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SHORT REPORT

Haematological Malignancy – Clinicals

A phase II study of ibrutinib in combination with ixazomib in patients with Waldenström macroglobulinaemia

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Summary

This phase II study evaluated time-limited (24 cycles) treatment with ibrutinib and ixazomib in newly diagnosed (NDWM; $n = 9$) and relapsed/refractory (RRWM; $n = 12$) Waldenström macroglobulinaemia (WM). The overall response rate (ORR) was 76.2% ($n = 16$) in 21 evaluable patients with no patient achieving a complete response (CR). The median duration of treatment was 15.6 months, and after a median follow-up time of 25.7 months, the median progression-free survival (PFS) was 22.9 months. While the primary end-point was not met (CR rate at any time) and 28.5% discontinued treatment due to toxicity, ibrutinib plus ixazomib led to a clinically meaningful ORR and PFS. Combined Bruton's tyrosine kinase (BTK) and proteasome inhibition merits further evaluation in WM.

KEYWORDS
clinical trials, non Hodgkin's lymphoma, Waldenstrom's macroglobulinaemia

Waldenström macroglobulinaemia (WM) is an indolent, immunoglobulin M (IgM)-producing lymphoproliferative disorder that represents 1%–2% of all non-Hodgkin lymphomas.[1] Efforts to elucidate WM biology have led to the discovery of two critical survival pathways in the WM cell: B-cell receptor (BCR) signalling and the ubiquitin proteasome degradation system (UPS).[2,3] The Bruton's tyrosine kinase (BTK) inhibitor ibrutinib resulted in high overall response rates (ORRs) in both newly diagnosed WM (NDWM) and relapsed/refractory WM (RRWM); however, no patients achieved a complete response (CR).[4] The proteasome inhibitor ixazomib has shown anti-WM activity when combined with rituximab and dexamethasone in WM.[5] However, CRs are also rare with proteasome inhibitor-based therapies, which highlights the need for combinatorial therapy in WM in efforts to achieve deeper responses. We report preclinical data evaluating the efficacy and mechanisms of action of ibrutinib and ixazomib in WM cell lines as well as the results from a phase II trial evaluating the efficacy of ixazomib and ibrutinib in patients with NDWM and RRWM.

NCT03506373 is a phase II, single-arm study to assess the efficacy, safety and tolerability of ibrutinib and ixazomib in patients with WM. Patients received ixazomib 4 mg po on Days 1, 8 and 15 and ibrutinib 420 mg po daily in 4-weekly cycles. Patients received up to a maximum of 24 cycles of treatment. This study was approved by the Institutional Review Board at Mayo Clinic Florida. Key inclusion criteria included histological confirmation of WM and indication for the initiation of therapy as per the second International Workshop on WM.[6] Ibrutinib-exposed patients were allowed so long as they did not develop disease progression while previously on a BTK inhibitor.

The primary objective was to estimate the CR rate. Secondary objectives included the evaluation of the ORR,

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time to progression (TTP), overall survival (OS) and the safety profile of ixazomib and ibrutinib. Correlative goals were included to determine the role of the members of the BTK signalosome in achievement or lack thereof of response to ibrutinib and ixazomib. Twenty-four cycles of therapy were chosen as the treatment duration because long-term follow-up of single-agent ibrutinib in patients with RRWM revealed that while no CRs were achieved, the median time to VGPR was 15.5 months and VGPR rate increased over time.[4] Hence, we hypothesized that 24 cycles of ibrutinib in combination with ixazomib would lead to synergistic levels of WM cell apoptosis and allow sufficient time for deepening of responses and achievement of CR. Response rates were assessed as per the VIth International Workshop on WM.[9] This study used a modified two-stage Simon optimum design. The modification to the Simon design was to allow accrual to continue during the interim analysis.

Materials and methods for correlative studies are included in Data S1. The combination of ibrutinib and ixazomib significantly decreased tumour cell viability as compared to single-agent treatment alone in all cell lines tested (Figure S1A). As anticipated, cotreatment of ibrutinib + ixazomib also led to increased apoptosis; mostly in BCWM.1 (~96%) and its isogenic ibrutinib-resistant clone BCWM.1/IR (~46.5%) (Figure S1B). As indicated in Figure S1D, ibrutinib cotreatment with ixazomib inhibited BCL-2, MCL-1 and PLCγ2 which was confirmed by western blot analysis in WT and ibrutinib-resistant WM cells and semi-quantified by Gel Quant software. As shown in Figure S1C, we observed decreased inner mitochondrial membrane potential (IMMP) for single-agent ibrutinib and ixazomib versus DMSO-treated control cells (indicating intact mitochondrial membrane). While not significantly decreased compared to ixazomib treatment, IMMP was significantly lower in combination-treated cells relative to single-agent ibrutinib-treated cells.

