



Ibrutinib for patients with rituximab-refractory Waldenström's macroglobulinaemia (iNNOVATE): an open-label substudy of an international, multicentre, phase 3 trial

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Summary

Background In the era of widespread rituximab use for Waldenström's macroglobulinaemia, new treatment options for patients with rituximab-refractory disease are an important clinical need. Ibrutinib has induced durable responses in previously treated patients with Waldenström's macroglobulinaemia. We assessed the efficacy and safety of ibrutinib in a population with rituximab-refractory disease.

Methods This multicentre, open-label substudy was done at 19 sites in seven countries in adults aged 18 years and older with confirmed Waldenström's macroglobulinaemia, refractory to rituximab and requiring treatment. Disease refractory to the last rituximab-containing therapy was defined as either relapse less than 12 months since last dose of rituximab or failure to achieve at least a minor response. Key exclusion criteria included: CNS involvement, a stroke or intracranial haemorrhage less than 12 months before enrolment, clinically significant cardiovascular disease, hepatitis B or hepatitis C viral infection, and a known bleeding disorder. Patients received oral ibrutinib 420 mg once daily until progression or unacceptable toxicity. The substudy was not prospectively powered for statistical comparisons, and as such, all the analyses are descriptive in nature. This study objectives were the proportion of patients with an overall response, progression-free survival, overall survival, haematological improvement measured by haemoglobin, time to next treatment, and patient-reported outcomes according to the Functional Assessment of Cancer Therapy-Anemia (FACT-An) and the Euro Qol 5 Dimension Questionnaire (EQ-5D-5L). All analyses were per protocol. The study is registered at ClinicalTrials.gov, number NCT02165397, and follow-up is ongoing but enrolment is complete.

Findings Between Aug 18, 2014, and Feb 18, 2015, 31 patients were enrolled. Median age was 67 years (IQR 58–74); 13 (42%) of 31 patients had high-risk disease per the International Prognostic Scoring System Waldenström Macroglobulinaemia, median number of previous therapies was four (IQR 2–6), and all were rituximab-refractory. At a median follow-up of 18·1 months (IQR 17·5–18·9), the proportion of patients with an overall response was 28 [90%] of 31 (22 [71%] of patients had a major response), the estimated 18 month progression-free survival rate was 86% (95% CI 66–94), and the estimated 18 month overall survival rate was 97% (95% CI 79–100). Baseline median haemoglobin of 10·3 g/dL (IQR 9·3–11·7) increased to 11·4 g/dL (10·9–12·4) after 4 weeks of ibrutinib treatment and reached 12·7 g/dL (11·8–13·4) at week 49. A clinically meaningful improvement from baseline in FACT-An score, anaemia subscale score, and the EQ-5D-5L were reported at all post-baseline visits. Time to next treatment will be presented at a later date. Common grade 3 or worse adverse events included neutropenia in four patients (13%), hypertension in three patients (10%), and anaemia, thrombocytopenia, and diarrhoea in two patients each (6%). Serious adverse events occurred in ten patients (32%) and were most often infections. Five (16%) patients discontinued ibrutinib: three due to progression and two due to adverse events, while the remaining 26 [84%] of patients are continuing ibrutinib at the time of this report.

Interpretation The sustained responses and median progression-free survival time, combined with a manageable toxicity profile observed with single-agent ibrutinib indicate that this chemotherapy-free approach is a potential new treatment choice for patients who had heavily pretreated, rituximab-refractory Waldenström's macroglobulinaemia.

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Introduction

Waldenström's macroglobulinaemia is characterised by lymphoplasmacytic lymphoma infiltration of the bone marrow and often other lymphatic organs as well as increases in circulating monoclonal IgM. Waldenström's

macroglobulinaemia is treated most often with rituximab as a monotherapy or in combination with alkylating agents (eg, cyclophosphamide or bendamustine) or nucleoside analogues (cladribine or fludarabine). Novel therapies, including proteasome inhibitors, thalidomide,

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See Online for appendix

Research in context

Evidence before this study

Because of the widespread and repeated use of rituximab and rituximab-based combinations for Waldenström's macroglobulinaemia, rituximab resistance is increasingly observed, limiting its use. Sustained infusion reactions and intolerance also contribute to treatment discontinuation in approximately 7% of patients. A pivotal phase 2 trial showed efficacy and acceptable safety of ibrutinib in patients with previously treated Waldenström's macroglobulinaemia, including patients previously treated with anti-CD20 antibody therapy.

Added value of this study

No data are available for the optimal therapy for patients with rituximab-refractory Waldenström's macroglobulinaemia. To our knowledge, this is the first study to report high activity

and everolimus, have also shown activity,^{1,2} but mainly in combination with rituximab. However, none of these options is curative and a standard of care has not been established. Short-term and long-term toxicities caused by traditional therapeutic agents (such as chemotherapy or chemoimmunotherapy) make these treatments challenging for patients with Waldenström's macroglobulinaemia who are generally aged 65 years and older and often have comorbidities.³ Furthermore, present treatment approaches for relapsed Waldenström's macroglobulinaemia provide a modest progression-free survival of 16–24 months in the second-line and third-line settings.⁴ More effective therapeutic options are needed to provide long-term disease control with reduced toxicity. Because rituximab combinations are widely used for Waldenström's macroglobulinaemia, effective treatment options are necessary for patients who become rituximab-refractory or intolerant.^{2,5}

Ibrutinib, a first-in-class inhibitor of Bruton's tyrosine kinase (BTK), displays a unique targeted mechanism of action by inhibiting downstream signalling after the interaction between the mutated MYD88 (Leu265Pro) protein and BTK. A somatic mutation in MYD88 (Leu265Pro) is present in more than 90% of patients with Waldenström's macroglobulinaemia.^{6,7} The resulting mutated protein signals through IRAK1 and BTK, leading to constitutive activation of the NF- κ B pathway. Ibrutinib attenuates the MYD88–BTK interaction, thus inhibiting BTK-dependent signalling and inducing cellular apoptosis.⁷ Additionally, ibrutinib inhibits HCK, an SRC family member that is transactivated by mutated MYD88 and triggers both AKT and ERK prosurvival signalling in Waldenström's macroglobulinaemia cells.⁸

The pivotal, single-arm, phase 2 trial⁹ in previously treated patients with Waldenström's macroglobulinaemia who were given ibrutinib had an overall response of 91%, defining ibrutinib as the most active single agent for relapsed or refractory Waldenström's macroglobulinaemia to date. On the basis of these results,

and positive risk-benefit ratio with single-agent ibrutinib in patients with rituximab-refractory Waldenström's macroglobulinaemia who have been heavily pretreated. Additionally, this is one of the first studies to prospectively collect patient-reported outcomes to assess the patient's perspective of the therapeutic benefit.

