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LATE BREAKING ABSTRACTS

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Ibrutinib Combined with Venetoclax in Patients with Relapsed/Refractory Mantle Cell Lymphoma: Primary Analysis Results from the Randomized Phase 3 Sympatico Study

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Background: Ibrutinib (Ibr) is a once-daily Bruton tyrosine kinase (BTK) inhibitor approved in multiple regions for patients (pts) with mantle cell lymphoma (MCL) who have received ≥1 prior therapy. Venetoclax (Ven) is a BCL-2 inhibitor approved in the US for pts with chronic lymphocytic leukemia and previously untreated acute myeloid leukemia. Ibr and Ven have distinct and complementary modes of action, and the combination has shown promising clinical activity in early phase studies in MCL (Tam, *N Engl J Med* 2018; Wang, *J Hematol Oncol* 2021). Here, we report the primary analysis results from the multinational, randomized, double-blind, phase 3 SYMPATICO (NCT03112174) study comparing Ibr+Ven vs Ibr + placebo (Pbo) in pts with relapsed/refractory (R/R) MCL.

Methods: Pts aged ≥18 y with R/R MCL after 1-5 prior therapies were randomly assigned 1:1 to receive oral Ibr 560 mg once daily concurrently with oral Ven (standard 5-wk ramp-up to a target dose of 400 mg once daily) or Pbo for 2 y, followed by single-agent Ibr until progressive disease (PD) or unacceptable toxicity. Randomization was stratified based on ECOG PS, prior lines of therapy, and tumor lysis syndrome (TLS) risk based on tumor burden and CrCl. The primary endpoint was progression-free survival (PFS) by investigator (INV) assessment using Lugano criteria; pts without PD or death were censored at the last non-PD assessment (per global censoring rules). Additional sensitivity analyses included PFS assessment by independent review committee (IRC) and censoring per US FDA rules (**Table**). Key secondary endpoints were tested hierarchically in the following order: complete response (CR) rate by INV assessment, time to next treatment (TTNT), overall survival (OS, interim analysis), and overall response rate (ORR) by INV assessment.

Results: A total of 267 pts were enrolled and randomly assigned to receive Ibr+Ven (n=134) or Ibr+Pbo (n=133). Median age was 68 y; 96% of pts had an ECOG PS of 0-1, 17% had ≥3 prior lines of therapy, and 22% were at increased risk for TLS. At baseline, pts in the Ibr+Ven vs Ibr+Pbo arms had median ages 69 vs 67 y, high-risk simplified MCL International Prognostic

Index score 38% vs 31%, bulky disease ≥5 cm 46% vs 40%, bone marrow involvement 46% vs 41%, splenomegaly 31% vs 25%, and *TP53* mutated 30% vs 28%; other baseline characteristics were generally similar between arms. With a median time on study of 51.2 mo, median PFS by INV assessment was significantly longer with Ibr+Ven vs Ibr+Pbo (31.9 vs 22.1 mo), with a hazard ratio (HR) of 0.65 (95% CI, 0.47-0.88; stratified log-rank *P*=0.0052) (**Figure**). PFS rates at 24 mo were 57% and 45% with Ibr+Ven and Ibr+Pbo, respectively. PFS benefit with Ibr+Ven vs Ibr+Pbo was generally consistent across prespecified subgroups, including those with blastoid variant or *TP53*-mutated MCL. Sensitivity analyses of PFS were consistent with the primary analysis (**Table**). Ibr+Ven significantly improved CR rates (54% vs 32%) and TTNT (median not reached [NR] vs 35.4 mo); at the current 51.2 mo median follow-up, median OS was 44.9 mo with Ibr+Ven vs 38.6 mo with Ibr+Pbo (HR 0.85 [95% CI, 0.62-1.19]) (**Table**). Median duration of treatment was 22.2 mo for the Ibr+Ven arm and 17.7 mo for the Ibr+Pbo arm; at the time of analysis, 30% of pts in the Ibr+Ven arm and 20% of pts in the Ibr+Pbo arm remained on single-agent Ibr. Grade ≥3 adverse events (AEs) occurred in 84% of pts with Ibr+Ven vs 76% with Ibr+Pbo; the most frequent (occurring in ≥5% of pts) were neutropenia (31% vs 11%), pneumonia (13% vs 11%), thrombocytopenia (13% vs 8%), anemia (10% vs 3%), diarrhea (8% vs 2%), leukopenia (7% vs 0%), MCL (7% vs 12%), atrial fibrillation (5% vs 5%), COVID-19 (5% vs 1%), and hypertension (4% vs 9%). Serious AEs occurred in 60% of pts in each arm. No clinical TLS occurred; laboratory TLS occurred in 5% and 2% of pts in the Ibr+Ven and Ibr+Pbo arms, respectively. COVID-19 deaths occurred in 10 pts in each arm and had no meaningful impact on PFS or OS HRs.

Conclusion: The Ibr+Ven combination demonstrated a statistically significant improvement in PFS compared with Ibr+Pbo in pts with R/R MCL; CR rates and TTNT were also significantly improved with Ibr+Ven. OS was numerically but not significantly improved at this interim analysis. The safety profile of Ibr+Ven was consistent with known AEs for each agent, with no new safety signals observed. Overall, these results demonstrate a favorable benefit-risk profile for Ibr+Ven in pts with R/R MCL.