As of 7 June 2021, the study accrued 24 patients before the study was closed due to early indications that the study likely would not pass the interim analysis. Twenty-one patients were evaluable for the primary end-point (CR rate at any time). The median age was 72 years (range: 54–79), 71.4% of patients were male and all 21 patients were non-Hispanic Whites. The median ISSWM score at the time of study entry was 1.0 (range: 0.0–3.0). Fifteen patients (71.4%) had mutated (mut) MYD88L265P, six patients (28.6%) had CXCR4mut (four nonsense mut and two frameshift mut) and 1 patient (4.8%) had MYD88L265P wild-type (wt) and CXCR4mut. Nine patients (42.9%) had NDWM and 12 patients (57.1%) had RRWM. Patients with RRWM had received a median of 2 (range: 1–4) prior lines of therapy; 10 (83.3%) received rituximab, 4 (33.3%) received bortezomib, 6 (50.0%) received alkylator-based therapy (i.e. bendamustine or cyclophosphamide-based). Two patients were previously treated with ibrutinib.

Five patients completed the planned 2 years of therapy. Among the 16 patients who did not complete 2 years of planned therapy, six discontinued due to adverse events (AEs), five due to PD, two due to withdrawal and three due to other reasons. The most common AEs were haematological and gastrointestinal. AEs are listed in Table 1. Six (29%) patients required dose reduction in ixazomib due to AEs and one (5%) patient required dose reduction in ibrutinib due to AEs. No treatment-related deaths were noted. The ORR was 76.2% ($n = 16/21$ responded) with no patients achieving a CR, thus the primary end-point was not met. ORRs were similar between NDWM (77.8%) and RRWM (75%) patients (Figure 1A). At best response, median serum IgM level decreased from 2500 mg/dL to 756 mg/dL (range, 0–4394 mg/dL) when compared with baseline. For the five patients who completed 24 cycles of therapy and had an end-of-treatment bone marrow biopsy, the median bone marrow WM involvement decreased from 40% to 10% (range, 0%–80%). In the eight patients that were MYD88mut/CXCRwt, the ORR was 75.0%.The ORR was 83.3% (5/6 with ≥PR) in CXCR4mut patients. The median duration of treatment was 15.6 months (range: 2.4–24.2) and patients received a median of 15 cycles (range: 2–24) of ibrutinib and ixazomib therapy. The median time to response for all patients was 108.5 days and the median time to best response was 111 days. The median follow-up time in patients that are still alive was 25.7 months (range: 9.5–53.4). The median time to progression (TTP) was 22.9 months (range: 17.2-NE; Figure 1B), and median progression-free survival (PFS) was 22.9 months (95% CI: 17.2-NE; Figure 1C). Eight patients have developed progressive WM since coming off the clinical trial treatment. Thirteen patients have received subsequent treatment with a median time to next treatment of 1.3 months (range: 0.0–21.3) after treatment discontinuation.

This is the first reported clinical trial evaluating a time-limited, all-oral therapeutic strategy with the combination of a BTK inhibitor and a proteasome inhibitor for the treatment of WM. Both NDWM and RRWM patients treated with ibrutinib and ixazomib achieved a similar ORR which compares favourably with other WM treatments such as bendamustine and rituximab (BR); rituximab, cyclophosphamide and dexamethasone (RCD); single-agent ibrutinib; single-agent zanubrutinib; and bortezomib, rituximab and dexamethasone (BDR).[7–11] However, the PFS in our study is less than with the aforementioned agents/regimens. Time-limited treatment for WM is increasingly becoming the focus of clinical trials in efforts to minimize financial as well as the long-term toxicities associated with continuous therapy. Continuous treatment with BTK inhibitors is estimated to cost over $1.5 million dollars.[12] Single-agent ibrutinib until disease progression is associated with an atrial fibrillation rate of 12.7% and a hypertension rate of 6.3% in WM patients, whereas in our study of time-limited ibrutinib and ixazomib, no patients developed atrial fibrillation and 10% developed hypertension.[4] The cardiovascular morbidity was low in our trial with no patient experiencing ventricular arrhythmias. However, in an ongoing trial of time-limited, all-oral ibrutinib and venetoclax (24 q28 day cycles) for patients with relapsed WM, albeit demonstrating an impressive estimated 12-month

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TABLE 1 Maximum severity of adverse events[a] ($N = 21$).

