


## ORIGINAL RESEARCH ARTICLE

# Rare lymphomas in routine practice—Treatment and outcome in Waldenström's macroglobulinaemia in the prospective German Tumour Registry Lymphatic Neoplasms

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## Abstract

Waldenström's macroglobulinaemia (WM) is a rare indolent B-cell lymphoma for which only little prospective phase III evidence exists. Thus, real world data are important to provide insight into treatment and survival. We present here data on choice and outcome of systemic treatment of patients with WM treated in German routine practice. In total, 139 patients with WM who had been documented in the prospective clinical cohort study Tumour Registry Lymphatic Neoplasms (NCT00889798) were included into this analysis. We analysed the most frequently used first-line and second-line treatments between 2009 and 2017 and examined best response, progression-free survival (PFS) and overall survival (OS). Bendamustine plus rituximab, with a median of six cycles, was by far the most frequently used first-line treatment (81%). Second-line treatment was more heterogeneous and mainly based on bendamustine, cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP), fludarabine or ibrutinib, the latter approved in 2014. Three-year PFS from start of first-line treatment was 83% (95% confidence interval [CI] 74%–88%), 3-year OS was 87% (95% CI 80%–92%). These prospective data give valuable insights into the management and outcome of non-selected patients with WM treated in German routine practice. In the lack of prospective phase III clinical trials, real world data can help bridging the gap of evidence.

## KEYWORDS

disease management, lymphoma, B-cell, outpatients, prognosis, registries, Waldenström's macroglobulinaemia

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## 1 | INTRODUCTION

Waldenström's macroglobulinaemia (WM) is a rare indolent B-cell lymphoma that accounts for 1% to 2% of non-Hodgkin's lymphomas (NHLs).<sup>1</sup> It is a disease of the elderly, with a range of median age at diagnosis from 63 to 75 years.<sup>1</sup> WM is characterised by immunoglobulin M (IgM) monoclonal gammopathy and infiltration of the bone marrow by clonal lymphoplasmacytic cells.<sup>2,3</sup> Lately, whole genome sequencing has identified activating mutations in *MYD88* present in more than 90% of patients with WM and mutations in *CXCR4* in approximately 30% to 40% of patients.<sup>4,5</sup> The age-adjusted incidence rate has been reported to be 5.5 per million European standard population using cancer registry data from the UK<sup>6</sup>; in Germany, the estimated incidence rate is 3.8 per million.<sup>7,8</sup> Patients with WM can remain asymptomatic for years without requiring therapy.<sup>9</sup> Systemic treatment is usually initiated in patients who present with anaemia, hyperviscosity or other constitutional symptoms.<sup>10</sup> Choice of first-line treatment is guided by the clinical presentation of the disease and/or complications<sup>1</sup> and individual patient's characteristics.<sup>11</sup> Since WM incidence is low, few phase III randomised clinical trials (RCTs) have been conducted so far.<sup>9,10,12-15</sup> Thus, treatment recommendations and individual decisions are mostly based on phase II data.<sup>16</sup> The lack of a clear standard of care for first-line treatment of WM is reflected by the heterogeneity in the treatment approaches used.<sup>9,16</sup> The anti-CD20 monoclonal antibody rituximab is the mainstay of most therapeutic regimens.<sup>1,2</sup> Rituximab is often combined with alkylating agents, such as bendamustine, chlorambucil and cyclophosphamide, or nucleoside analogues, such as fludarabine or proteasome inhibitors, such as bortezomib.<sup>1,9,10,14,17-20</sup> Recently, the irreversible Bruton's tyrosine kinase inhibitor ibrutinib has broadened the treatment options for patients with WM.<sup>10,21,22</sup> The International Prognostic Scoring System for WM (ISSWM<sup>23</sup>) based on patient and disease parameters evaluated at start of first-line treatment (including age, haemoglobin, platelet counts, beta-2 microglobulin and monoclonal IgM concentration) is the most widely established prognostic index which helps predict prognosis for patients with WM.<sup>11</sup> However, the current ISSWM is challenged by data analysing factors with additional impact on early mortality including non-WM-related mortality in specific age clusters (>75 years)<sup>24</sup> as well as LDH and serum albumin.<sup>25</sup> The latter are well-established prognostic factors in other indolent lymphomas. Although overall survival (OS), WM-related and non-WM-related mortality have improved over time,<sup>26</sup> WM—like other indolent lymphomas—remains incurable.<sup>27</sup>

Owing to the scarce evidence from prospective phase III RCTs, routine data are of great importance to identify treatment and survival of patients with WM, particularly, when data have been prospectively collected. In this article, we present data on 139 patients with WM who all underwent systemic treatment. Data were collected within the prospective clinical cohort study TLN (Tumour Registry Lymphatic Neoplasms) which had recruited patients with indolent NHL<sup>28-30</sup> or aggressive NHL<sup>31</sup> treated by office- and hospital-based haematologists in Germany. We show the choice of first-line treatment (2009-2014) and second-line treatment (2010-2017) and the treatment outcome by analysing best response, progression-free survival (PFS) and OS.

