason for treatment discontinuation was disease progression in both groups (figure 1). In the ibrutinib–venetoclax group and ibrutinib–placebo group, 60 (45%) of 134 patients and 46 (35%) of 133 patients, respectively, completed the planned 2 years of venetoclax or placebo; 40 (30%) patients and 26 (20%) patients, respectively, remained on single-agent ibrutinib at data cutoff (figure 1). The median duration of treatment was 22·2 months (IQR 5·7–47·2) in the ibrutinib–venetoclax group and 17·7 months (5·6–39·2) in the ibrutinib–placebo group.

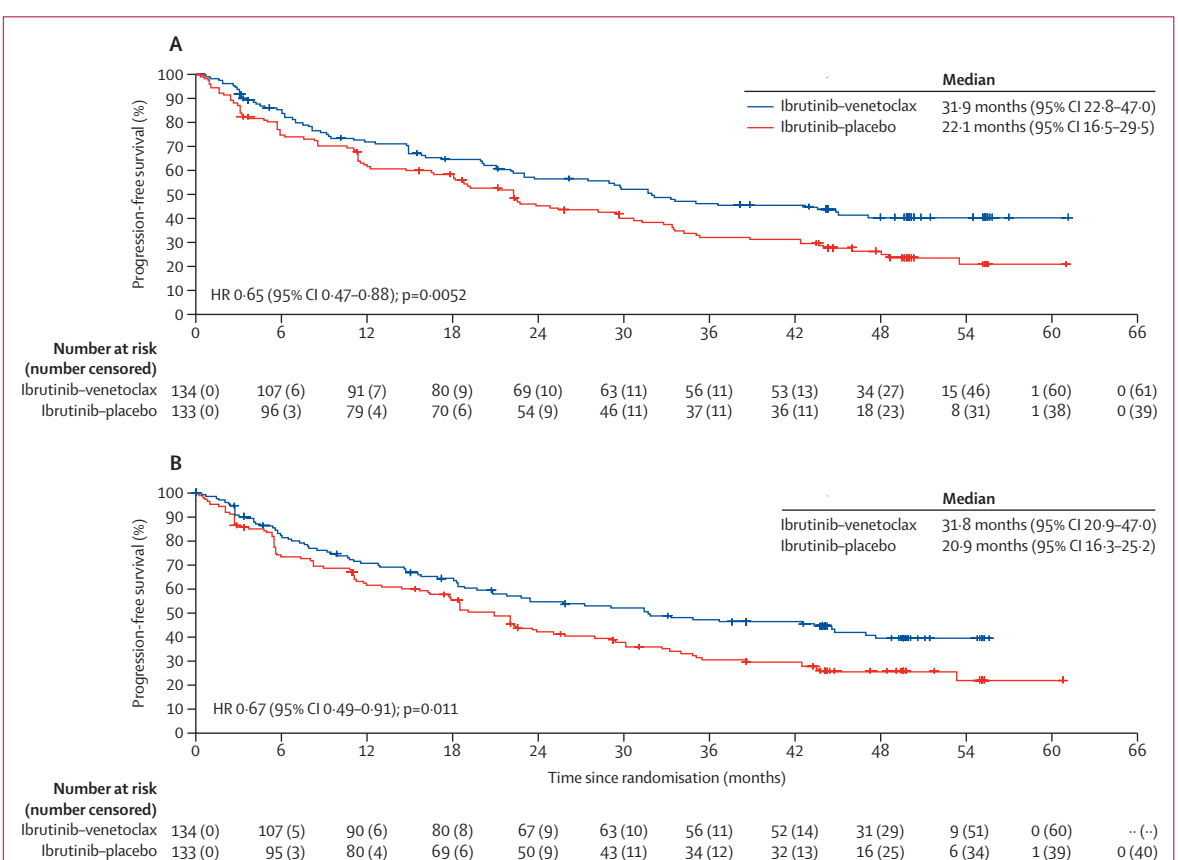
At data cutoff, disease progression or death had occurred in 73 (54%) of 134 patients in the ibrutinib–venetoclax group and in 94 (71%) of 133 patients in the ibrutinib–placebo group. Median progression-free survival by investigator assessment was significantly longer in the ibrutinib–venetoclax group (31·9 months [95% CI 22·8–47·0]) than in the ibrutinib–placebo group (22·1 months [16·5–29·5]; HR 0·65 [95% CI 0·47–0·88]; p=0·0052; figure 2A). In the post-hoc analysis, estimated 24-month progression-free survival rates in each group were 57% (95% CI 48–65) and 45% (37–54), respectively.

Reasons for censoring are described in the appendix (p 15). Sensitivity analysis of progression-free survival with stratified testing based on all three randomisation stratification factors yielded a HR of 0·65 (95% CI 0·48–0·89; p=0·0066). Sensitivity analyses of progression-free survival by IRC assessment using global censoring rules (figure 2B) and by investigator and IRC assessment using US FDA censoring rules (appendix p 8) all showed statistically significant improvements with ibrutinib–venetoclax versus ibrutinib–placebo. Progression-free survival benefit was generally consistent across prespecified subgroups (figure 2C; appendix p 9).

Complete response rates improved significantly in the ibrutinib–venetoclax group versus the ibrutinib–placebo group; overall response rates showed no statistically significant difference between the groups (figure 3A). Duration of complete response and duration of response are shown in figures 3B and figure 3C, respectively. 72 patients had a complete response in the ibrutinib–venetoclax group versus 43 patients in the ibrutinib–placebo group; MRD was evaluable in peripheral blood in 31 patients and in bone marrow in 26 patients versus eight patients in peripheral blood and seven patients in bone marrow, in each group, respectively. 113 (42%) of 267 patients were not evaluable for MRD in peripheral blood and 106 (40%) of 267 patients were not evaluable for MRD in bone marrow due to MRD-negative status at baseline; 46 (17%) patients were not evaluable for MRD in peripheral blood and 61 (23%) patients were not evaluable for MRD in bone marrow due to no sample or non-evaluable samples at baseline. MRD-negative rates in peripheral blood were 77% (95% CI 59–90) in the ibrutinib–venetoclax group versus 13% (0–53; p=0·0014) in the ibrutinib–placebo group and 62% (41–80) versus 29% (4–71; p=0·20), respectively, in bone marrow (appendix p 16).

