Ibrutinib in combination with rituximab for relapsed mantle cell lymphoma: an update from a Phase II clinical trial

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Introduction

Mantle cell lymphoma (MCL), a rare but distinct subset of B-cell non-Hodgkin lymphoma, is characterized by a t(11;14) chromosomal translocation that causes cyclinD1 overexpression and cell cycle dysregulation.[1] MCL initially responds to current frontline treatments but usually relapses.[2,3] Relapsed patients respond poorly to standard therapy and often develop chemoresistance, which often leads to death from progressive MCL. Innovative approaches are urgently needed to overcome these poor treatment outcomes.[4]

Ibrutinib is a first-in-class, once-daily, oral covalent inhibitor of Bruton's tyrosine kinase (BTK),[5] an important component of the B-cell receptor signaling pathway.[6,7] Ibrutinib binds covalently to a cysteine residue (Cys-481) in the BTK active site ATP-binding domain,[8] which blocks B-cell receptor signaling within the malignant B-cell and inhibits cell growth and proliferation, survival, adhesion, and migration.[9,10] In a previous single-agent, single-arm Phase 1b/2 study of ibrutinib in MCL patients who had received at least one prior therapy, an overall response rate (ORR) of 68% was reported, with a complete response (CR) rate of 21%.[11] A longer-term follow-up (median 26.7 months) of this study recently reported a median PFS of 13.0 months and a median overall survival of 22.5 months.[12] Based on the results of the phase 1b/2 study, ibrutinib has now been approved in the United States, European Union, and other countries to treat MCL patients who have received at least one prior line of therapy.

In MCL patients treated with ibrutinib, we observed a transient increase in lymphocytes in the peripheral blood, termed the compartmental shift phenomenon, of 34% of patients during the tumor reduction phase.[11] Based on this finding, we hypothesized that rituximab, an anti-CD20 monoclonal antibody with minimal activity and toxicity in MCL patients, can target these lymphocytes present in the peripheral blood, leading to rituximab-induced apoptosis and rituximab-dependent cytotoxicity. To determine whether the combination of ibrutinib and rituximab exhibit greater anti-MCL activity compared with either agent alone and is an efficacious therapy in relapsed or refractory MCL patients, we first conducted preclinical studies to assess the effects of ibrutinib and rituximab in MCL-bearing SCID-hu mice,[13] which led to the initiation of a single-arm, open-label phase 2 clinical trial to assess the safety and efficacy of this combination in MCL patients. Here, we report the preclinical and clinical findings supporting the synergistic effect of ibrutinib in combination with rituximab in relapsed/refractory MCL. In addition, we discuss the association between the levels of the proliferation marker, Ki-67, and treatment outcomes, as assessed in the present study.

Patient Characteristics (N=50)

Median Age (Range)	67 (45-86)
Male (%)	38 (76%)
ECOG Performance Status (0 or 1)	50 (100%)
Median Prior Therapies (Range)	3 (1 - 9)
≥ 3	27 (54 %)
Previous Therapy	
Hyper-CVAD	32 (64%)
Lenalidomide	10 (20%)
Bortezomib	18 (36%)
Simplified MIPI	
Low Risk	22 (44%)
Intermediate Risk	22 (44%)
High Risk	6 (12%)
Tumor Features	
Bulky Mass	3 (6%)
At least one node ≥ 5 cm	17 (34%)
Refractory disease	35 (70%)
Advanced disease	15 (30%)

Table 1. Patient baseline demographic and disease characteristics.