Implications of all the available evidence

Our findings showed robust responses and an acceptable safety profile of single-agent ibrutinib in patients with rituximab-refractory Waldenström's macroglobulinaemia, with durable progression-free survival and overall survival, thus offering a chemotherapy-free option for this difficult to treat patient population.

ibrutinib is approved for the treatment of Waldenström's macroglobulinaemia by the US Food and Drug Administration and by the European Medicines Agency for patients who have relapsed after receiving one or more previous treatments.

The study population in this trial differs in a clinically significant way from the above phase 2 study, with respect to the higher median number of previous regimens and its focus on patients refractory to the most recent rituximab-containing therapy. This substudy is part of the iNNOVATE study, an ongoing, randomised, placebo-controlled study of ibrutinib plus rituximab compared with rituximab plus placebo in patients with Waldenström's macroglobulinaemia. The non-randomised, single-group substudy analysed patients refractory to rituximab who were treated with ibrutinib alone. To our knowledge, this is the first prospective clinical trial designed to evaluate efficacy of any therapy specifically in patients who have become rituximab-refractory.

Methods

Study design and participants

This international, multicentre, open-label substudy of single-agent ibrutinib was done in 19 sites in seven countries (appendix p 10). The intent of this substudy was to assess the safety and efficacy of ibrutinib in patients with Waldenström's macroglobulinaemia refractory to their last rituximab-containing therapy.

Eligible patients were 18 years old or older and had a centrally confirmed diagnosis of Waldenström's macroglobulinaemia requiring treatment as per the Second International Workshop on Waldenström's Macroglobulinaemia (IWWM) criteria.¹⁰ Rituximab-refractory disease was defined as either relapse after the last rituximab-containing therapy less than 12 months since the last dose of rituximab or failure to achieve at least a minor response [$\geq 25\%$ reduction of serum IgM from baseline] after the last rituximab-containing therapy. Progression on the previous treatment was determined

on the basis of the sixth IWWM investigator assessment criteria for response and progression and at least 30 days should have elapsed since the previous treatment. Additional inclusion criteria included Eastern Cooperative Oncology Group [ECOG] performance status 0–2, haemoglobin 8 g/dL or more, platelet count more than $50 \times 10^9/L$, absolute neutrophil count more than $0.75 \times 10^9/L$, serum aspartate or alanine aminotransferase less than $3.0 \times$ upper limit of normal (ULN), bilirubin $1.5 \times$ ULN or less, IgM more than 0.5 g/dL, and estimated creatinine clearance 30 mL/min or more. Key exclusion criteria included CNS involvement, stroke or intracranial haemorrhage less than 12 months before enrolment, clinically significant cardiovascular disease, active hepatitis B or hepatitis C viral infection, and a known bleeding disorder. A complete list of inclusion and exclusion criteria is provided in the appendix (pp 4–6).

All patients provided written informed consent before enrolment. The Institutional Review Board, Research Ethics Board, and Independent Ethics Committee at each site reviewed and approved the protocol before initiation of the study.

Procedures

Patients received oral ibrutinib 420 mg (three capsules of 140 mg each once a day). Plasmapheresis was permitted, at the investigator's discretion, both before or during ibrutinib treatment when clinically indicated by disease burden or symptoms of hyperviscosity (baseline IgM was obtained >35 days from the most recent plasmapheresis). Patients received ibrutinib continuously until disease progression, unacceptable toxicity, or withdrawal of consent.

Ibrutinib was withheld for the following study drug related grade 3 or worse toxicities: grade 4 neutropenia (absolute neutrophil count $<500/\mu L$) for more than 7 days; grade 3 thrombocytopenia (platelets $<50\,000/\mu L$) in the presence of grade 2 or higher bleeding events or grade 4 thrombocytopenia (platelets $<25\,000/\mu L$); grade 3 or 4 nausea, vomiting, or diarrhoea if persistent, despite optimal supportive interventions; or any other grade 4 or unmanageable grade 3 toxicity. After the first occurrence of an adverse event, ibrutinib was withheld until resolution of the adverse event to baseline or grade 1 or lower after which resuming treatment at full dose was permitted. If the toxicity recurred, dose reductions to 280 mg, 140 mg, and then discontinuation were required. Treatment was also discontinued if ibrutinib was withheld for more than 28 days because of an unmanageable toxicity.

Efficacy and safety assessments were done every 4 weeks for the first 6 months, then every 8 weeks thereafter, by laboratory assessment and physical exam. Additionally, all patients had baseline imaging by CT of the neck, chest, abdomen, and pelvis with contrast. Patients with evidence of nodal or extranodal disease by central review were followed up by CT scans every 16 weeks for the first 2 years

and every 24 weeks thereafter until disease progression was confirmed. Baseline bone marrow biopsy and aspirate were done with repeat assessments at weeks 49 and 97. Response assessments were done according to the modified consensus criteria from the sixth IWWM¹¹ (appendix p 7) and used for all efficacy analyses. Two validated instruments, the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire and EuroQol 5 Dimension Questionnaire (EQ-5D-5L), were used (details on the schedule of assessment are provided in the appendix).^{12,13} After treatment discontinuation, patients were followed up for progression every 12 weeks, then for survival every 3 months.

Adverse events were collected until 30 days after the last dose of treatment and graded according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03. Serious adverse events were defined according to standard regulatory descriptions.

MYD88 and CXCR4 mutational status was assessed using the Personalis ACE Extended Cancer Panel (appendix p 3).¹⁴

Outcomes

The study objectives were the proportion of patients with an overall response, progression-free survival, overall survival, haematological improvement measured by haemoglobin, time to next treatment, and patient reported outcomes according to FACT-An and EQ-5D-5L. Progression-free survival was defined as the duration from the date of treatment initiation to the date of disease progression or death, whichever occurred first. Progression-free survival was assessed by the investigators. The proportion of patients with an overall response was defined as the proportion of patients who achieved a minor response or better. Major response was defined as a partial response ($\geq 50\%$ reduction of serum IgM concentrations from baseline) or better.¹⁵ The safety of single-agent ibrutinib in patients with rituximab-refractory Waldenström's macroglobulinaemia was also assessed through capture of all adverse events from the time of the first dose, regardless of attribution.

