





# Dexamethasone, rituximab and cyclophosphamide for relapsed and/or refractory and treatment-naïve patients with Waldenstrom macroglobulinemia

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Received 9 March 2017; accepted for publication 15 May 2017

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## Summary

The management of Waldenström macroglobulinaemia (WM) relies predominantly on small trials, one of which has demonstrated activity of dexamethasone, rituximab and cyclophosphamide (DRC) in the frontline setting. We report on the efficacy of DRC, focusing on relapsed/refractory (R/R) patients. Ibrutinib, a recently approved agent in WM demonstrated limited activity in patients with *MYD88*<sup>WT</sup> genotype. Herein, we additionally report on the activity of DRC based on the *MYD88*<sup>L265P</sup> mutation status. Of 100 WM patients evaluated between January 2007 and December 2014 who received DRC, 50 had R/R WM. The overall response rate (ORR) was 87%. The median progression-free survival (PFS) and time-to-next-therapy (TTNT) were 32 (95% confidence interval [CI]: 15–51) and 50 (95% CI: 35–60) months, respectively. In the previously untreated cohort ( $n = 50$ ), the ORR was 96%, and the median PFS and TTNT were 34 months (95% CI: 23–not reached [NR]) and NR (95% CI: 37–NR), respectively. Twenty-five (86%) of 29 genotyped patients harbored *MYD88*<sup>L265P</sup>. The response rates and outcomes were independent of *MYD88* mutation status. Grade  $\geq 3$  adverse effects included neutropenia (20%), thrombocytopenia (7%) and infections (3%). Similar to the frontline setting, DRC is an effective and well-tolerated salvage regimen for WM. In contrast to ibrutinib, DRC offers a less expensive, fixed-duration option, with preliminary data suggesting efficacy independent of the patients' *MYD88* status.

**Keywords:** indolent lymphoma, IgM monoclonal gammopathy, *MYD88*.

Waldenström macroglobulinaemia (WM) is classified by the World Health Organization as a low-grade, non-Hodgkin lymphoma (Campo *et al*, 2011). It is a unique clinicopathological entity characterized by the presence of a lymphoplasmacytic infiltrate in the bone marrow and IgM monoclonal gammopathy (Owen *et al*, 2003). The incidence of WM in the Western hemisphere is estimated to be 3.5–5.5 cases per million-person/years (Groves *et al*, 1998).

Although our understanding of the pathophysiology of WM has broadened with the seminal discoveries of *MYD88*<sup>L265P</sup> and *CXCR4*<sup>WHIM</sup> mutations in a significant proportion of patients with WM, it remains an incurable malignancy (Trean *et al*, 2012; Xu *et al*, 2015). The optimal management approach for WM patients is yet to be fully delineated and relies heavily on data garnered through phase

2 trials. Ibrutinib, an oral irreversible Bruton Tyrosine Kinase (BTK) inhibitor, (Cameron & Sanford, 2014) was recently approved for the treatment of WM owing to remarkable clinical efficacy in patients with relapsed and/or refractory (R/R) WM. Subsequent data suggested that the drug is primarily active only in WM patients who harbor the *MYD88*<sup>L265P</sup> mutation (Trean *et al*, 2015a,b). Ibrutinib therapy mandates continuation of this agent until disease progression or the development of intolerable adverse effects, (Trean *et al*, 2015a; Dimopoulos *et al*, 2016) with an estimated annual wholesale cost of approximately \$147 000 in the USA (Lexicomp® 2016).

Dexamethasone, rituximab, cyclophosphamide (DRC) is a frequently prescribed regimen, given the substantial activity that was noted in the treatment-naïve setting in a phase II

trial published in 2007 (Dimopoulos *et al*, 2007). However, its efficacy in the R/R setting has not been systematically evaluated. The average whole sale price for a full course of DRC i.e. 6 cycles is approximately \$50 000. Herein, we present the outcomes associated with the use of DRC in frontline and salvage settings, with a primary focus on the relapsed-refractory patient-population requiring salvage therapy. Additionally, we assess the impact of patients' *MYD88* mutational status on outcomes with this regimen.