Results

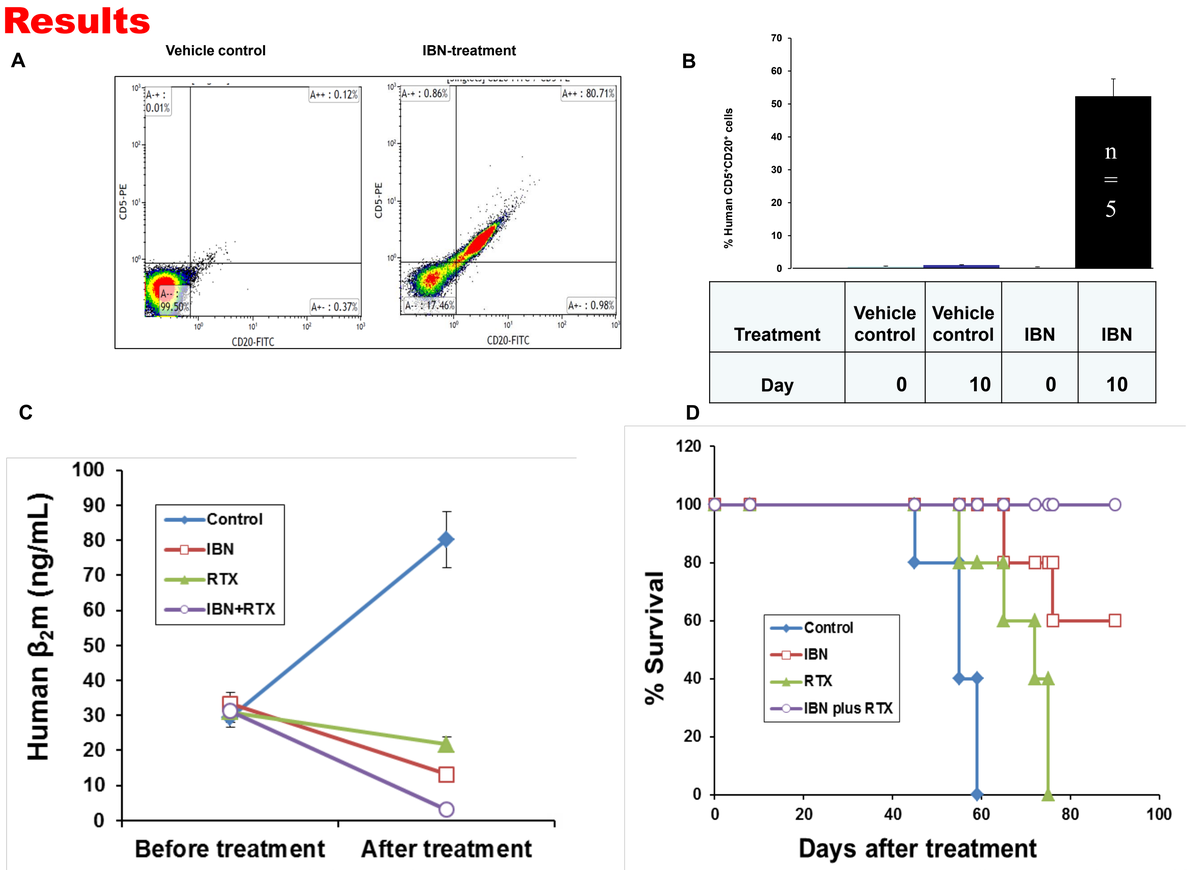

Figure 1. Ibrutinib induces compartmental shift of primary MCL cells and its combination with subsequent rituximab enhances the therapeutic effect in patient MCL-bearing SCID-hu mice (PDX model). Six to 8 week-old SCID mice were subcutaneously implanted with human fetal bone chips (SCID-hu). After 6 weeks of bone implantation, the freshly isolated MCL cells from patients were directly engrafted into the human fetal bone chips. The engrafted MCL cells produced measurable levels of human β_2-microglobulin (β_2m) in mouse serum. Once human β_2m had been detected, the primary MCL-bearing SCID-hu mice were treated with 25 mg/kg ibrutinib oral gavage daily. A transient increase of human CD5$^+$CD20$^+$ cells in mouse peripheral blood was detected by flow cytometry on treatment day 10, representing a shift of human MCL cells from human fetal bone chip to mouse peripheral blood. Once a transient increase of human CD5$^+$CD20$^+$ cells in mouse peripheral blood was detected, 10 mg/kg rituximab was intravenously administered every 3 days for a total of 7 doses. Vehicle control, ibrutinib alone, and rituximab alone were treatment comparisons. (**A**) Representative flow cytometry data and (**B**) pooled data showing that ibrutinib-induced a shift of human CD5$^+$CD20$^+$ cells from the bone chip to mouse peripheral blood. (**C**) Tumor burden was monitored by human β_2m levels in mouse serum before treatment (day 0) and after treatment (day 30; $P < 0.01$, IBN plus RTX versus vehicle control or RTX; $P < 0.05$, IBN plus RTX versus IBN). (**D**) Kaplan-Meier survival curves of primary MCL-bearing SCID-hu mice were analyzed ($P < 0.01$, IBN plus RTX versus vehicle control, RTX, or IBN). RTX: rituximab; IBN: ibrutinib.