At data cutoff, 42 (31%) of 134 patients in the ibrutinib–venetoclax group and 60 (45%) of 133 patients in the ibrutinib–placebo group had started next-line treatment. Time to next treatment significantly improved in the ibrutinib–venetoclax group versus the ibrutinib–placebo group (figure 4A). Subsequent anticancer treatments are summarised in the appendix (p 17).

At this interim analysis for overall survival, no statistically significant difference was observed with ibrutinib–venetoclax versus ibrutinib–placebo (figure 4B). In the post-hoc analysis, estimated 24-month overall survival rates were 66% (95% CI 57–73) and 61% (53–69), respectively. Death occurred in 69 (51%) of 134 patients in the ibrutinib–venetoclax group and 75 (56%) of



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	Number of patients (events)		HR (95% CI)
	Ibrutinib–venetoclax	Ibrutinib–placebo	
All patients	**134 (73)**	**133 (94)**	**0·65 (0·47–0·88)**
Age, years			
<65	41 (21)	47 (29)	0·61 (0·35–1·08)
≥65	93 (53)	86 (65)	0·67 (0·47–0·97)
Sex			
Male	103 (55)	108 (76)	0·62 (0·44–0·88)
Female	31 (18)	25 (18)	0·84 (0·44–1·62)
Race			
White	116 (65)	115 (84)	0·64 (0·46–0·88)
Other	18 (8)	18 (10)	0·79 (0·31–2·01)
Geographical region			
Europe	99 (55)	96 (69)	0·68 (0·48–0·97)
North America	27 (15)	30 (20)	0·63 (0·32–1·23)
Asia–Pacific	8 (3)	7 (5)	0·54 (0·13–2·31)
Previous lines of therapy			
1–2	112 (60)	110 (76)	0·68 (0·48–0·95)
≥3	22 (13)	23 (18)	0·58 (0·28–1·81)
ECOG performance status			
0	74 (30)	74 (47)	0·50 (0·32–0·79)
1–2	60 (43)	59 (47)	0·88 (0·58–1·33)
TLS risk category			
Low risk	105 (55)	104 (69)	0·70 (0·49–1·00)
Increased risk	29 (18)	29 (25)	0·55 (0·30–1·01)
Simplified MIPI score			
Low risk	18 (5)	23 (11)	0·47 (0·16–1·35)
Intermediate risk	63 (33)	68 (50)	0·62 (0·40–0·97)
High risk	51 (34)	41 (33)	0·64 (0·40–1·03)
Bulky disease			
<5 cm	72 (40)	80 (51)	0·82 (0·54–1·24)
≥5 cm	62 (33)	53 (43)	0·48 (0·31–0·76)
Splenomegaly			
Yes	42 (25)	3 (25)	0·61 (0·35–1·06)
No	87 (44)	98 (67)	0·62 (0·42–0·90)
Extranodal disease			
Yes	70 (43)	72 (48)	0·50 (0·31–0·79)
No	64 (30)	61 (46)	0·82 (0·55–1·25)
Blastoid variant			
Yes	19 (15)	17 (14)	0·65 (0·31–1·35)
No	115 (58)	116 (80)	0·63 (0·45–0·89)
Blastoid or pleomorphic variant (or both)			
Yes	27 (22)	23 (18)	0·94 (0·50–1·75)
No	107 (51)	110 (76)	0·56 (0·39–0·80)
Previous stem cell transplantation			
Yes	39 (17)	50 (32)	0·51 (0·28–0·92)
No	95 (56)	83 (62)	0·70 (0·49–1·01)
***TP53* status**			
Mutated	40 (24)	37 (30)	0·57 (0·33–0·97)
Not mutated	66 (32)	57 (39)	0·52 (0·32–0·82)
Not performed or missing (or both)	28 (17)	39 (25)	1·16 (0·63–2·16)
Lactate dehydrogenase			
≤185 U/L	26 (5)	40 (25)	0·23 (0·09–0·59)
>185 U/L	106 (67)	92 (69)	0·74 (0·53–1·03)