## Patients and methods

Following institutional review board approval, the medical records of WM patients who were seen consecutively at Mayo Clinic Rochester, Arizona and Florida between January 2007 and December 2014 were reviewed. WM was defined by the presence of 10% or greater monoclonal lymphoplasmacytic cells in the bone marrow plus detection of serum monoclonal IgM of any size (Owen *et al*, 2003). Treatment was typically offered to symptomatic patients or those with bulky disease, WM-associated haemolytic anemia or cytopenias in accordance with the Second International Workshop on WM (IWWM) Consensus indications for initiation of therapy in WM (Kyle *et al*, 2003).

Only patients who received at least one cycle of DRC were included in the final analysis. The DRC regimen consisted of dexamethasone, 20 mg IV on day 1, rituximab, 375 mg/m<sup>2</sup> IV on day 1, and cyclophosphamide 100 mg/m<sup>2</sup> PO daily on days 1–5. DRC was given every 3 weeks for up to 6 cycles. Disease response was assessed by using the Consensus Response Criteria from the Sixth IWWM (Owen *et al*, 2013). Refractory disease was defined by a lack of response to prior therapy or progression within 3 months of last treatment. Overall response rate (ORR) was assessed by measuring the rate of a minor response or better. Time-to-best response was defined as the time from initiation of DRC to the IgM nadir before initiation of another line of therapy.

The patients' *MYD88* mutation status was recorded when available. It was assessed as previously described by the amplification-refractory mutation system (ARMS), a variant of allele-specific polymerase chain reaction (AS-PCR), with an analytical sensitivity of approximately 1% mutation detection in a wild-type background (Kapoor *et al*, 2017). Using this methodology, the *MYD88* control amplification yielded a polymerase chain reaction (PCR) product of 141 base pairs (bp), and an additional specific 72-bp product denoting the L265P mutation, if present. Toxicity was graded according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE) version 4.0. ([http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE\\_4.03\\_2010-06-14\\_QuickReference\\_8.5x11.pdf](http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf)) All time-to-event analyses were performed from DRC initiation date using the Kaplan–Meier method and the log-rank test. Progression-free survival (PFS) was defined as the time from initiation of DRC to the time of first event (progression of disease or death). Patients without the event

were censored for PFS at the last date they were found to be in remission and alive. Time-to-next therapy (TTNT) was measured from the time from commencement of DRC to initiation of the next treatment regimen or death, whichever came first. Patients without initiation of next therapy or death were censored at the date they were last known to be alive. TTNT is a clinically relevant end point in WM patients who often fulfill the criteria for progressive disease (>25% increase in IgM protein), but remain clinically asymptomatic and are observed until the re-emergence of WM-associated symptoms or the laboratory parameters that warrant re-initiation of therapy as per the consensus recommendations.

For disease-specific survival (DSS), the patients dying from causes unrelated to WM were censored. The cause of death was considered “WM-related” if death resulted from progressive disease, amyloidosis-related end-organ failure, transformation to myelodysplastic syndrome [MDS] or diffuse large B-cell lymphoma [DLBCL], infections, or treatment-related complication; “unrelated” if patients died while WM was in remission, were off therapy, and death occurred from causes other than WM and without evidence of disease progression or relapse. A *P*-value < 0.05 was considered statistically significant and analysis was performed using JMP 10.0 software (SAS Institute, Cary, NC, USA).

## Results

### *Patient and disease characteristics*

Of 100 symptomatic WM patients, 50 patients received at least one cycle of DRC in the R/R setting and 50 patients received at least one cycle of DRC in the frontline setting, and were included in our analyses. Of the R/R patients, 40% were refractory to the prior chemotherapy regimen when DRC was initiated. Constitutional symptoms, lymphadenopathy, splenomegaly and hyperviscosity symptoms at time of diagnosis were evident in 36%, 26%, 10% and 6%, respectively. A majority of patients were males (58%). Table I shows the patients' baseline characteristics at the time of WM diagnosis.

### *DRC as salvage therapy*

DRC was the second line (range 2–8) therapy in 58% of R/R WM patients. The median number of cycles administered was 6 (range 2–6), and 71% of patients completed 6 cycles of therapy. Rituximab monotherapy was used in 20 (40%) patients as the only therapy prior to DRC. The median IgM levels declined from 38.7 g/l (range, 5.14–100 g/l) to 18.46 g/l (range, 1.77–58.3 g/l; *P* = 0.0001) and median M-spike declined from 28 g/l (range, 5.0–57 g/l) to 11 g/l (range, 1.0–36 g/l; *P* = 0.0001) at best response, with the median time-to-best response being 6.8 months (range, 0.5–28 months).