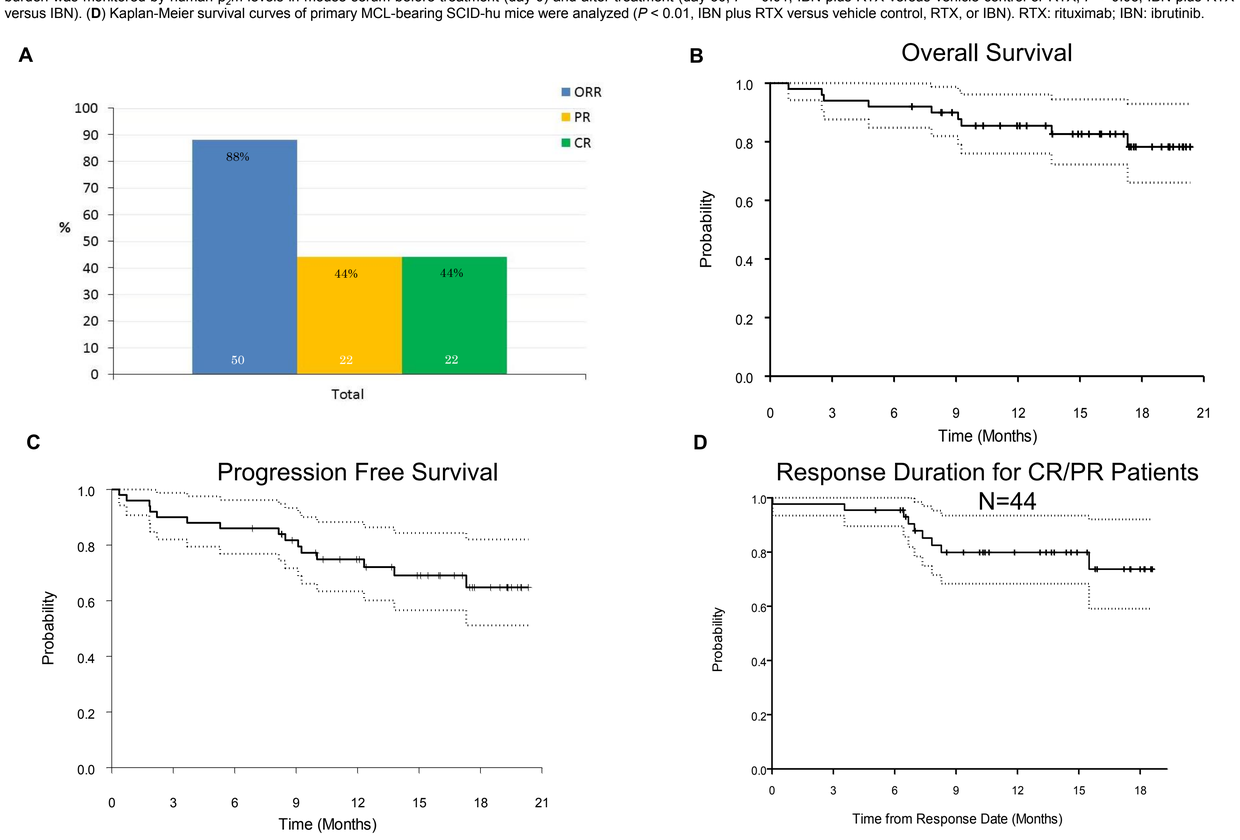

Figure 2. Efficacy outcomes for ibrutinib combined with rituximab in the phase 2 trial. (A) ORR, CR and PR rates of all patients (N=50) enrolled in the study. (B) Overall survival of all patients enrolled in the study. (C) Progression free survival of all patients enrolled in the study. (D) Duration of response among patients who achieved a response.