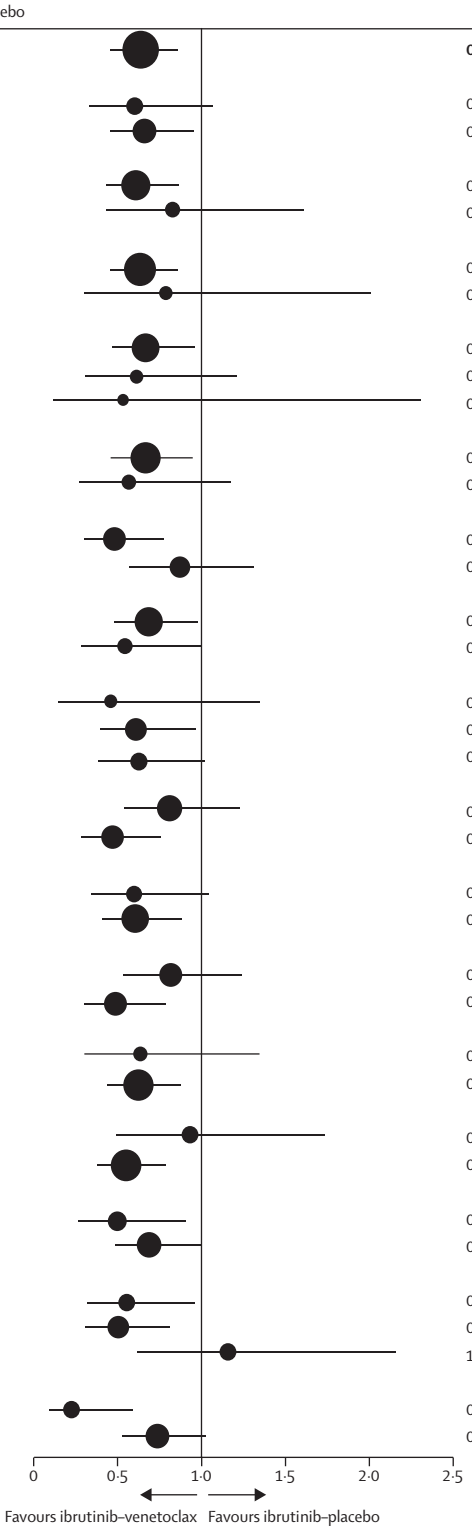

Figure 2: **Progression-free survival**

Kaplan–Meier curves for progression-free survival as assessed by the investigators (A) and as assessed by the independent review committee (B), and forest plot of HRs for progression-free survival as assessed by the investigators across patient subgroups (C). Patients without progression or death were censored at the last adequate disease assessment (global censoring rules). Tick marks indicate patients with censored data (A, B). All subgroup analyses (C) were prespecified, except lactate dehydrogenase, which was analysed post hoc. ECOG=Eastern Cooperative Oncology Group. MIPI=MCL International Prognostic Index. TLS=tumour lysis syndrome.

133 patients in the ibrutinib–placebo group (appendix p 18). In a post-hoc analysis, median overall survival was 36·7 months (95% CI 11·1–not estimable [NE]) in the ibrutinib–venetoclax group versus 15·4 months (10·9–38·5) in the ibrutinib–placebo group in patients with *TP53* mutations, and not reached (33·4–NE) versus 52·6 months (24·6–NE) in each group, respectively, in patients without *TP53* mutations (appendix pp 9–10).

Adverse events of grade 3 or worse occurred in 112 (84%) of 134 patients in the ibrutinib–venetoclax group and in 100 (76%) of 132 patients in the ibrutinib–placebo group. The most common grade 3–4 adverse events were neutropenia (42 [31%] of 134 patients *vs* 14 [11%] of 132 patients), thrombocytopenia (17 [13%] *vs* ten [8%]), and pneumonia (16 [12%] *vs* 14 [11%]; table 2; appendix pp 19–22). Serious adverse events occurred in 81 (60%) of 134 patients in the ibrutinib–venetoclax group and in 79 (60%) of 132 patients in the ibrutinib–placebo group (appendix p 23); serious adverse events related to ibrutinib occurred in 45 (34%) patients and 35 (27%) patients in each group, respectively, and serious adverse events related to venetoclax or placebo occurred in 31 (23%) patients and 25 (19%) patients, respectively.

Adverse events led to death in 22 (16%) of 134 patients in the ibrutinib–venetoclax group and in 18 (14%) of 132 patients in the ibrutinib–placebo group (appendix p 24). Adverse events leading to death were considered related to ibrutinib in three (2%) patients in the ibrutinib–venetoclax group (n=1 COVID-19 infection, n=1 cardiac arrest, and n=1 respiratory failure) and in two (2%) patients in the ibrutinib–placebo group (n=1 cardiac failure and n=1 COVID-19-related pneumonia). Adverse events leading to death were considered related to venetoclax or placebo in no patients in the ibrutinib–venetoclax group and in one (1%) patient in the ibrutinib–placebo group (n=1 cardiac failure).

Adverse events led to discontinuation of ibrutinib in 39 (29%) of 134 patients in the ibrutinib–venetoclax group and in 41 (31%) of 132 patients in the ibrutinib–placebo group and discontinuation of venetoclax or placebo in 30 (22%) patients and in 38 (29%) patients (appendix p 25). Adverse events led to dose reduction of ibrutinib in 34 (25%) patients and in 22 (17%) patients and led to dose reduction of venetoclax or placebo in 31 (23%) patients and in 15 (11%) patients, respectively (appendix p 26). Concomitant neutrophil growth factors were used in 36 (27%) patients in the ibrutinib–venetoclax group and in 14 (11%) patients in the ibrutinib–placebo group, and concomitant anti-diarrhoeal medications were used in 64 (48%) patients and in 24 (18%) patients, respectively.

Adverse events associated with laboratory tumour lysis syndrome (assessed per Howard criteria) occurred in five (4%) of 134 patients in the ibrutinib–venetoclax group and one (1%) of 132 patients in the ibrutinib–placebo group; adverse events associated with clinical tumour lysis syndrome were not reported.