Adverse event[b]	Gr. 1	Gr. 2	Gr. 3	Gr. 4	Gr. 5	Total	Total severe[c]
Abdominal pain	0	0	1	0	0	1	1
Allergic reaction	0	0	1	0	0	1	1
Anaemia	14	1	2	0	0	17	2
Arthralgia	0	0	1	0	0	1	1
Aspiration	0	0	1	0	0	1	1
Bone pain	0	0	1	0	0	1	1
Chest pain—cardiac	0	0	1	0	0	1	1
Confusion	1	1	0	0	0	2	0
Diarrhoea	5	0	1	0	0	6	1
Dyspnoea	0	0	1	0	0	1	1
Fatigue	12	3	1	0	0	16	1
Fever	1	0	0	0	0	1	0
Headache	0	1	0	0	0	1	0
Heart failure	0	0	0	1	0	1	1
Haematuria	0	0	1	0	0	1	1
Hypertension	0	0	2	0	0	2	2
Hypoalbuminaemia	0	0	1	0	0	1	1
Hyponatraemia	0	0	1	0	0	1	1
Hypoxia	0	0	3	0	0	3	3
Leucocytosis	0	0	1	0	0	1	1
Lymphocyte count decreased	0	0	0	1	0	1	1
Nausea	11	3	0	0	0	14	0
Neutrophil count decreased	0	0	3	0	0	3	3
Pain in extremity	0	1	0	0	0	1	0
Peripheral motor neuropathy	6	1	1	0	0	8	1
Peripheral sensory neuropathy	7	0	2	0	0	9	2
Platelet count decreased	9	1	1	0	0	11	1
Small intestinal obstruction	0	0	1	0	0	1	1
Syncope	0	0	1	0	0	1	1
Upper respiratory infection	0	1	0	0	0	1	0
Vomiting	6	3	1	0	0	10	1
White blood cell decreased	0	0	1	0	0	1	1
Oedema limbs	1	0	1	0	0	2	1
Lung infection	0	0	1	1	0	2	2
Generalized muscle weakness	0	1	0	0	0	1	0

[a]Regardless of attribution.
[b]CTCAE v4.0.
[c]Severe is grades 3, 4, and 5.

PFS rate of 92%, cardiac arrest/ventricular arrhythmia occurred in three patients (7%).[13] In our study, six patients (28.5%) came off study due to ongoing low-grade AEs such as arthralgias, allergic reaction (facial swelling) and nausea and vomiting attributed to ixazomib, and exacerbation of atrial fibrillation, presumably due to ibrutinib. When combining ibrutinib and ixazomib, gastrointestinal and musculoskeletal toxicities (arthralgias/myalgias) are common side-effects of these drugs, and their incidence may increase when both drugs are combined which may explain the toxicities in the majority of patients who came off study due to AEs. It is possible that combining ixazomib with a newer generation BTK inhibitor such as zanubrutinib may result in better tolerability given that zanubrutinib has less gastrointestinal, musculoskeletal and cardiovascular toxicity compared to ibrutinib.[14]

Limitations of our study include the fact that the study failed to meet its primary end-point as no patient achieved