Statistical analysis

The intent of this substudy was to provide a descriptive analysis of the safety and efficacy of single-agent ibrutinib for the treatment of patients with Waldenström's macroglobulinaemia who were considered refractory to their last previous rituximab-containing therapy. Thus, the substudy was not prospectively powered for statistical comparisons, and as such, all the analyses are descriptive in nature.

For overall response and major response, 95% exact confidence intervals were provided. The Kaplan-Meier method was used for time-to-event analyses with censoring. For patients who had no disease progression or death, progression-free survival was censored at the date of the last disease assessment. Overall survival was

	Proportion of participants (n=31)
Median time from diagnosis (months)	91 (28–120)
Median age (years)	67 (58–74)
Age ≥70 years	11 (35%)
ECOG	
0–1	25 (81%)
2	6 (19%)
IPSSWM*	
Low	7 (23%)
Intermediate	11 (35%)
High	13 (42%)
Genetic subtype	
MYD88 (Leu265Pro)/CXCR4 (wild type)	17 (55%)
MYD88 (Leu265Pro)/CXCR4 (WHIM)	7 (23%)
MYD88 (wild type)/CXCR4 (wild type)	1 (3%)
Missing data†	6 (19%)
Bone marrow infiltration	
Median intertrabecular space (%)	53% (25–67)
Median serum IgM (mg/dL)	3920 (2200–5500)
Median β2-microglobulin (mg/L)	3.6 (2.9–5.2)
Median haemoglobin levels (g/dL)	10.3 (9.3–11.7)
Median platelet count (10 ⁹ /L)	218 (161–269)
Median absolute neutrophil count (10 ⁹ /L)	2.9 (1.8–4.3)
Median number of previous therapies	4 (2–6)
Types of previous therapy	
Rituximab	31 (100%)
Antibody combinations	25 (81%)
Alkylating agent	28 (90%)
Corticosteroid	27 (87%)
Nucleoside analogue‡	18 (58%)
Vinca alkaloids	15 (48%)
Anthracyclines	12 (39%)
Proteasome inhibitor	13 (42%)
Immunomodulator	3 (10%)
Other§	7 (23%)
Types of most recent previous therapy	
Monotherapy	10 (32%)
Rituximab	6 (19%)
Nucleoside analogue	2 (6%)
Everolimus	2 (6%)
Combination therapy without rituximab	9 (29%)
Combination therapy with rituximab	12 (39%)
Previous autologous stem-cell transplant	2 (6%)
Data are n (%) or median (IQR), unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. IPSSWM=International Prognostic Scoring System for Waldenström's Macroglobulinemia. WHIM=warts, hypogammaglobulinaemia, immunodeficiency, and myelokathexis. *IPSSWM was measured at the time of screening. †Samples could not be tested because of low tumour yield or absence of a usable sample. ‡16 patients received fludarabine or cladribine (class purine analogue), and two patients received cytarabine (class nucleoside analogue). §Other previous therapies included carboplatin, etoposide, everolimus, and mitoxantrone.	

Table 1: Demographics and baseline characteristics

censored at the date that the patient was last known to be alive. Haematological improvement and other efficacy parameters were summarised descriptively. For quality-of-life assessments, descriptive statistics were provided (appendix p 2). All patients who received at least one dose of ibrutinib were included in all analyses. All analyses were done with SAS software, version 9.3 (ie, per protocol analysis). This study is registered with ClinicalTrials.gov, number NCT02165397.

Role of the funding source

This study was sponsored by Pharmacyclics LLC, an AbbVie company. Pharmacyclics was involved in study design, data collection, and statistical analysis. All authors had full access to all of the data. The corresponding author, MAD, had final responsibility to submit for publication.

Results

All 31 patients with rituximab-refractory Waldenström's macroglobulinaemia who were enrolled between Aug 18, 2014, and Feb 18, 2015, were included in the analysis. Baseline characteristics are described in table 1. Patients received a median of four previous therapies (IQR 2–6) with 22 (71%) of 31 patients having three or more previous therapies. All patients received rituximab in a previous treatment regimen and common previous treatments are shown in table 1. Notably, 21 of 31 patients received rituximab either alone or in varied combinations in multiple lines of rituximab-containing therapy (range 2–6). Of the four patients who did not receive rituximab in combination, three had no response to the most recent administration and one relapsed less than 4 months after treatment completion. Five patients entered the study having received one previous therapy; of these, three received rituximab in combination and two received monotherapy. Of the two that received rituximab monotherapy, one had no response and the other relapsed less than 4 months after treatment completion.

The proportion of patients with an overall response to the most recent therapy was 14 (45%) of 31, and 10 (32%) had a major response. Of the 31 enrolled patients, nine (29%) patients had progressed on the most recent treatment or within 60 days from last dose and 16 (52%) patients had no response. Overall, 19 (61%) of 31 patients were refractory to their most recent treatment. Common reasons for treatment initiation in the 31 enrolled patients were fatigue unrelieved by rest in 22 (71%) patients, constitutional symptoms (as defined in appendix p 4) in 13 (42%) patients, anaemia in 13 (42%) patients, and lymphadenopathy in seven (23%) patients. Additionally, five (16%) of 31 patients initiated therapy for hyperviscosity and four (13%) patients for peripheral neuropathy.

At a median follow-up of 18.1 (IQR 17.5–18.9), the median duration of ibrutinib therapy was 17.1 months (IQR 16.2–18.2). The proportion of patients with an overall response was 28 (90%), and 22 (71%) of 31 patients

had a major response (including four [13%] patients with very good partial responses; table 2). Median baseline IgM of 3920 mg/dL (IQR 2200–5500) declined by 48% after 4 weeks, with continued improvement over time (a decline of 75%, median 970 mg/dL [420–2450] at week 49; figure 1). The median time to response (defined as minor response or better) was 1.00 month (IQR 0.95–2.00) and the median time to best response was 2 months (1–4). For some patients, the quality of response improved with continued time on treatment; four patients achieved a best response after more than 6 months of treatment (appendix p 11).