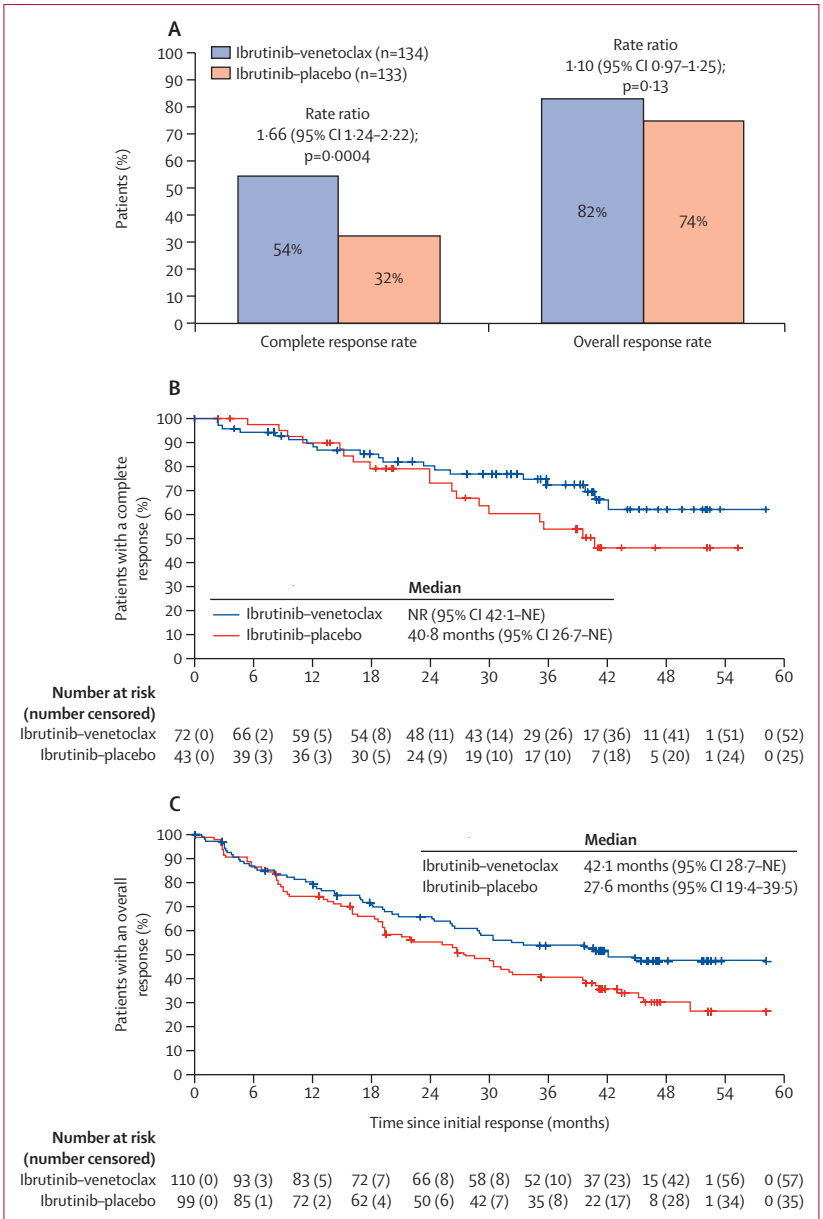

Figure 3: **Best overall response**
Complete response rates and overall response rates as assessed by investigators (A). Kaplan–Meier curves of duration of complete response (B) and duration of overall response (C). Patients without progression or death were censored at the last adequate disease assessment (global censoring rules). Tick marks indicate patients with censored data. NE=not estimable. NR=not reached.

COVID-19-related adverse events occurred in 25 (19%) of 134 patients in the ibrutinib–venetoclax group and 15 (11%) of 132 patients in the ibrutinib–placebo group. Deaths due to COVID-19 occurred in ten (7%) patients and ten (8%) patients in each group, respectively, (appendix p 27). Deaths due to COVID-19 had no meaningful effect on HRs for progression-free survival or overall survival (appendix p 11).

Mean steady-state venetoclax exposures when co-administered with 560 mg ibrutinib (area under the

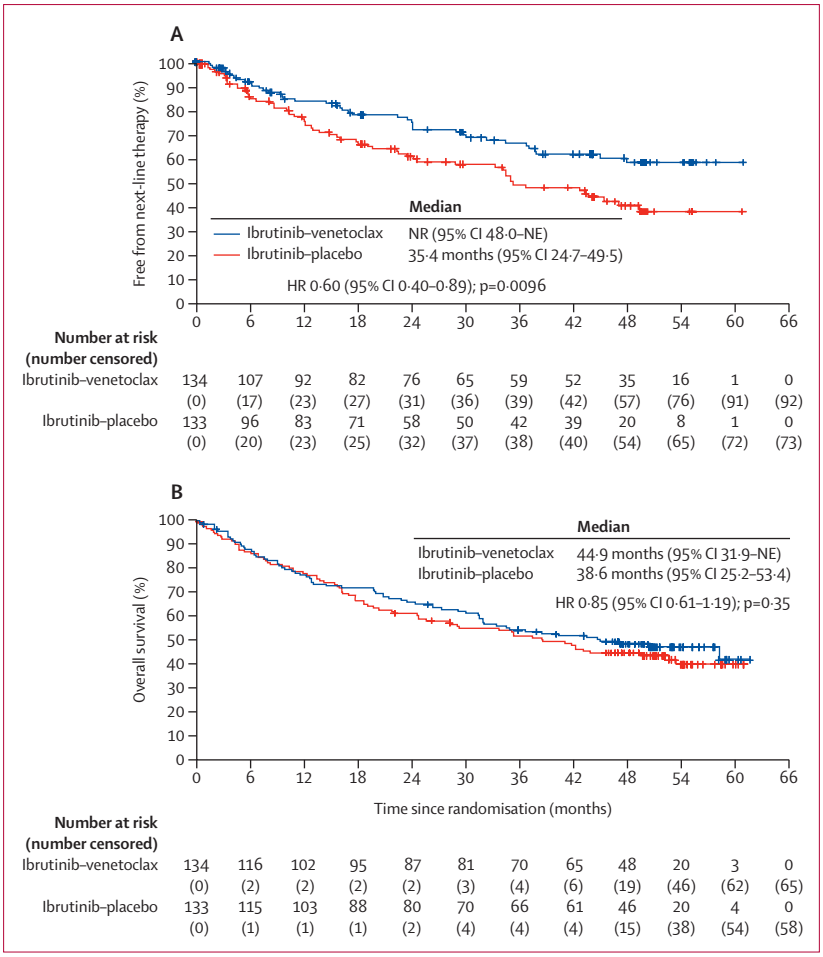

Figure 4: **Time to next treatment and overall survival**
Kaplan–Meier curves of time to next treatment (A) and overall survival (B). Tick marks indicate patients with censored data. NE=not estimable. NR=not reached.

concentration–time curve from 0 h to 24 h [AUC_{0-24h}] 65·0 µg×h/mL [SD 32·9]) were twice those of historical data for single-agent venetoclax 400 mg (32·8 µg×h/mL [16·9]; appendix p 12). Mean steady-state AUC_{0-24h} of ibrutinib was not increased (<25% change) with ibrutinib–venetoclax versus ibrutinib–placebo (1090 ng×h/mL [SD 870] *vs* 1440 ng×h/mL [SD 1060]; appendix p 12).