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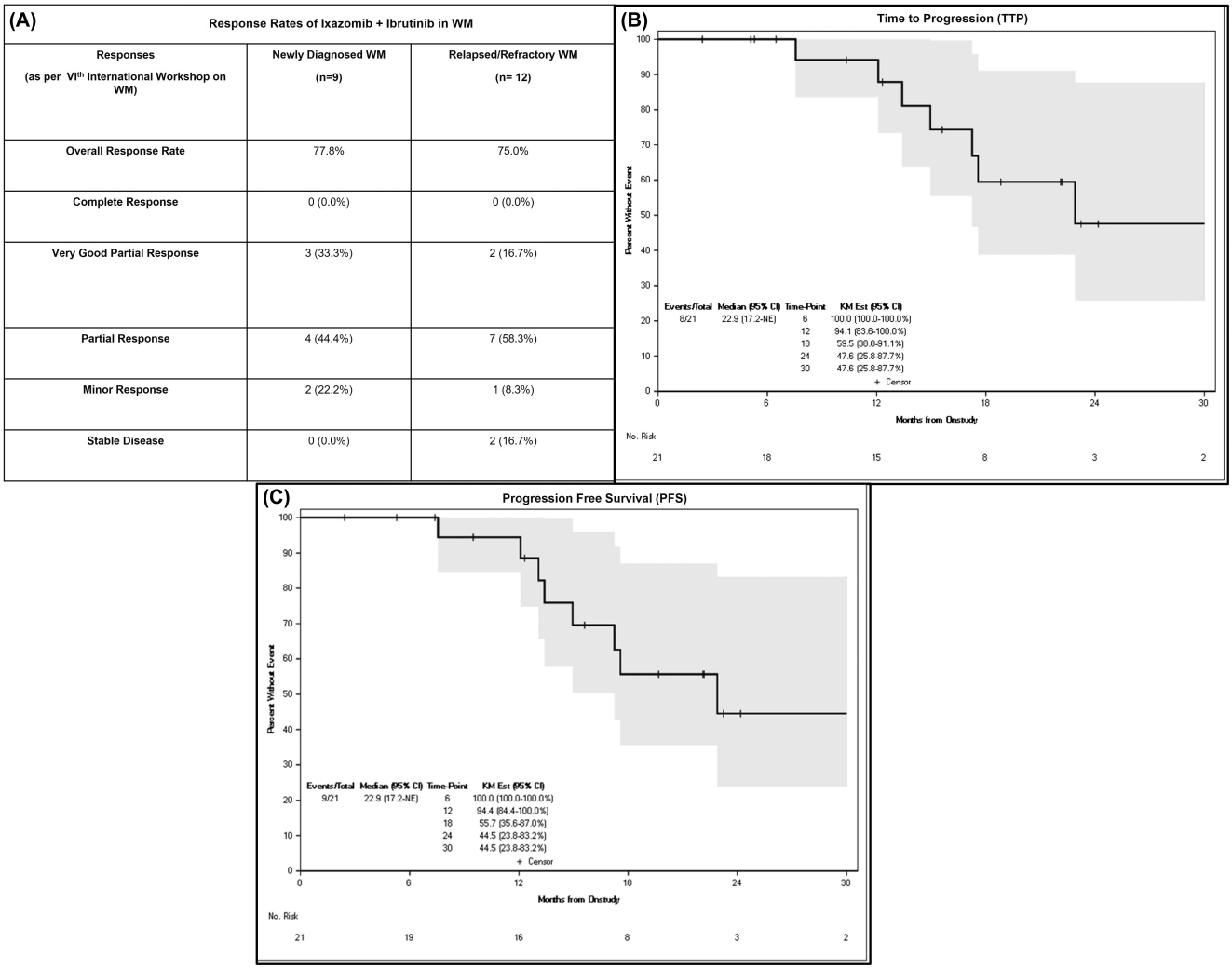

(A) Response Rates of Ixazomib + Ibrutinib in WM

Responses (as per VIth International Workshop on WM)	Newly Diagnosed WM (n=9)	Relapsed/Refractory WM (n= 12)
Overall Response Rate	77.8%	75.0%
Complete Response	0 (0.0%)	0 (0.0%)
Very Good Partial Response	3 (33.3%)	2 (16.7%)
Partial Response	4 (44.4%)	7 (58.3%)
Minor Response	2 (22.2%)	1 (8.3%)
Stable Disease	0 (0.0%)	2 (16.7%)

FIGURE 1 (A) Response rates of ixazomib + ibrutinib in WM. (B) Time to progression (TTP). (C) Progression-free survival (PFS).

a CR. The primary objective of the study was perhaps overly ambitious with success being defined as a CR rate of ≥20% and perhaps ORR or toxicity rate would have been better primary end-points. As our preclinical in vitro data showed the synergism between ibrutinib and ixazomib, we anticipated deep responses by targeting both the BCR signalling and the UPS pathway. Patients experienced disease progression soon after treatment discontinuation with a median time to next treatment of 1.3 months, likely due to IgM rebound related to ibrutinib discontinuation. In a retrospective study of 189 WM patients treated with ibrutinib, 52 discontinued ibrutinib therapy and an IgM rebound was observed in 37 patients (73%) following the discontinuation of ibrutinib with a median increase of 70% (range 25%–1702%).[15] This IgM rebound effect may have been mitigated if ixazomib would have been continued for a few cycles after ibrutinib discontinuation. The preliminary data from this clinical trial provide a basis for further evaluation of time-limited treatment with BTK and a proteasome inhibition for patients with WM.

AUTHOR CONTRIBUTIONS

ACK, SA, AP and RDP designed the study. ND, GC, BH and AP performed all laboratory studies. RDP, ND and AP wrote the manuscript. BL, RDP, ND, AP, AR, GC, BH, SA, VR, TS, KH, VA, AZ and CD collected/analysed the data for the study. All authors critically revised the manuscript and approved the final version.

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CONFLICT OF INTEREST STATEMENT

Dutta, LaPlant, Alegria, Elliott, Zimmerman, Ciccio, Han, Heslop, Chapin, Sher, Roy, Rasheed and Paulus have no conflicts of interest to declare. Parrondo serves on the advisory board for Sanofi Aventis and has received research funding

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by the Institutional Review Board at Mayo Clinic Florida (IRB# 18–000580).

CLINICAL TRIAL REGISTRATION NUMBER

This clinical trial is registered at clinicaltrials.gov NCT03506373.

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SUPPORTING INFORMATION

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