Initial mutational analysis at baseline was evaluable for 25 patients; six samples could not be tested due to low tumour yield or absence of usable sample. 17 patients had mutations in *MYD88* (Leu265Pro) and were wild type for *CXCR4*. Of these 17 patients, 15 (88%) had an overall response. Seven patients had an *MYD88* (Leu265Pro) mutation together with *CXCR4* (WHIM) mutation,¹⁶ and all of these patients had an overall response (table 2). A continued improvement in IgM was noted in patients whose genotype was *MYD88* (Leu265Pro) and *CXCR4* (wild type), and patients whose genotype was *MYD88* (Leu265Pro) and *CXCR4* (WHIM) over time. However, the magnitude of IgM reduction was greater, and achieved earlier in those patients with *MYD88* (Leu265Pro) mutation and who were wild type for *CXCR4* (appendix p 12) compared with patients who had *MYD88* (Leu265Pro) and *CXCR4* (WHIM) mutations. However, these data must be interpreted with caution due to the small numbers of patients. One patient who was wild type for both genes (*MYD88* and *CXCR4*) had a best response of stable disease; more data for patients with this genotype will be obtained from the results of the randomised phase of the study. Baseline disease characteristics by mutational subtype are summarised in the appendix (p 8).

At a median follow-up of 18.1 months, median progression-free survival had not been reached. Four disease-progression or death events occurred and the 18 month progression-free survival estimate was 86% (95% CI 66–94). Estimated 18 month progression-free survival was 100% (95% CI 100–100) for patients with 1–2 previous therapies (n=9; no disease progression events or deaths) compared with 80% (95% CI 55–92) for those with three or more previous therapies (n=22; three disease progression events and one death). One patient died during follow-up due to progressive disease. The overall survival at 18 months was 97% (95% CI 79–100; table 2). No patients died on study treatment. Progression-free survival and overall survival was analysed for the overall population (figures 2, 3), by number of previous therapies (figure 4), and by genetic subtypes (appendix pp 13, 14).

Baseline median haemoglobin of 10.3 g/dL (IQR 9.3–11.7) increased to 11.4 g/dL (10.9–12.4) after 4 weeks and reached 12.7 g/dL (11.8–13.4) at week 49

	All* (N=31)	MYD88 (Leu265Pro)/ CXCR4 (wild type; n=17)†	MYD88 (Leu265Pro)/ CXCR4 (WHIM; n=7)
Very good partial response	4 (13%)	3 (18%)	0
Partial response	18 (58%)	11 (65%)	5 (71%)
Minor response	6 (19%)	1 (6%)	2 (29%)
Overall response (%)	28 (90%)	15 (88%)	7 (100%)
Major response (%)	22 (71%)	14 (82%)	5 (71%)
18 month progression-free survival (%; 95% CI)	86% (66–94)	94% (63–99)	86% (33–98)
18 months overall survival (%; 95% CI)	97% (79–100)	100% (100–100)	100% (100–100)

IWWM=International Workshop on Waldenström's Macroglobulinaemia. WHIM= warts, hypogammaglobulinaemia, immunodeficiency, and myelokathexis. Shown are genotype categories for which more than one patient was classified (one patient was classified as *MYD88* [wild type]/*CXCR4* [wild type]). Six patients were not evaluable because of a low tumour content or an unusable sample. *Two patients had stable disease, one patient was not evaluable. †One patient was not evaluable and one patient had stable disease.

Table 2: Proportion of patients with best response, as defined by IWWM criteria progression-free survival, overall survival and by mutation status

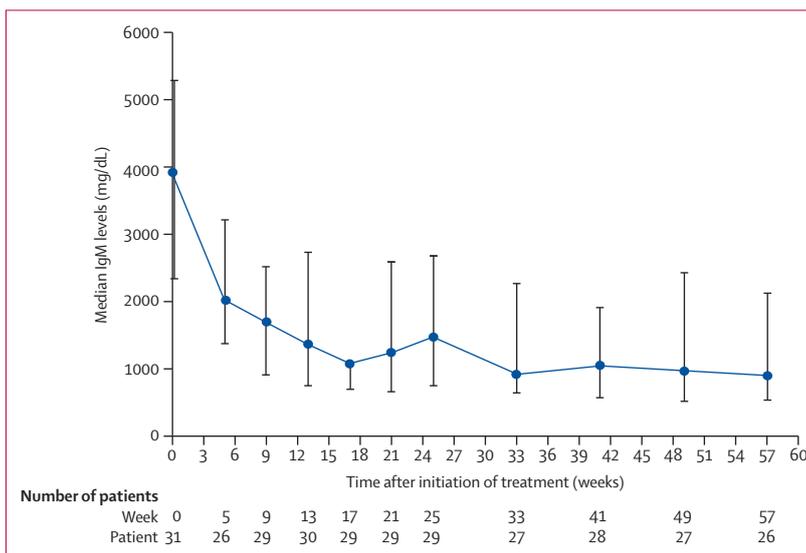


Figure 1: Median IgM levels of patients treated with ibrutinib
Error bars denote 95% CI.

(figure 5). Of the five patients requiring plasmapheresis at treatment initiation, four discontinued plasmapheresis within the first 4 weeks. Similarly, all patients with a baseline haemoglobin <11 g/dL showed an increase in haemoglobin on treatment with a more notable improvement and earlier onset observed in those with the *MYD88* (Leu265Pro) mutation who were also wild type for *CXCR4* (appendix p 15).