Median time to worsening in FACT-Lym was 9·3 months (95% CI 6·5–12·7) in the ibrutinib–venetoclax group versus 12·5 months (8·3–17·9) in the ibrutinib–placebo group (HR 1·17 [95% CI 0·88–1·55]; p=0·29). Mean EQ-5D-5L utility scores remained stable over time in both treatment groups in a post-hoc analysis (appendix p 13).

Discussion

This SYMPATICO study showed that in patients with relapsed or refractory MCL, progression-free survival significantly improved with ibrutinib–venetoclax treatment compared with ibrutinib–placebo treatment. Secondary endpoints, such as complete response rate and time to next treatment, also significantly improved with ibrutinib–venetoclax treatment, whereas the overall response rate and overall survival (at interim analysis) were not statistically significant.

The median progression-free survival of 31·9 months in the ibrutinib–venetoclax group appeared favourable compared with single-agent BTK inhibitors[2,3,14–16] and single-agent venetoclax in patients pre-treated with BTK inhibitors (2·8–3·2 months; 11·3 months in patients naive to BTK inhibitors),[4–6] noting the inherent limitations of cross-trial comparisons. Given the short progression-free survival observed with single-agent venetoclax after BTK inhibitor treatment in previous studies, combined ibrutinib and venetoclax achieved better outcomes than might be expected with a sequenced approach, implying synergy. Median progression-free survival with ibrutinib–venetoclax treatment was better than other treatment options for relapsed or refractory MCL, including 11·1 months with lenalidomide–rituximab (median of two previous regimens),[17] 6·5 months with bortezomib (one previous regimen),[18] 17·2 months with bendamustine–rituximab (two previous regimens),[19] and 18·0 months with ibrutinib–lemalidomide–rituximab (two previous regimens).[20] Other venetoclax-based regimens have demonstrated promising activity in early-phase clinical trials in relapsed or refractory MCL, including venetoclax–lenalidomide–rituximab,[21] ibrutinib–venetoclax–obinutuzumab,[22] and venetoclax–ibrutinib–prednisone–obinutuzumab–lenalidomide (ViPOR).[23] In heavily pretreated patients with relapsed or refractory MCL after previous BTK inhibitor therapy, subsequent treatment options include pirtobrutinib (median three previous regimens, including BTK inhibitors), providing a median progression-free survival of 7·4 months,[24] and chimeric antigen receptor T-cell (CAR-T) therapy with brexucabtagene autoleucel (median three previous regimens, including BTK inhibitors), providing a median progression-free survival of 25·8 months.[25] Importantly, the progression-free survival benefit in this study was generally robust across prespecified subgroups and in sensitivity analyses per IRC assessment, and with additional censoring per US FDA censoring rules.

TP53 mutations confer high risk of early progression with standard chemoimmunotherapy in patients with MCL.[1] Data from small single-group analyses suggest that outcomes with novel treatment options remain poor for patients with *TP53* mutations.[1] In this study, a high proportion of patients (75%) had known *TP53* status, enabling analysis of outcomes in patients with *TP53* mutations. HRs for progression-free survival in the ibrutinib–venetoclax group versus ibrutinib–placebo group were similar in patients with and without *TP53* mutations, albeit with wide CIs, suggesting that ibrutinib–venetoclax treatment might mitigate the poor prognosis associated with *TP53* mutations. However, no formal