Overall response rate in the R/R setting was 87%, including 4% very good partial response (VGPR), 64% partial response (PR) and 19% minimal response (MR). Four

**Table I.** Baseline characteristics at time of DRC initiation.

Parameter, median (range)	Relapsed/Refractory	Treatment naive	All patients
Age, years	68 (48–90)	68 (37–95)	68 (37–95)
Haemoglobin, g/l	105 (70–140)	106 (53–150)	105 (53–150)
Platelet count, $\times 10^9/l$	221 (22–609)	183 (27–461)	197 (22–609)
$\beta 2$ microglobulin, mg/l	3.4 (1.9–13)	3.3 (1.6–14)	3.4 (1.6–14)
IgM, g/l	387 (5.14–100)	413 (8.17–986)	320.8 (1.72–1240)
Serum M-spike, g/l	28 (5.0–57)	21 (7.0–80)	24 (5.0–80)
Bone marrow involvement, %	50 (10–90)	50 (5–95)	50 (5–95)
<i>MYD88</i> <sup>L265P</sup> , <i>n</i> (%)	17 (89)	8 (80)	25 (86)
Lines of therapy prior to DRC,	1 (1–7)	–	–
Treatment regimens prior to salvage DRC, <i>n</i> (%)*			
Rituximab monotherapy	34 (68)		
Chlorambucil	8 (16)		
R-CVP	5 (10)		
Fludarabine	4 (8)		
Everolimus	3 (6)		
Cladribine	2 (4)		
ASCT	2 (4)		
Bortezomib	2 (4)		

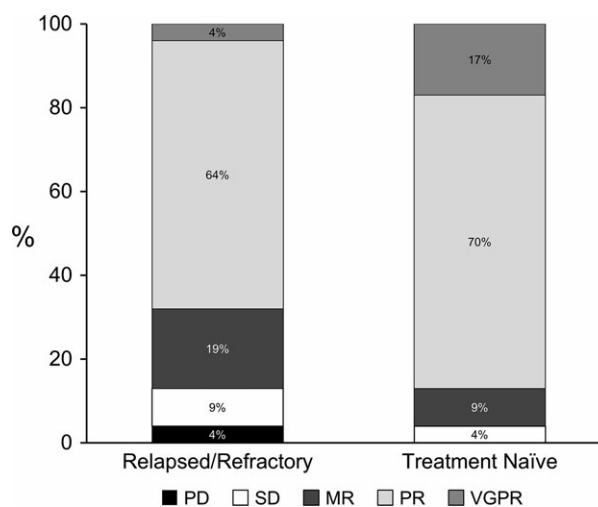
ASCT, autologous stem cell transplant; DRC, dexamethasone, rituximab, cyclophosphamide; *MYD88*, Myeloid Differentiation Primary Response 88 gene; R-CVP, rituximab, cyclophosphamide, vincristine, prednisone.

\*Included only regimens used in more than a one patient.

patients (9%) achieved stable disease and two patients (4%) had progressive disease (Fig 1). ORR was similar in patients who only received rituximab monotherapy alone prior to salvage DRC (ORR: 95%) compared to those who received other regimens (ORR 81%,  $P = 0.22$ ). Among the rituximab-refractory patients ( $n = 6$ ), the ORR from DRC was 83%. Furthermore, age above 65 years at DRC initiation ( $n = 31$ , 62%), relapsed or refractory status did not impact ORR.

The median follow-up from initiation of DRC was 51 months (95% confidence interval [CI]: 38–55) in the R/R setting. The median PFS was 32 months (95% CI: 15–51) with a 2- and 4-year PFS of 54% and 34%, respectively. The median TTNT was 50 months (95% CI: 35–60), with a 2- and 4-year TTNT of 87% and 68%, respectively (Fig 2). In patients who only received rituximab monotherapy prior to DRC, there was a trend towards a longer PFS [40 months (95% CI: 16–59) vs. 20 months (95% CI: 9–51),  $P = 0.11$ ] and TTNT [52 months (95% CI: 42–NR) vs. 36 months (95% CI: 19–62),  $P = 0.10$ ]. A trend towards a longer median PFS was evident in patients with relapsed disease [50 months (95% CI: 12–59)] compared to those with refractory disease prior to initiation of DRC [20 months (95% CI: 15–40),  $P = 0.5$ ]. However, no such difference was noted for TTNT of patients with relapsed [57 months (95% CI: 20–62)] or refractory [52 months (95% CI: 20–NR),  $P = 0.74$ ] disease. The PFS and TTNT were not impacted by the patients' age ( $\geq 65$  years) at the commencement of DRC.