A clinically meaningful improvement from baseline in FACT-An score, anaemia subscale score, and the EQ-5D-5L visual analogue scale were reported at all post-baseline visits (appendix pp 16–18). In exploratory analyses, the Pearson's correlation coefficient showed a trend towards a positive correlation between haemoglobin values and the FACT-An total score, as

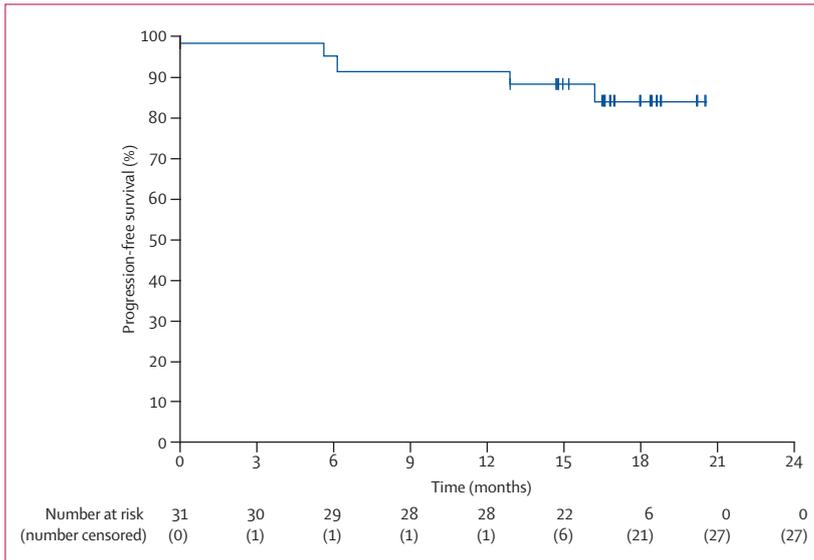


Figure 2: Kaplan-Meier analysis of progression-free survival

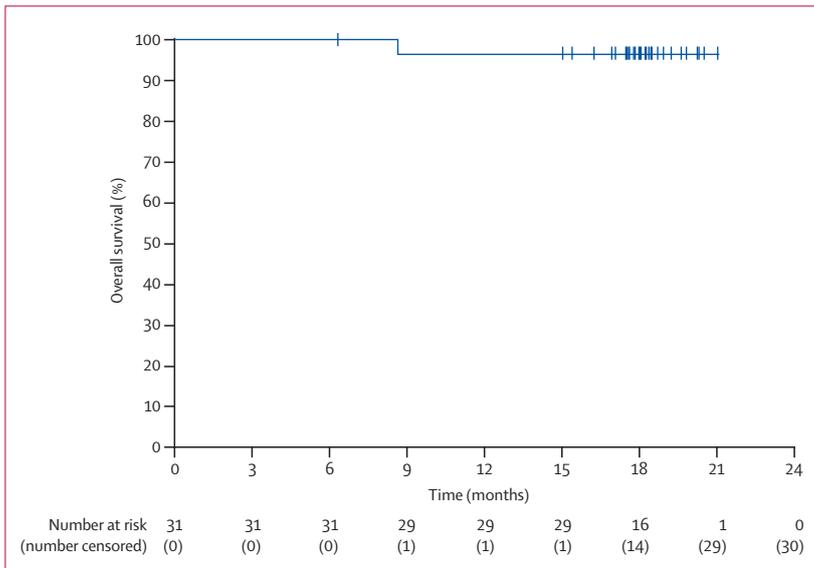


Figure 3: Kaplan-Meier analysis of overall survival

well as the anaemia subscale score (appendix p 9). The improvement in quality-of-life measures observed at week 5 was accompanied by a decrease in IgM levels and an increase in haemoglobin levels. Given the small number of patients in this substudy, however, no final conclusions on the correlations between improvements in quality of life and outcomes can be drawn at this time.

CT-identified lymphadenopathy was reported in 23 (74%) of 31 patients with a median lymph node diameter of 3.1 cm; 12 (52%) of 23 patients had at least one lymph node with a diameter larger than 3 cm, one patient had bulky adenopathy (diameter \geq 5 cm). Adenopathies larger than 3 cm were reported in nine

(53%) of 17 patients with *MYD88* (Leu265Pro) mutation who were wild type for *CXCR4* and in one (14%) of seven patients with both the *MYD88* (Leu265Pro) and *CXCR4* (WHIM) mutations (appendix p 8). Serial imaging in 22 evaluable patients showed decreased adenopathies in all patients (appendix p 19) with 17 (77%) patients with a maximum reduction of more than 25% in the sum of the product of diameters. A continued reduction in the median sum of the product of diameters was observed over time (appendix p 20). CT-identified splenomegaly ($>$ 13 cm) was reported in six (19%) of 31 patients at baseline. A reduction in splenic enlargement was reported for five of six patients with splenomegaly who were evaluable; one patient discontinued treatment before response assessment.

The extent of bone marrow involvement by Waldenström’s macroglobulinaemia can be characterised by quantification of the intertrabecular space occupied by the infiltrate; response to treatment can be determined by quantification of the change from baseline to after treatment of the intertrabecular space occupied by the infiltrate.¹¹ Overall, in patients treated with ibrutinib, a reduction in bone marrow infiltration by Waldenström’s macroglobulinaemia was observed. The number of patients with bone marrow infiltration at baseline was 29 (94%). The median intertrabecular space occupied by the infiltrate at baseline in these patients was 53% (IQR 24.8–67.0) and this changed to a median of 26% (12.5–40.0) by week 49 with change from baseline ranging from –71% to 30% in the 21 patients for whom follow-up samples were available. 16 (76%) of 21 evaluable patients had a reduction in bone marrow infiltration. Of note, the other five patients without improvement in infiltration had reductions in IgM ranging from 28% to 97%.

Of four patients initiating therapy for peripheral neuropathy, two remained stable and two had subjective improvement in symptoms. These two patients reported improvements starting at week 9 with continued amelioration of symptoms over time and complete resolution of the peripheral neuropathy in one patient.

One patient discontinued treatment after 3 days due to an adverse event (gastrointestinal amyloid) and went on to subsequent treatment; thus given the low event number and the small number of patients in this study, time to next treatment data were not analysed, but are planned to be analysed in the future.

Any-grade treatment-emergent adverse event occurred in 30 (97%) of 31 patients and grade 3 or worse adverse events occurred in 20 (65%) patients (table 3). Common grade 3 or worse adverse events included neutropenia in four (13%) of 31 patients, hypertension in three (10%) patients, and anaemia, thrombocytopenia, and diarrhoea in two (6% each) patients (table 3). Overall, five (16%) of 31 patients received concomitant growth factors, including neutrophil growth factors for three (10%) patients and erythropoiesis-stimulating agents for two (6%) patients. Two patients (6%) received

red cell transfusion for anaemia. All patients with grade 3 or higher cytopenias (n=7) had received four or more previous therapies. Serious adverse events occurred in ten (32%) patients and were most commonly infections.