	Ibrutinib–venetoclax group (n=134)				Ibrutinib–placebo group (n=132)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Any adverse event	22 (16%)	62 (46%)	28 (21%)	22 (16%)	30 (23%)	62 (47%)	20 (15%)	18 (14%)
Diarrhoea	76 (57%)	10 (7%)	1 (1%)	0	42 (32%)	3 (2%)	0	0
Neutropenia	4 (3%)	19 (14%)	23 (17%)	0	5 (4%)	7 (5%)	7 (5%)	0
Nausea	39 (29%)	3 (2%)	0	0	18 (14%)	4 (3%)	0	0
Fatigue	35 (26%)	4 (3%)	0	0	33 (25%)	3 (2%)	0	0
Anaemia	17 (13%)	11 (8%)	2 (1%)	0	12 (9%)	4 (3%)	0	0
Pyrexia	28 (21%)	0	0	0	26 (20%)	0	0	0
Cough	27 (20%)	0	0	0	35 (27%)	1 (1%)	0	0
Asthenia	25 (19%)	1 (1%)	0	0	18 (14%)	0	0	0
Thrombocytopenia	9 (7%)	8 (6%)	9 (7%)	0	11 (8%)	7 (5%)	3 (2%)	0
Vomiting	23 (17%)	2 (1%)	0	0	12 (9%)	3 (2%)	0	0
Pneumonia	7 (5%)	15 (11%)	1 (1%)	1 (1%)	6 (5%)	12 (9%)	2 (2%)	0
Vision blurred	23 (17%)	1 (1%)	0	0	23 (17%)	0	0	0
Upper respiratory tract infection	21 (16%)	2 (1%)	0	0	13 (10%)	3 (2%)	0	0
Decreased appetite	20 (15%)	2 (1%)	0	0	15 (11%)	0	0	0
Arthralgia	20 (15%)	1 (1%)	0	0	21 (16%)	2 (2%)	0	0
Hypokalaemia	16 (12%)	5 (4%)	0	0	8 (6%)	0	0	0
Constipation	19 (14%)	0	0	0	21 (16%)	1 (1%)	0	0
COVID-19	13 (10%)	3 (2%)	1 (1%)	2 (1%)	14 (11%)	0	1 (1%)	0
Dyspepsia	19 (14%)	0	0	0	10 (8%)	0	0	0
Visual acuity reduced	18 (13%)	1 (1%)	0	0	15 (11%)	0	0	0
Dry eye	18 (13%)	0	0	0	19 (14%)	0	0	0
Hypertension	12 (9%)	6 (4%)	0	0	9 (7%)	12 (9%)	0	0
Rash maculopapular	16 (12%)	2 (1%)	0	0	14 (11%)	0	0	0
Dyspnoea	15 (11%)	2 (1%)	0	0	15 (11%)	3 (2%)	0	0
Lacrimation increased	16 (12%)	1 (1%)	0	0	16 (12%)	0	0	0
Abdominal pain	12 (9%)	3 (2%)	0	0	10 (8%)	0	0	0
Oedema peripheral	15 (11%)	0	0	0	18 (14%)	3 (2%)	0	0
Atrial fibrillation	7 (5%)	7 (5%)	0	0	7 (5%)	7 (5%)	0	0
Dizziness	13 (10%)	1 (1%)	0	0	20 (15%)	0	0	0
Headache	14 (10%)	0	0	0	21 (16%)	1 (1%)	0	0
Hypomagnesaemia	13 (10%)	0	1 (1%)	0	3 (2%)	1 (1%)	0	0
Oropharyngeal pain	14 (10%)	0	0	0	15 (11%)	0	0	0
Pruritus	14 (10%)	0	0	0	15 (11%)	0	0	0
Urinary tract infection	12 (9%)	2 (1%)	0	0	8 (6%)	3 (2%)	0	0
Eye irritation	13 (10%)	0	0	0	20 (15%)	0	0	0
Myalgia	13 (10%)	0	0	0	16 (12%)	1 (1%)	0	0
Leukopenia	2 (1%)	8 (6%)	2 (1%)	0	0	0	0	0
Muscle spasms	11 (8%)	0	0	0	32 (24%)	0	0	0
Epistaxis	9 (7%)	1 (1%)	0	0	14 (11%)	0	0	0
Fall	8 (6%)	1 (1%)	1 (1%)	0	7 (5%)	2 (2%)	0	0
Back pain	6 (4%)	3 (2%)	0	0	14 (11%)	2 (2%)	0	0
MCL*	0	5 (4%)	0	4 (3%)	3 (2%)	4 (3%)	2 (2%)	10 (8%)
Atrial flutter	2 (1%)	5 (4%)	0	0	0	1 (1%)	0	0
Blood pressure increased	3 (2%)	4 (3%)	0	0	1 (1%)	1 (1%)	0	0
Hypotension	4 (3%)	3 (2%)	0	0	3 (2%)	2 (2%)	1 (1%)	0
Tumour lysis syndrome	1 (1%)	4 (3%)	2 (1%)	0	0	3 (2%)	0	0
Chest pain	6 (4%)	0	0	0	5 (4%)	0	1 (1%)	0
Syncope	5 (4%)	1 (1%)	0	0	1 (1%)	3 (2%)	0	0
COVID-19-related pneumonia	0	3 (2%)	0	2 (1%)	0	0	0	2 (2%)

(Table 2 continues on next page)

	Ibrutinib–venetoclax group (n=134)				Ibrutinib–placebo group (n=132)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Hyperglycaemia	2 (1%)	2 (1%)	1 (1%)	0	0	0	1 (1%)	0
Lymphopenia	3 (2%)	2 (1%)	0	0	0	0	1 (1%)	0
Paraesthesia	5 (4%)	0	0	0	14 (11%)	0	0	0
Acute kidney injury	0	3 (2%)	1 (1%)	0	2 (2%)	2 (2%)	0	0
Platelet count decreased	3 (2%)	0	1 (1%)	0	3 (2%)	2 (2%)	0	0
Pleural effusion	2 (1%)	1 (1%)	1 (1%)	0	4 (3%)	3 (2%)	0	0
Gastrointestinal haemorrhage	0	2 (1%)	1 (1%)	0	0	1 (1%)	0	0
Hyponatraemia	0	2 (1%)	1 (1%)	0	4 (3%)	1 (1%)	1 (1%)	0
Cardiac arrest	0	0	0	2 (%1)	0	0	0	0
Cardiac death	0	0	0	1 (1%)	0	0	0	0
Clostridium colitis	1 (1%)	0	0	1 (1%)	0	0	0	0
General physical health deterioration	1 (1%)	0	1 (1%)	0	1 (1%)	0	0	0
Haemorrhage intracranial	1 (1%)	0	0	1 (1%)	0	0	0	0
Hyperphosphataemia	1 (1%)	1 (1%)	0	0	3 (2%)	0	0	0
Neutrophil count decreased	1 (1%)	0	1 (1%)	0	1 (1%)	3 (2%)	1 (1%)	0
Pancytopenia	0	1 (1%)	1 (1%)	0	0	0	0	0
Respiratory failure	0	0	0	2 (1%)	0	1 (1%)	1 (1%)	2 (2%)
Appendicitis	0	1 (1%)	0	0	0	0	1 (1%)	0
Cardiomyopathy	1 (1%)	0	0	0	0	0	1 (1%)	0
Cerebrovascular accident	0	0	0	1 (1%)	0	0	0	0
Death	0	0	0	1 (1%)	0	0	0	0
Duodenal ulcer haemorrhage	0	0	1 (1%)	0	0	0	0	0
Gastric ulcer perforation	0	0	0	1 (1%)	0	0	0	0
Leucocytosis	1 (1%)	0	0	0	1 (1%)	3 (2%)	1 (1%)	0
Lymphoma	0	0	0	1 (1%)	0	0	0	0
Metabolic acidosis	0	1 (1%)	0	0	0	0	0	1 (1%)
Mitral valve disease	0	0	1 (1%)	0	0	0	0	0
Myelodysplastic syndrome	0	1 (1%)	0	0	0	0	1 (1%)	0
Staphylococcal sepsis	0	0	1 (1%)	0	0	0	1 (1%)	0
Subarachnoid haemorrhage	0	0	0	1 (1%)	1 (1%)	0	0	0
Sudden death	0	0	0	1 (1%)	0	0	0	0
Suicide attempt	0	0	1 (1%)	0	0	0	0	0
Acute respiratory distress syndrome	0	0	0	0	0	0	1 (1%)	0
Cardiac failure congestive	0	0	0	0	0	3 (2%)	0	0
Intestinal ischaemia	0	0	0	0	0	0	0	1 (1%)
Metastatic malignant melanoma	0	0	0	0	0	0	1 (1%)	0
Necrotising fasciitis	0	0	0	0	0	0	0	1 (1%)
Non-small-cell lung cancer	0	0	0	0	0	0	1 (1%)	0
Peripheral vascular disorder	0	0	0	0	0	0	1 (1%)	0
Sepsis	0	0	0	0	0	2 (2%)	1 (1%)	0
Upper gastrointestinal haemorrhage	0	0	0	0	1 (1%)	0	1 (1%)	0
Ventricular fibrillation	0	0	0	0	0	0	1 (1%)	0
Wound sepsis	0	0	0	0	0	0	1 (1%)	0