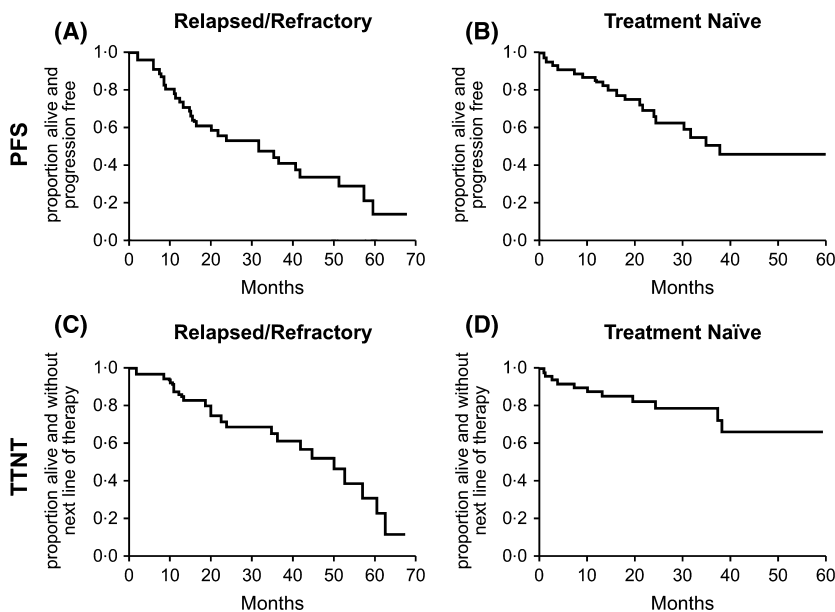
Of the 16 deaths (32%) noted at time of analysis, 11 were related to progressive disease. The median DSS from DRC was not reached (NR) (95% CI: NR–NR). The 2- and 4-year DSS from DRC were 81% and 74%, respectively.



**Figure 1.** Best response rates from DRC. DRC, dexamethasone, rituximab, cyclophosphamide; MR, minimal response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response. Maximal Overall response rate in the R/R setting was 87%, including 4% VGPR, 64% PR, 19% and MR. Stable disease and progressive disease was noted in 9% and 4% of patients, respectively. Overall response rate for the treatment-naïve patient-population was 96%, which included 17% VGPR, 70% PR and 9% MR. Stable disease was noted as the best response in 4% of patients.

### DRC as primary therapy

In newly diagnosed WM patients, the median IgM levels declined from 41.3 g/l (range, 8.71–98.6 g/l) to 12.5 g/l (range, 0.25–71.8 g/l;  $P = 0.0001$ ) and median M-spike declined from 21 g/l (range, 7.0–80 g/l) to 11 g/l (range,



**Figure 2.** Progression-free survival (PFS) and Time-to-next therapy (TTNT) in relapsed/refractory and treatment-naïve patients. (A) The median progression-free survival (PFS) was 32 months (95% CI: 15–51) in patients with WM who had relapsed and/or refractory disease. (B) The median PFS was 34 months (95% CI: 23–NR) for treatment-naïve patients. (C) The median time-to-next-therapy (TTNT) was 50 months (95% CI: 35–60) in patients with WM who had relapsed and/or refractory disease. (D) The median TTNT for treatment-naïve patients was NR (95% CI: 37–NR).

3.0–42 g/l;  $P = 0.0001$ ) at best response. The median time to best response was 11 (0.6–47) months. The median number of cycles administered was 6 (range 2–6), and 93% of patients completed 6 cycles of therapy.

All treatment-naïve patients achieved at least stable disease with DRC, with an ORR of 96%, which included 17% VGPR, 70% PR and 9% MR. Stable disease was noted as the best response in the remaining 4% of patients (Fig 1). The presence of constitutional symptoms, lymphadenopathy or splenomegaly at time of diagnosis did not impact the ORR. Age above 65 years at DRC initiation and bone marrow involvement >50% had no significant impact on the ORR in treatment-naïve patients with WM.