Infections were reported in 21 (68%) of 31 patients (grade 3 or worse in five [16%] patients), with respiratory tract infection being the most common occurring in ten (32%) patients. Grade 3 or worse infections included one case each of pneumonia, respiratory tract infection, cellulitis, paronychia, aspergillus infection, orchitis, and prostatic abscess. No events of IgM flare, atrial fibrillation, or major bleeding were reported. Grade 1 or 2 bleeding events occurred in 12 (39%) of 31 patients; bruising in seven (23%) patients was the only bleeding event that occurred in more than two patients.

Four (13%) patients had dose reductions (three patients had reductions to 280 mg and one patient had a reduction to 140 mg) due to adverse events (grade 2 diarrhoea [n=2], grade 3 arthralgia [n=1], and grade 2 iron deficiency anaemia [n=1]). Dose interruptions due to adverse events occurred in 13 (42%) of 31 patients. The adverse events leading to dose withholding were infection (n=7), diarrhoea (n=3), nausea (n=2), acute cholecystitis (n=1), constipation (n=1), cough (n=1), dehydration (n=1), dizziness (n=1), dyspnoea (n=1), femoral fracture (n=1), gouty arthritis (n=1), hypertension (n=1), ileus (n=1), neutropenia (n=1), and syncope (n=1). Five (38%) of these 13 patients had their dose withheld on more than one occasion. Nine (69%) of the 13 patients had dose withheld for more than 7 consecutive days, two of which were followed up by dose reduction for management of grade 1 and 2 diarrhoea. Ten of the patients who had a dose withheld, including three who had dose withheld on more than one occasion, resumed ibrutinib at full dose (420 mg) with no dose reductions needed.

Five patients (16%) discontinued ibrutinib: three patients due to progressive disease, including one with transformation to diffuse large B-cell lymphoma, and two due to an adverse events (gastrointestinal amyloid light-chain amyloidosis and diarrhoea). The patient with *MYD88* (wild type) and *CXCR4* (wild type) genotype had progressive disease and died 93 days after discontinuing ibrutinib. Overall, 26 (84%) of 31 patients continued on ibrutinib and 30 (97%) of 31 patients are alive at the time of this analysis.

Discussion

In this study, we provide evidence that single-agent ibrutinib is a highly active and well-tolerated treatment with a high proportion of patients achieving an overall response (90%) and major response (71%) in patients with rituximab-refractory Waldenström's macroglobulinaemia with a median of four previous therapies, including 61% with either non-responsive or refractory disease to their most recent treatment. It is important to note that patients in the phase 2 study of single-agent

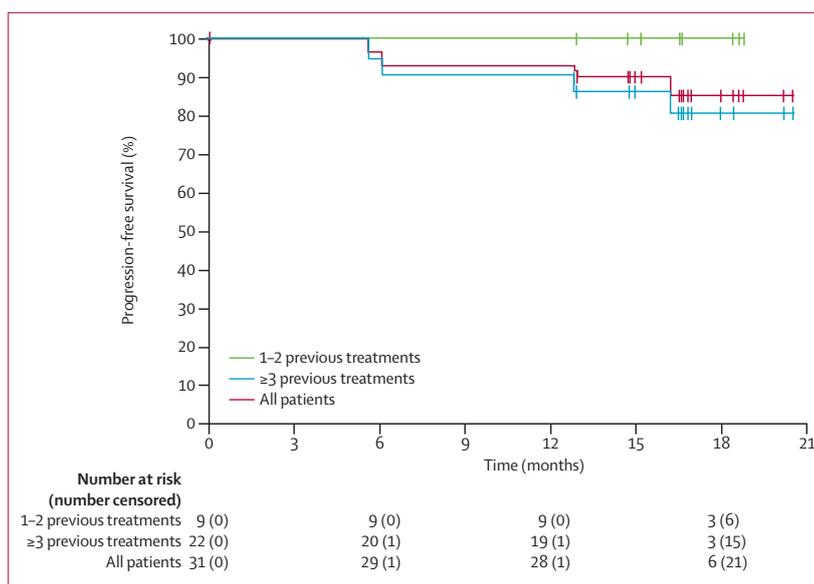


Figure 4: Kaplan-Meier analysis of progression-free survival by number of previous treatments

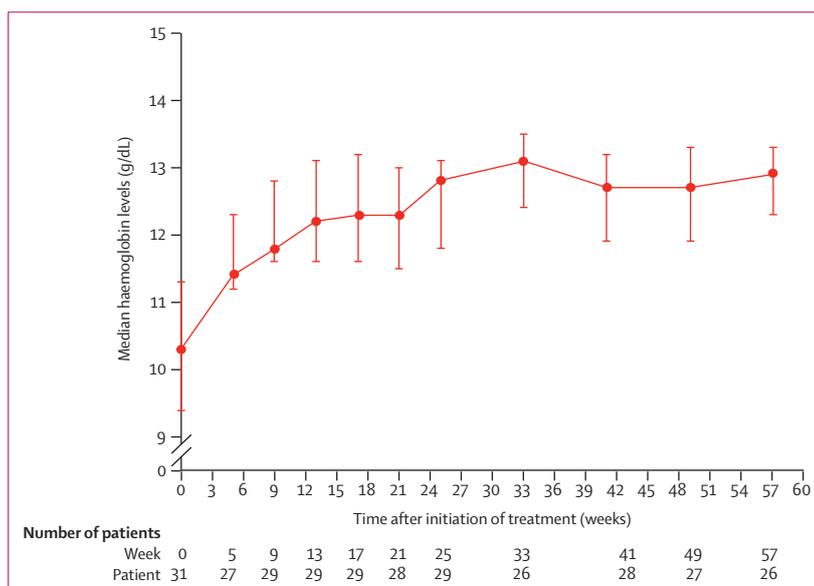


Figure 5: Median haemoglobin levels of patients treated with ibrutinib. Error bars denote 95% CI.

ibrutinib by Treon and colleagues⁹ had a median of two previous therapies with only 40% refractory to their previous treatment. Despite these differences in patient characteristics, the proportion of patients with overall response and major response in this trial was similar to the Treon study,⁹ which reported an overall response of 91% and a major response of 73% in patients with previously treated Waldenström's macroglobulinaemia. Additionally, ibrutinib as a chemotherapy-free treatment option leads to a rapid and dramatic decline in IgM and increase in haemoglobin, both observed after only 4 weeks, with continued improvement over time. Of