Data are n (%). Treatment-emergent adverse events are grade 1 or 2 occurring in 10% or more of patients, grade 3 adverse events occurring in 2% or more of patients, and all adverse events of grade 4 or 5, regardless of attribution to study treatment. MCL=mantle cell lymphoma. *Worsening of MCL not meeting protocol criteria for progressive disease.

Table 2: **Treatment-emergent adverse events (safety population)**

comparative statistical testing was done to establish whether *TP53* mutations significantly affected progression-free survival or overall survival. To our knowledge, this analysis represents the largest single-study cohort of patients with MCL and *TP53* mutations reported to date and the first randomised trial to

demonstrate improved progression-free survival in patients with relapsed or refractory MCL and *TP53* mutations. In the first-line setting, a trend towards numerically improved outcomes was also shown in patients with *TP53* mutations treated with ibrutinib–bendamustine–rituximab versus bendamustine–rituximab in the SHINE study (median progression-free survival 28·8 months *vs* 11·0 months; HR 0·95 [95% CI 0·50–1·80])[26] and in patients with high p53 expression by immunohistochemistry (>50%) treated with ibrutinib plus chemoimmunotherapy plus transplantation versus chemoimmunotherapy plus transplantation in the TRIANGLE study (failure-free survival not reported; HR 0·14 [one-sided 98·3% CI 0·0–0·57]), whereas a trend towards worse outcomes was shown in patients with high p53 expression treated with chemoimmunotherapy plus transplantation versus ibrutinib plus chemoimmunotherapy without transplantation (failure-free survival not reported; HR 3·24 [one-sided 98·3% CI 0·0–8·50]).[27] Zanubrutinib–obinutuzumab–venetoclax also showed promising response rates in 25 patients with *TP53* mutations in the BOVen study.[28] Similar to *TP53* mutations, blastoid and pleomorphic variants of MCL also typically have an aggressive disease course and poor outcomes with chemoimmunotherapy.[1] In this study, HRs for progression-free survival in the ibrutinib–venetoclax group versus ibrutinib–placebo group were similar between patients with and without blastoid variant.

Consistent with previous findings,[9,10] the complete response rate observed with ibrutinib–venetoclax treatment (54%) is substantially higher than that observed with single-agent ibrutinib (19–28%)[2,3] or single-agent venetoclax (18–21%).[4,5] These findings are consistent with preclinical synergistic antitumour activity between ibrutinib and venetoclax.[7,8] Complete responses appeared durable (median duration not reached with ibrutinib–venetoclax). Although data suggest higher MRD-negative rates are achievable with ibrutinib–venetoclax than with ibrutinib–placebo, an unexpectedly high proportion of patients had negative (~40%) or unknown (~20%) baseline MRD status; therefore, interpretation is limited by the small numbers of evaluable patients. Overall survival was not statistically significantly improved in the ibrutinib–venetoclax group in this interim analysis, and overall survival curves remain immature. Analysis of overall survival can also be confounded by use of subsequent anti-lymphoma therapies, which had occurred in 45% of patients in the ibrutinib–placebo group and 31% patients in the ibrutinib–venetoclax group.

The safety profile of ibrutinib–venetoclax was consistent with known adverse events for each single agent, with no new safety signals observed. Overlapping toxicities, such as cytopenias and gastrointestinal toxicity, were more frequent with combination treatment. Cardiac adverse events were generally well balanced between groups and led to death in less than 2% of patients in each group. Rates of atrial fibrillation in both groups were consistent with rates observed in pooled data from randomised ibrutinib trials. More adverse events led to treatment discontinuation in the ibrutinib–placebo group than in the ibrutinib–venetoclax group, probably because worsening of MCL not yet meeting progressive disease criteria (one of the most frequent reasons for discontinuation in both groups) was captured as a treatment-emergent adverse event. Consequently, patients remained longer on treatment in the ibrutinib–venetoclax group than the ibrutinib–placebo group (median 22·2 months *vs* 17·7 months).

Patients were accrued early and treated throughout the COVID-19 pandemic. Deaths due to COVID-19 were balanced between groups and had no meaningful effect on progression-free survival or overall survival benefit. Censoring for deaths due to COVID-19 resulted in longer estimates for median progression-free survival and overall survival, whereas HRs estimating the treatment effect with ibrutinib–venetoclax versus ibrutinib–placebo were consistent with the primary endpoint analysis.