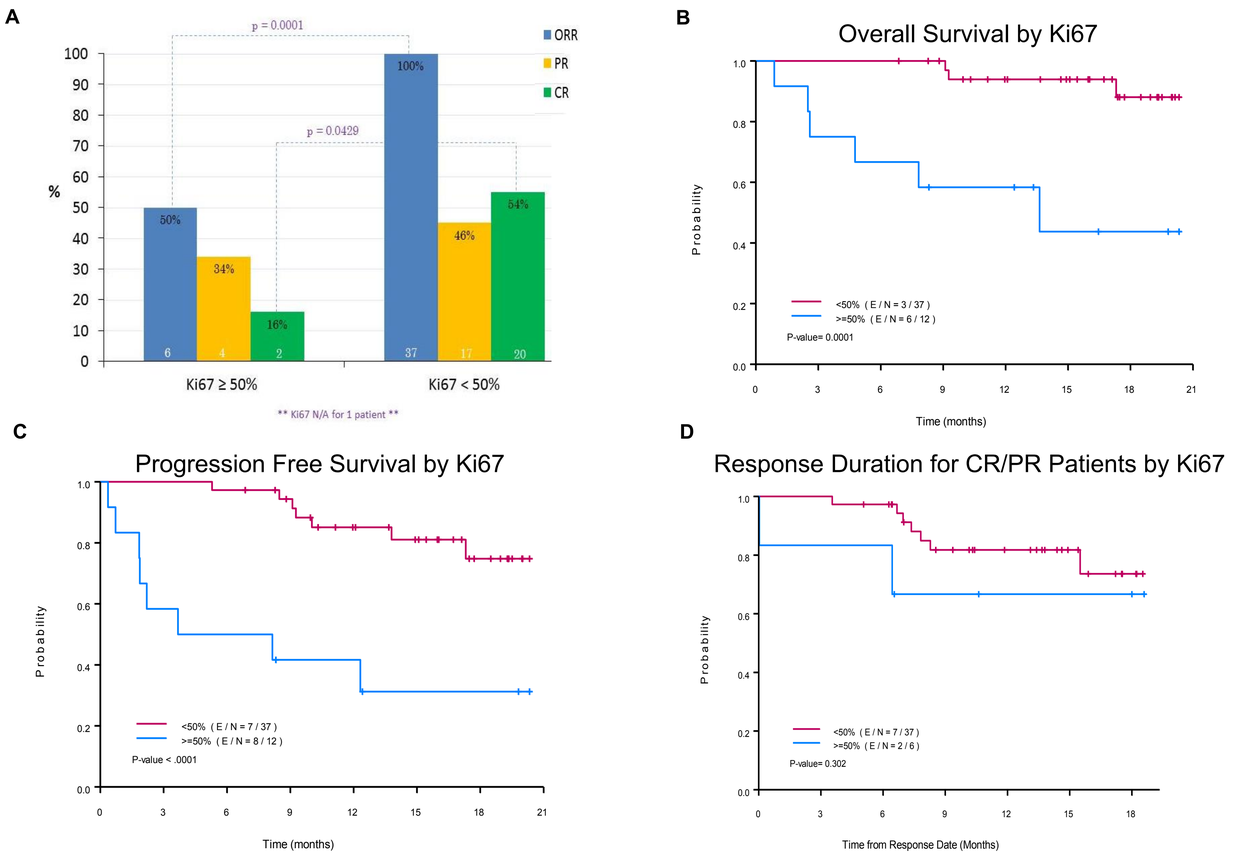

Figure 3. Efficacy outcomes for ibrutinib combined with rituximab based on Ki-67 levels. (A) ORR, CR and PR rates evaluated in 49 patients with measurable Ki-67 values. (B) Overall survival of 49 patients with Ki-67 values. (C) Progression free survival of 49 patients with Ki-67 values. (D) Duration of response among patients who achieved a response and had measurable Ki-67 values.

Conclusions

The combination of ibrutinib and rituximab demonstrated encouraging activity in relapsed/refractory MCL, with an ORR of 88% and a CR in 44% of patients. After approximately 16.5 months of follow-up, the median DOR, PFS, and OS have still not been reached. Consistent with the toxicity profile of single-agent ibrutinib in the phase 2 study,[11,12] fatigue, diarrhoea, nausea, and dyspnoea were the most common AEs reported with the combination treatment. The majority of AEs were grade 1-2, with only 8 patients experiencing grade 3 haematological events. The enhanced efficacy of ibrutinib in combination with rituximab observed in this trial relative to single-agent ibrutinib is a practice-changing concept in the treatment of patients with relapsed/refractory MCL. Although our trial is a single-centre trial, this study provides encouraging results with this treatment combination in a substantial proportion of patients with advanced MCL. With the ease of administration and lack of severe toxicities, this regimen is likely to become a widely used combination regimen in daily practice, particularly in elderly patients. In conclusion, ibrutinib in combination with rituximab is a safe and effective therapy for relapsed/refractory MCL.

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