	Grades 1–2	Grade 3
Haematological adverse events		
Neutropenia	3 (10%)	3 (10%)
Anaemia	3 (10%)	2 (6%)
Thrombocytopenia	4 (13%)	1 (3%)
Non-haematological adverse events		
Diarrhoea	11 (36%)	2 (6%)
Hypertension	4 (13%)	3 (10%)
Increased tendency to bruise	7 (23%)	0
Back pain	7 (23%)	0
Constipation	5 (16%)	1 (3%)
Arthralgia	4 (13%)	1 (3%)
Upper respiratory tract infection	6 (19%)	0
Pyrexia	6 (19%)	0
Nausea	6 (19%)	0
Respiratory tract infection (unspecified)	3 (10%)	1 (3%)
Fatigue	3 (10%)	1 (3%)
Tinnitus	4 (13%)	0
Peripheral oedema	4 (13%)	0
Dry skin	4 (13%)	0
Cough	4 (13%)	0
Conjunctivitis	4 (13%)	0
Pain in extremity	3 (10%)	0
Muscle spasms	3 (10%)	0
Headache	3 (10%)	0
Dizziness	3 (10%)	0
Decreased appetite	3 (10%)	0
Asthenia	3 (10%)	0
Abdominal discomfort	3 (10%)	0
Syncope	1 (3%)	1 (3%)
Pneumonia	1 (3%)	1 (3%)
Paronychia	1 (3%)	1 (3%)
Cellulitis	1 (3%)	1 (3%)
Renal cell carcinoma	0	1 (3%)
Prostatic abscess	0	1 (3%)
Orchitis	0	1 (3%)
Gouty arthritis	0	1 (3%)
Femoral fracture	0	1 (3%)
Diffuse large B-cell lymphoma	0	1 (3%)
Aspergillus infection	0	1 (3%)
Acute cholecystitis	0	1 (3%)
Faecalith	0	1 (3%)
Hyponatraemia	0	1 (3%)
Ileus	0	1 (3%)
Transient ischaemic attack	0	1 (3%)

Data are n (%). Two patients had grade 4 adverse events: one (3%) had neutropenia and one (3%) had thrombocytopenia.

Table 3: Overview of treatment-emergent adverse events grade 1–2 (occurring in ≥10% of patients), all grade 3 and worse adverse events, and all serious adverse events

note, a corresponding clinically meaningful improvement in quality of life, an additional important measure of treatment activity, was observed at the first follow-up visit and was maintained or further improved with continued treatment. However, these data must be interpreted with caution, given the small number of patients analysed. Our study suggests that ibrutinib is an active therapeutic option for the treatment of patients with rituximab-refractory disease, a challenging population to treat for whom only a few effective treatment options are available. There are scarce data for the optimal therapy for this patient group with outcomes reported only in small, phase 2 studies that enrolled few such patients.

In this study, we defined patients having rituximab-refractory disease as those who did not have at least a minor response or who relapsed less than 12 months after the last rituximab dose. We acknowledge that there is currently no widely accepted definition of rituximab-refractoriness for patients with Waldenström's macroglobulinaemia and that a standardised definition needs to be determined to assess future agents in this population with a difficult-to-treat disease.

Another important aspect of this study is the centralised assessment of lymph nodes and spleen at baseline. All patients with measurable nodal and extranodal disease showed improvement; a more than 25% reduction in the sum of the product of diameters was noted in most patients with improvement in splenomegaly. Furthermore, a continued reduction in lymph node diameters was observed over time. Although the response criteria for Waldenström's macroglobulinaemia require a reduction in lymphadenopathy or splenomegaly if present at baseline, there is no consensus on the method of assessment and reporting of improvement in nodal or extranodal disease. In fact, present guidelines suggest that imaging of lymph nodes should be considered at baseline and after completion of treatment; however, periodic imaging after treatment to monitor response is recommended when enlargement is noted at baseline, but the frequency of imaging assessments is not specified.¹⁷

Previous studies have shown that clinical response to ibrutinib could be adversely affected in patients with genotype *MYD88* (wild type) or *MYD88* (Leu265Pro) and *CXCR4* (WHIM) mutations.^{18,19} The proportion of patients with the *MYD88* (Leu265Pro) and *CXCR4* (wild type) genotype who had an overall response was similar to the proportion of patients with the *MYD88* (Leu265Pro) and *CXCR4* (WHIM) genotype who achieved an overall response, although patient numbers were small. Slower response kinetics in serum IgM and improvements in haemoglobin were observed in patients with *CXCR4* (WHIM), similar to previous findings. The randomised portion of this trial might further elucidate the importance of these genotypes on clinical outcomes.

There were no unexpected toxic effects in this population of patients with rituximab-refractory disease, and overall treatment was well tolerated: diarrhoea (occurring in 42%

of patients, including 6% of grade 3 events), back pain, bruising, neutropenia, and hypertension (in 23% of patients each) were the most commonly reported adverse events. Most events of diarrhoea were grade 1 or 2 and managed with supportive care interventions, with only one patient discontinuing treatment despite dose reduction, due to this adverse event. All patients with grade 3 hypertension (10%) had pre-existing hypertension, which was managed medically with no dose reductions of ibrutinib or discontinuations. No major bleeding or atrial fibrillation events were reported to date in this study, which could reflect the short duration of follow-up.²⁰ Of note, in Treon and colleagues' study,⁹ grade 2 or worse bleeding events occurred in four patients (two events of epistaxis related to the use of fish oil supplements), and grade 2 or worse atrial fibrillation occurred in three patients. The frequency of grade 3 or worse thrombocytopenia was low (6%) in our study despite the heavily pretreated population and no cases of febrile neutropenia were reported. Dose reductions were mainly for gastrointestinal toxicity, with no dose modifications for haematological toxicity. Five patients (16%) discontinued study treatment, including two patients for adverse events.