The median follow-up from initiation of DRC was 30 months (95% CI: 21–36) in the treatment-naïve setting. The median PFS was 34 months (95% CI: 23–NR) with 2- and 4-year PFS of 67% and 47%, respectively. The median TTNT for treatment-naïve patients was NR (95% CI: 37–NR), 2- and 4-year TTNT were 79% and 67%, respectively (Fig 2). There were no differences evident in the PFS or the TTNT based on age above 65 years at DRC initiation ( $n = 34$ , 68%).

Of the seven deaths (14%) at the time of analysis, four were related to progression of WM. The median DSS from DRC was NR (95% CI: NR–NR), with 2- and 4-year DSS from DRC of 95% and 82%, respectively.

**MYD88 status**

The MYD88 mutation status was available in 29 patients (29%) from the entire cohort (19 patients in the relapsed/refractory cohort and 10 patients in the treatment-naïve cohort), of whom 25 patients (86%) harboured the MYD88<sup>L265P</sup> mutation. The ORR in MYD88<sup>L265P</sup> patients was

92% compared to 100% in MYD88<sup>WT</sup> patients,  $P = 1.0$ . For MYD88<sup>L265P</sup> patients, the median PFS was 41 months (95% CI: 16–59) compared to 34 months (95% CI: 15–34) in MYD88<sup>WT</sup> patients,  $P = 0.45$ . The median TTNT in MYD88<sup>L265P</sup> patients was 56 months (95% CI: 38–NR) compared to 37 months (95% CI: 20–37) in MYD88<sup>WT</sup> patients,  $P = 0.23$ .

**Safety**

The toxicities attributable to the DRC therapy are summarized in Table II. Grade 3 or worse adverse events for the entire cohort were evident with respect to neutropenia (20%), thrombocytopenia (7%) and infections (3%). One previously untreated patient had a stroke after the first cycle of DRC leading to the discontinuation of treatment even though the chemotherapy was not deemed to be the cause of the stroke. Out of 65 patients with available data regarding the duration of therapy, treatment was shortened due to toxicities in 7 (11%) patients, all of whom had received DRC as

**Table II.** Major toxicities from DRC for the entire cohort.

Toxicity	Grade (%)				
	0	1	2	3	4
Neutropenia	61	13	6	11	9
Thrombocytopenia	80	1	12	6	1
Nausea/Vomiting	93	7	0	0	0
Fever/Chills	97	3	0	0	0
Headache	96	4	0	0	0
Hypotension	98	1	1	0	0
Infections	85	8	4	3	0

DRC, dexamethasone, rituximab, cyclophosphamide.

salvage therapy. No deaths related to DRC were recorded. Therapy-related MDS (t-MDS,  $n = 2$ ) and transformation to DLBCL ( $n = 4$ ) was noted at a median of 9 months (range, 5–49 months) after DRC. Five of these six patients had also received an alkylating agent and/or a nucleoside analogue prior to the diagnosis of t-MDS or transformation to DLBCL.

Stem cell mobilization and harvest was successful in all 16 patients in whom this procedure was attempted following DRC therapy, with a median collection count of  $5.99 \times 10^6$  CD34<sup>+</sup> cells/kg (range,  $2.04$ – $10.95 \times 10^6$  CD34<sup>+</sup> cells/kg).

## Discussion

Despite significant advances in our understanding of WM, it remains incurable. The goals of management of this typically indolent malignancy are to mitigate disease-related symptoms and decrease the risk of organ damage without incurring significant toxicity, particularly because a high proportion of the WM patients ultimately receive more than a single line of therapy during the course of their disease (Kapoor *et al*, 2015, 2017). Our study suggests that DRC is not only a reasonable therapeutic option in the treatment-naïve setting, but also demonstrates its high efficacy as a salvage regimen. Furthermore, our data suggest that DRC is equally effective in *MYD88*<sup>WT</sup> and *MYD88*<sup>L265P</sup> mutated patients.