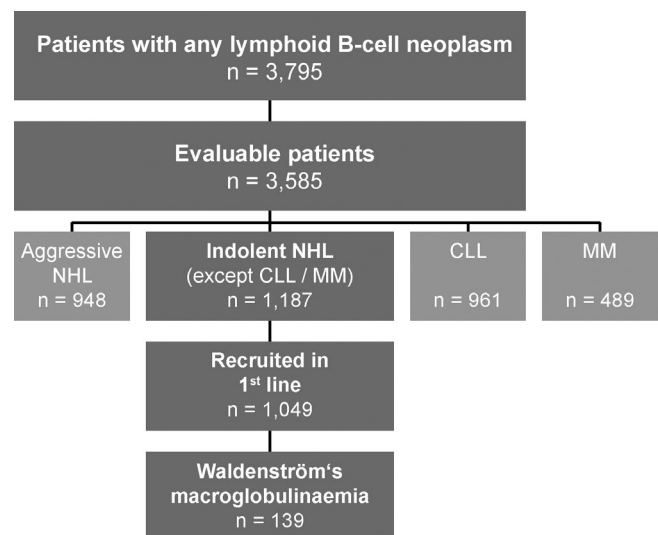
## 2 | METHODS

### 2.1 | Data source

The TLN is an open, longitudinal, multicentre, observational, prospective cohort study collecting data on the treatment of patients with lymphoid B-cell neoplasms. The study started in 2009 and was approved by the responsible ethics committee; it is registered at ClinicalTrials.gov (NCT00889798). Patients aged  $\geq 18$  years with indolent or aggressive NHL at start of their first- or second-line treatment were recruited into the TLN. Written informed consent was obtained from all patients. Treatment of patients started within 4 weeks prior or until 8 weeks after signing the informed consent. Patients were treated according to physicians' choice and visited their physician on their individual schedule. Patients were followed for up to 5 years from enrolment or until death, loss to follow-up or withdrawal of consent. Further details on the methodology of the TLN have been previously described elsewhere.<sup>28-31</sup>

### 2.2 | Cohort definition

By the end of the enrolment period in August 2014, 3795 patients with lymphoid B-cell neoplasms had been recruited into the TLN (Figure 1). Two hundred and ten patients were not evaluable due to incomplete data on treatment or withdrawal of consent. Out of the remaining 3585 evaluable patients, 1187 were diagnosed with indolent NHL (excluding chronic lymphocytic leukaemia and multiple



**FIGURE 1** Cohort definition. Number of patients enrolled in the TLN from April 2009 until August 2014, split up according to different types of lymphoid B-cell neoplasms. Of all evaluable patients with indolent NHL (other than CLL or MM), those patients with WM who had been prospectively enrolled at the start of their first-line treatment were included into this analysis ( $n = 139$ ). Data cut-off for this analysis was 31 August 2018. CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, non-Hodgkin's lymphoma; TLN, Tumour Registry Lymphatic Neoplasms; WM, Waldenström's macroglobulinaemia

myeloma); 1049 of them had been enrolled at start of their first-line treatment. Among them, we identified 139 patients with WM who had been enrolled in 73 office- and hospital-based medical oncology centres across Germany between April 2009 and January 2014. Data cut-off for this analysis was 31 August 2018.

### 2.3 | Statistical analysis

Time-to-events was analysed by the Kaplan-Meier method. PFS was defined as the interval between start of first-line treatment and date of progression or death prior to start of second-line treatment; patients without such an event were censored at either the start of second-line treatment or at the last documented contact. OS was defined as the interval between start of first-line treatment until death from any cause. Data of patients alive or lost to follow-up were censored at the last documented contact. The median observation time was calculated using the reverse Kaplan-Meier estimate.<sup>32</sup> Confidence limits for the survivor function were calculated employing a log-log transformation.<sup>33</sup> Confidence intervals for median survival were calculated as described by Brookmeyer and Crowley.<sup>34</sup> All analyses were performed using Dell, Inc. (2016), Dell Statistica, version 13.1. software.dell.com and SAS software, version 9.4 of the SAS System for Windows (Copyright© 2002-2012 SAS Institute Inc. SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina).