Modest median progression-free survival has been reported for newer single-agent therapies in relapsed or refractory Waldenström's macroglobulinaemia, ranging from 6.6 months to 22.0 months.^{21–24} By comparison, single-agent ibrutinib showed high activity and low toxicity in patients with Waldenström's macroglobulinaemia, with a median progression-free survival not reached after a median follow-up of 18.1 months (IQR 17.5–18.9). Similar to other novel therapies, such as bortezomib, the reduction in bone marrow infiltration with ibrutinib did not correlate with the reduction in serum IgM levels.^{25,26} Furthermore, the occurrence of peripheral neuropathy, haematological toxicities, pulmonary toxicities, and prolonged myelosuppression has been a concern with existing therapies and several of the newer agents.^{21–24,27} In this study, ibrutinib was associated with manageable toxicity, with most adverse events being grade 1 or 2, and a toxicity profile consistent with previous studies of single-agent ibrutinib. In view of these findings, the high proportion of patients achieving a response, longer median progression-free survival, and acceptable safety profile of ibrutinib observed in our study are notable. A retrospective chart review⁴ of a large patient population across Europe indicated a decrease in median progression-free survival of patients with Waldenström's macroglobulinaemia from 31 months after front-line therapy to 24 months in second-line settings and 16 months in third-line settings. The better outcomes at 18 months (progression-free survival of 86% [95% CI 66–94] and overall survival of 97% [79–100]) observed in our study in a heavily pretreated (median four treatment lines), rituximab-refractory population, in comparison with those observed in the retrospective analysis of historical therapies for Waldenström's

macroglobulinaemia, as well as in the phase 2 study, support the robust activity of single-agent ibrutinib in these patients. Ibrutinib is, therefore, being assessed as a single-agent, as well as in combination, in the front-line setting. Longer follow-up will be important to determine the long-term clinical benefit for these patients.

Contributors

Together with Pharmacyclics authors (TG and EB), MAD, EK, ST, and CB were responsible for study protocol design, data interpretation, and data analysis. All investigators and their respective research teams recruited patients to the study and contributed to data collection. Pharmacyclics authors (PS and JL) confirmed data accuracy and compiled data for summation and analysis. JL did the data analysis and interpretation. MAD, CB, EK, EB, and TG contributed to the first draft of the manuscript; MAD, CB, EK, EB, ST, and TG further contributed to final manuscript writing. All authors carefully reviewed the manuscript and approved the final version.

Declaration of interests

MAD received honoraria and had a consultancy and advisory role with Janssen, Celgene, Onyx, Amgen, and Novartis, and research funding from Genesis Pharma. JT received research funding from Janssen. AT had a consultancy and advisory role with Janssen. JVM has a consultancy and advisory role with Celgene, Speaker's Bureau for Celgene, Millennium, and Amgen. DM received honoraria and had a consultancy and advisory role with Roche, Lundbeck Canada, Gilead, Amgen, and Celgene, and had a consultancy and advisory role with Janssen, research funding from Roche, Gilead, Pharmacyclics, and Janssen, and travel accommodations from Lundbeck Canada and Roche Canada. CT received honoraria, had a consultancy and advisory role in and research funding from Janssen. OT received honoraria, had a consultancy and advisory role, and research funding from Roche, Celgene, and Mundipharma; honoraria from Janssen and Gilead; a consultancy and advisory role with Janssen, Gilead, and Novartis; research funding from GSK and Amgen, Pierre Fabre and Chugai; and travel accommodation from Roche, Mundipharma, Celgene, GSK, Amgen, Janssen, Gilead, and Sanofi. SM received honoraria from, has had a consultancy and advisory role with, and is on the speaker's bureau for Pharmacyclics, Janssen, Gilead, and Genentech; and research funding from Novartis, Xeme, Pharmacyclics, Gilead, AbbVie, and Celgene. AO had a consultancy and advisory role with and expert testimony for Celgene, Janssen, and Amgen. LTH had a consultancy and advisory role for Amgen and Pfizer, and research funding from Amgen, Pfizer, Micromet, Gilead, Biotest, Genentech, Pharmacyclics, Idera, ADC Therapeutics, and Kite. CS had honoraria from and consultancy and advisory role with Amgen and Takeda, honoraria from Janssen, and gave expert testimony for Takeda and Janssen. RG-S had honoraria and travel accommodation from Janssen and Takeda, honoraria from Pharmacyclics, research funding from Hospira, and travel accommodation from Celgene. RFC declares no competing interests. CFdL received honoraria from, consultancy and advisory role with, and travel accommodation from Celgene, Janssen, and Amgen. JJC received honoraria from Alexion, Janssen, and Celgene, consultancy and advisory role with Otsuka and Biogen, and research funding from Millennium, Pharmacyclics, Gilead, and AbbVie. MG had a consultancy and advisory role with Celgene and Bristol-Myers Squibb, and research funding from Celgene and Janssen. M-CK received honoraria from Genesis, and research funding from Millennium, Lilly, and Amgen. VL had a consultancy and advisory role with and speaker's bureau for Janssen, Roche, Gilead, and GSK; received honoraria from Roche, Mundipharma, Gilead, Janssen, BMS, and GSK; and had travel accommodation from Roche. AS had a consultancy and advisory role with Novartis, Celgene, Janssen, Roche, Amgen, Pfizer, MSD, and Gilead; research funding from Takeda, Actelion, Proton-Pharma, Astellas, Teva, MSD, ApoPharma, Celgene, Novartis, Janssen, Genzyme, Pfizer, Amgen, Alexion, and Gilead; gave expert testimony for Genesis Pharma, Novartis, MSD, Pfizer, Amgen, and Glaxo; and had travel accommodation from Genzyme, Astellas, MSD, Alexion, Novartis, Teva, Amgen, Janssen, Celgene, Roche, Pfizer, and Gilead. EK received honoraria from and consultancy and advisory role with Amgen and

Takeda, consultancy and advisory role with Janssen, and travel accommodation from Janssen and Takeda. PS is employed with Pharmacyclics LLC (an AbbVie Company), and equity ownership in AbbVie. JL is employed with Pharmacyclics LLC (an AbbVie Company), and has equity ownership in AbbVie, BMS, Pfizer, Abbott, Amgen, Gilead, Biogen, Celgene, Medivation, Merck, Exelixis, Juno, Isis, Aduro, and Merrimack. TG is employed and has patents with Pharmacyclics LLC (an AbbVie Company) and equity ownership in AbbVie. EB is employed with Pharmacyclics LLC (an AbbVie Company), and has equity ownership in AbbVie. ST has a consultancy and advisory role with, research funding in, and travel accommodation from Pharmacyclics and Janssen. CB has honoraria, research funding, consultancy, an advisory role from Roche and Janssen, and honoraria from Pfizer.

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