Although this was a randomised, double-blind, placebo-controlled, phase 3 trial, several limitations exist. Small numbers of patients in some subgroups, such as those with blastoid or pleomorphic histology (or both), limit the ability to draw conclusions on the relative benefit of ibrutinib–venetoclax treatment for these subgroups. Despite high testing rates, *TP53* mutation status was unknown for 25% of patients. Although the importance of Ki-67 as a prognostic factor in MCL is recognised, the limited available tissue was prioritised for *TP53* central testing; consequently, Ki-67 results are not available for this analysis. Additionally, evaluation of MRD-negative remission was limited by the small proportion of patients with detectable MRD at baseline, particularly in the ibrutinib–placebo group. Although MRD samples from peripheral blood and bone marrow aspirates were collected from 228 (85%) of 267 patients and 213 (80%) of 267 patients, respectively, fewer than 50% of patients had detectable MCL cells at baseline, suggesting insufficient sensitivity of the assay. For future studies, an MRD-guided treatment approach could be considered; a sufficiently sensitive assay would be needed for informative results.

In conclusion, results from the SYMPATICO study showed that the addition of venetoclax to ibrutinib in an all-oral regimen improved outcomes compared with ibrutinib alone in patients with relapsed or refractory MCL. The ibrutinib–venetoclax combination demonstrated an acceptable safety profile. Overall, these results suggest that ibrutinib–venetoclax has a favourable benefit–risk profile in patients with relapsed or refractory MCL.

Contributors

MW, WJ, MT, DB, TW, NG, M-MK, TvM, RFA, GvK, CT, FP, MA, MH, and CST collected data. MW, JKN, and CST provided clinical and scientific input on the study design and protocol. MW and JKN accessed and verified the study data. All authors interpreted the data. JL did the statistical analysis. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MW reports 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, TS Oncology, Miltenyi Biomedicine, Moffit Cancer Center, Mumbai Hematology Group, Newbridge Pharmaceuticals, OMI, OncLive, Pharmacyclics (an AbbVie Company), Physicians Education Resources, Practice Point Communications, Scripps, and The First Affliliated Hospital of Zhejiang University; consulting or an advisory role for AstraZeneca, Bayer Healthcare, BeiGene, BioInvent, CSTone, DTRM Biopharma (Cayman), Epizyme, Genentech, InnoCare, Janssen, Juno Therapeutics, Kite Pharma, Loxo Oncology, Miltenyi Biomedicine, Oncternal, Pharmacyclics (an AbbVie Company), and VelosBio; research funding from Acerta Pharma, AstraZeneca, BeiGene, BioInvent, Celgene, Genentech, InnoCare, Janssen, Juno Therapeutics, Kite Pharma, Lilly, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics (an AbbVie Company), and VelosBio; and funding for travel or accommodation from Acerta Pharma, AstraZeneca, BioInvent, Celgene, Janssen, Juno Therapeutics, Kite, Loxo Oncology, Molecular Templates, Oncternal, Pharmacyclics (an AbbVie Company), Physician Education Resources, VelosBio, and Verastem. WJ reports consulting and an 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. MT reports honoraria from AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, F Hoffmann-La Roche, Gilead Sciences, Incyte, Janssen, MorphoSys, Novartis, Portola, and Takeda; consulting or an advisory role for AbbVie, Amgen, Bristol Myers Squibb, Gilead Sciences, Incyte, Janssen, MorphoSys, Novartis, Roche, and Takeda; and funding for travel or accommodation from AbbVie, Bristol Myers Squibb, Gilead Sciences, Janssen, Roche, and Takeda. DB reports consulting or an advisory role for Gilead Sciences, Janssen-Cilag, Novartis, Roche, and Takeda; research funding from Genmab, Janssen-Cilag, MorphoSys, and Roche; and funding for travel or accommodation from Gilead Science, Roche, and Takeda. TW reports honoraria from BeiGene, Bristol Myers Squibb, Celgene, Gilead, Janssen-Cilag, Novartis, Roche, Sanofi, and Takeda; consulting or an advisory role for BeiGene, Bristol Myers Squibb, Celgene, Gilead, GSK, Janssen-Cilag, Novartis, Pfizer, Roche, Sanofi, and Takeda; and research funding from Roche. NG reports consulting or an advisory role for AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Genentech, Gilead/Kite Pharma, Incyte, Janssen, Lava Therapeutics, Lilly, and Novartis; and research funding from AbbVie, Bristol Myers Squibb, Genentech, Gilead/Kite Pharma, MorphoSys, and Pharmacyclics (an AbbVie Company). M-MK reports consulting or an advisory role for Janssen and Roche. TvM reports honoraria from Bristol Myers Squibb, Celgene, Gilead, and Kite; consulting or an advisory role for Gilead, Janssen, and Kite; and research funding from Celgene or Bristol Myers Squibb and Genentech. GvK reports honoraria from AbbVie, Pharmacyclics (an AbbVie Company), Incyte, and Merck; consulting or an advisory role for AbbVie, Incyte, Merck, and Pharmacyclics (an AbbVie Company); and research funding from AbbVie, Janssen, Merck, Syndax, and TG Therapeutics. MH reports honoraria from AstraZeneca, BeiGene, Janssen, Kite, Novartis, Pharmacyclics (an AbbVie Company), and TG Therapeutics and consulting or an advisory role for AstraZeneca, BeiGene, Janssen, Kite, Novartis, Pharmacyclics (an AbbVie Company), and TG Therapeutics. ES-G, JL, JPD, and JKN report employment and stock or other ownership with AbbVie. CST reports honoraria from AbbVie, BeiGene, Janssen, and LOXO and research funding from AbbVie, BeiGene, and Janssen. RFA, CT, FP, and MA declare no competing interests.

Data sharing

Access to clinical trial data, such as anonymised, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, analysis plans, or data dictionaries), can be requested by any qualified researchers who engage in rigorous, independent, scientific research. These data will be provided following review and approval of a research proposal, statistical analysis plan, and execution of a Data Sharing Agreement. Data requests can be submitted at any time after approval in the USA and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered. For more information on the process or to submit a request, see https://vivli.org/ourmember/abbvie/.

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