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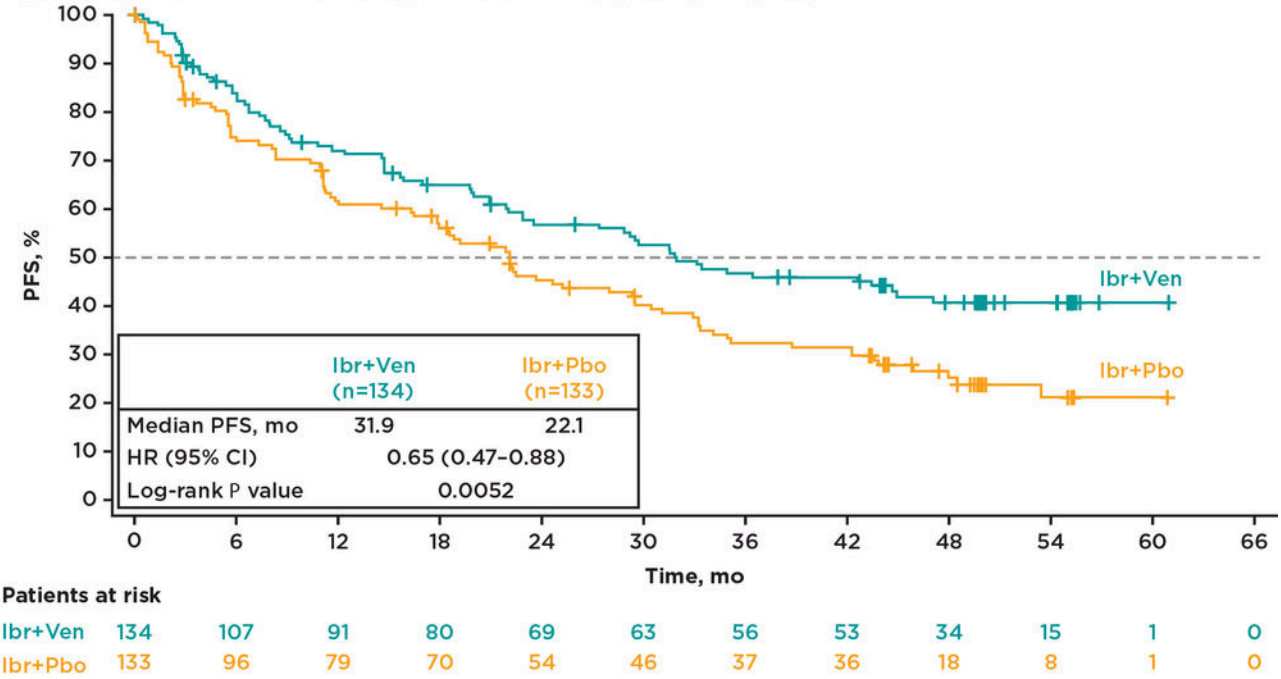
OffLabel Disclosure: The combination of ibrutinib + venetoclax is not approved for the treatment of MCL in any region.

Figure. PFS per INV Assessment Using Global Censoring (primary endpoint)



Patients at risk

Ibr+Ven	134	107	91	80	69	63	56	53	34	15	1	0
Ibr+Pbo	133	96	79	70	54	46	37	36	18	8	1	0

Table. Primary and Secondary Efficacy Endpoints

	Ibr+Ven (n=134)	Ibr+Pbo (n=133)	HR (or rate ratio) (95% CI)[a]	*P* value[b]
Median PFS by INV, mo				
Global censoring[c]	31.9	22.1	0.65 (0.47–0.88)	0.0052
US FDA censoring[d]	42.6	22.1	0.60 (0.44–0.83)	0.0021
Median PFS by IRC, mo				
Global censoring[c]	31.8	20.9	0.67 (0.49–0.91)	0.0108
US FDA censoring[d]	43.5	22.1	0.63 (0.45–0.87)	0.0057
Median TTNT, mo	NR	35.4	0.60 (0.40–0.89)	0.0096
ORR, %	82	74	1.10 (0.97–1.25)	0.1279
CR rate, %	54	32	1.66 (1.24–2.22)	0.0004
Median duration of response, mo	42.1	27.6		
Median duration of CR, mo	NR	40.8		
Median OS, mo (interim analysis)	44.9	38.6	0.85 (0.62–1.19)	0.3465

[a]HRs are reported for PFS, TTNT, and OS; rate ratios are reported for CR rate and ORR.
[b]*P* values were determined by stratified log-rank test for PFS, TTNT, and OS, and by stratified Cochran-Mantel-Haenszel test for CR rate and ORR (stratification factors: prior lines of therapy [1–2 vs ≥3] and TLS risk category [low vs increased risk]).
[c]Global censoring: pts without PD or death were censored at last follow-up without PFS event.
[d]US FDA censoring: pts without PD or death, with subsequent anticancer therapy, or with 2 or more missed visits prior to the PFS event were censored at last follow-up without PFS event.

Figure 1

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