Historically, the outcomes of R/R patients with WM have been generally worse than previously untreated patients (Gertz *et al*, 2004, 2009; Treon *et al*, 2009a, 2014a; Ghobrial *et al*, 2010a,b). In the R/R setting, rituximab monotherapy has demonstrated an ORR of approximately 50%, with the majority of patients achieving only a minor response (31%), and a 2-year PFS of 46% (Gertz *et al*, 2004). The combination of rituximab plus other agents leads to deeper responses and longer PFS than those evident with rituximab monotherapy. Fludarabine, a nucleoside analogue, in combination with rituximab yields an ORR of 94%, but the PFS is not better (2-year PFS of 38%) than rituximab monotherapy (Treon *et al*, 2009b). Moreover, FCR may be associated with profound myelosuppression and is unsuitable for elderly/unfit patients (Treon *et al*, 2009b). Nucleoside analogues have also been linked with higher incidence of t-MDS or transformation to high-grade lymphoma (Leleu *et al*, 2009a,b). A combination of bortezomib, a proteasome inhibitor, with rituximab in the relapsed/refractory setting has demonstrated ORR of 81% and 2-year PFS of approximately 25%, (Ghobrial *et al*, 2010a) however, a high incidence of treatment-emergent neuropathy, leading to discontinuation of therapy in 44% to 61% of patients, has been a major shortcoming of bortezomib-based regimens (Chen *et al*, 2007; Treon *et al*, 2009a). In a pivotal phase II study, ibrutinib showed an ORR of 90% and an estimated 2-year PFS of 69%. The presence of *MYD88*<sup>L265P</sup> and *CXCR4*<sup>WHIM</sup> mutations impacted response to ibrutinib, with higher response rates seen in patients with *MYD88*<sup>L265P</sup> and *CXCR4*<sup>WT</sup> (ORR 100%),

followed by *MYD88*<sup>L265P</sup> and *CXCR4*<sup>WHIM</sup> (ORR 86%) and *MYD88*<sup>WT</sup> and *CXCR4*<sup>WT</sup> (ORR 60%) (Hunter *et al*, 2014; Treon *et al*, 2015a). No patient with *MYD88*<sup>WT</sup> genotype achieved a major response. (Treon *et al*, 2015b) Idelalisib, a PI3K inhibitor, has demonstrated ORR of 80% in 10 patients with R/R WM, (Gopal *et al*, 2014) but has been associated with substantial hepatotoxicity (Castillo *et al*, 2017). Venetoclax, a BCL2 inhibitor, has demonstrated an ORR of 75% in 4 R/R WM patients treated in a phase I trial (Davids *et al*, 2014; Kapoor *et al*, 2015, 2016).

Acknowledging the limits of cross-study comparisons, our findings suggest that DRC in the salvage setting appears comparable to other regimens and shows a remarkable ORR of 87% and a 2-year PFS of 54% (median PFS and TTNT of 32 and 50 months, respectively).

In the frontline setting, rituximab monotherapy remains an adequate option for patients with mild to moderate cytopenias or isolated peripheral neuropathy showing an ORR of 53% and 2-year PFS of 51% (Gertz *et al*, 2004). Rituximab has also been studied in the treatment-naïve setting in combination with alkylating agents, proteasome inhibitors or nucleoside analogues. Bendamustine, an alkylating agent, in association with rituximab as primary therapy for symptomatic WM patients, is a relatively well-tolerated, stem cell-sparing regimen and demonstrated an ORR of 95% and a 2-year PFS of approximately 75% in a phase III trial compared to R-CHOP (Rummel *et al*, 2013). The phase II study by Dimopoulos *et al* (2007), of DRC as frontline therapy for WM patients showed an ORR of 83% and a 2-year PFS of 67%. A recent update of this study reported a median PFS of 35 months and a median TTNT of 51 months. Transformation to high-grade lymphoma or t-MDS occurred in 2.7% and 11.4% patients respectively with documented exposure, in two of these three patients, to nucleoside analogues prior to the development of these complications (Kastritis *et al*, 2015). Bortezomib as frontline therapy showed an ORR of 88% and an estimated 1-year PFS of 75% in a phase II trial in combination with rituximab. Peripheral neuropathy was seen in 54% of the patients (Ghobrial *et al*, 2010b; Kapoor, 2017). Fludarabine, in association with rituximab as frontline therapy, demonstrated an ORR of 96% and 2-year PFS of 67%. Grade  $\geq 3$  neutropenia was seen in 63% of patients. Transformation to high-grade lymphoma or t-MDS was seen in 7% and 2% of patients, respectively (Treon *et al*, 2009b). A randomized phase III trial of DRC with or without bortezomib in WM patients is ongoing (NCT01788020) (Kapoor, 2017). The outcomes of treatment-naïve WM patients treated with DRC in our non-clinical trial setting (ORR 96%; median PFS 34 months; 2-year PFS of 67%) is quite comparable to that observed in the Greek study (Dimopoulos *et al*, 2007; Treon *et al*, 2009b; Ghobrial *et al*, 2010b; Kastritis *et al*, 2015).

The absence of stem-cell toxicity, as shown by uniformly successful peripheral blood stem cell collection in our study, makes DRC a particularly suitable option for stem-cell transplant-eligible patients. No difference in ORR, PFS and TTNT

or grade  $\geq 3$  adverse events were seen in patients aged 65 years or older at initiation of DRC ( $n = 65$ , 65%) suggesting that DRC is a reasonable option even in the elderly, transplant-ineligible patient (Dimopoulos *et al*, 2007). A favourable toxicity profile was noted even in R/R WM patients, quite in line with the previously reported results in the treatment-naïve setting. A decline in IgM levels, even beyond the completion of DRC therapy was observed in 97% of patients, and led to a prolonged time-to-best response in our study. In contrast, discontinuation of ibrutinib therapy has been associated with increase in the IgM levels in WM patients and rebound lymphocytosis in patients with chronic lymphocytic leukaemia, usually within 1 week, (Maddocks *et al*, 2015; Castillo *et al*, 2016) reinforcing the need for continuous therapy with this agent. A discordant response between IgM levels and bone marrow involvement is also observed with ibrutinib therapy, suggesting a cytostatic effect in favour of cytotoxicity, and underscores the importance of performing bone marrow biopsies for adequate response assessment in patients receiving ibrutinib therapy (Treon *et al*, 2015a).

Given the heterogeneity between the treatment-naïve and R/R patient-populations, we elected not to formally compare these two sub-groups, but our data suggest profound efficacy of this combination irrespective of the disease setting. We elected to combine the R/R and treatment-naïve populations to analyse the impact of the *MYD88*<sup>L265P</sup> mutation on outcomes related to DRC therapy because the ORR appeared to be comparable in the two cohorts, and the number of patients in whom the *MYD88* mutation status was available was small. Furthermore, as in other indolent diseases, TTNT offers a more clinically relevant measure of disease progression than the PFS and should be the preferred end-point for assessment of efficacy of any regimen in WM.

While the inherent biases associated with a retrospective cohort study are limitations of our report, our data from patients treated by a group of haematologists adhering to uniform off-study practices across the three Mayo Clinic sites offer substantial clinical value in addressing management related issues with this rare malignancy.

In conclusion, similar to the frontline setting, DRC is an active and well-tolerated salvage regimen for WM patients.

In contrast to ibrutinib, DRC offers a less expensive, limited-duration treatment option, with preliminary data suggesting activity independent of patients' *MYD88* mutation status.

## Authors contributions

J.P., P.K., S.A. and M.G. designed the research. J.P., J.A., A.S., S.A., R.K., A.D. and P.K. collected and assembled the data. J.P., J.A. and P.K. analysed the data. All authors interpreted the data. J.P., J.A., S.K. and P.K. wrote the draft of the paper and all authors contributed in writing, and approved the final version of the manuscript.

## Disclosures

Dr Kumar has received honoraria from Skyline Diagnostics. Research support from Abbvie, Celgene, Novartis, Amgen, Takeda, Sanofi and Janssen has been provided to the Institution for conduct of clinical trials on which Dr Kumar serves as a principal investigator. Dr Ailawadhi has served as a consultant for Novartis Pharmaceuticals, Amgen Pharmaceuticals, Pharmacyclics, Inc, and Takeda, and has received research funding from Pharmacyclics, Inc. Dr Gertz has received research support from Ionis Pharmaceuticals and Prothena and honoraria from Celgene, Millennium Pharmaceuticals and Novartis. Dr Reeder has received research support from Celgene, Novartis and Millennium. No other disclosures are reported. Dr Dingli has received research funding from Takeda, Karyopharm and Amgen. Dr Witzig reports receiving research funding from Celgene (Institution), Novartis (Institution), Spectrum Pharmaceuticals (Institution) and Acerta Pharma (Institution). Dr Dispenzieri has received research support from Celgene, Millennium, Pfizer, Janssen and Alnylam. Dr Lacy receives research funding from Celgene. Dr Lin receives research funding from Janssen. Dr Ansell has received research funding from Bristol-Myers Squibb, Celldex, Merck, Affimed and Seattle Genetics. Dr Kapoor has received research funding from Takeda (Institution), Onyx (Institution) and Celgene (Institution), and consulting fees from Celgene and Sanofi (Institution).

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