## 3 | RESULTS

### 3.1 | Patient demographics and clinical characteristics

Table 1 presents the demographics and clinical characteristics of patients with WM included into this analysis (n = 139). Most patients were male (62%); the median age at start of first-line treatment was 72 years. In total, 66% of patients experienced at least one concomitant disease at start of first-line treatment, mainly arterial hypertension (31%). A total of 28% of patients had comorbidities considered for the Charlson comorbidity index (CCI; CCI ≥1). In total, 28% of patients were in good general condition (ECOG = 0), whereas for 10% a poor performance status (ECOG ≥2) was reported. B-symptoms were present in almost one-third of patients (30%).

### 3.2 | Choice of systemic treatment

#### 3.2.1 | First-line treatment

Figure 2 displays the most frequently used first-line treatments between 2009 and 2014 (n = 139), clustered by substance groups.

By far, bendamustine-based therapies were the most common first-line treatments (85%, n = 118), with bendamustine combined with rituximab used for most of patients (81%, n = 112). Of those

**TABLE 1** Patient demographics and clinical characteristics at start of first-line treatment

Characteristic	Patients with WM (n = 139)	
Age	Years	Min-Max
Median	71.5	37.1 to 93.4
	n	%
<65 y	41	29.5
65 to 74 y	49	35.3
≥75 y	49	35.3
	kg/m <sup>2</sup>	SD
BMI, mean <sup>a</sup>	24.9	4.0
	n	%
Missing	2	1.4
Sex		
Female	53	38.1
Male	86	61.9
Patients with comorbidity		
Any comorbidity <sup>b</sup>	92	66.2
CCI = 0 <sup>c</sup>	99	71.2
CCI ≥1 <sup>c</sup>	39	28.1
Hypertension	43	30.9
Cardiac disorders <sup>d</sup>	19	13.7
Diabetes	13	9.4
Chronic pulmonary disease	11	7.9
Performance status		
ECOG = 0	39	28.1
ECOG = 1	78	56.1
ECOG ≥2	14	10.1
Unknown	8	5.8
B symptoms <sup>e</sup>		
Present	41	29.5
Unknown	4	2.9
Haemoglobin		
<12 g/dL	96	69.1
LDH		
>ULN	35	25.2
Unknown	5	3.6
Median time from diagnosis to treatment	Months	25%/ 75% quantiles
	1.6	0.7-22.3

Note: Some percentages might not add up to 100% due to rounding. Abbreviations: BMI, body mass index; CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; SD, standard deviation; ULN, upper limit of normal; WM, Waldenström's macroglobulinaemia.

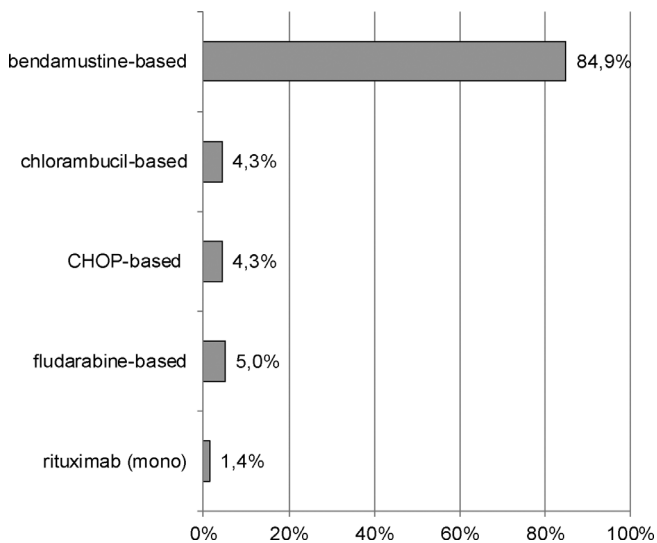
<sup>a</sup>At enrolment.

<sup>b</sup>At least one comorbidity according to Charlson and/or additional concomitant diseases.

<sup>c</sup>Charlson comorbidity index (CCI) according to Quan et al<sup>35,36</sup>; WM (two points) was not counted as a comorbidity.

<sup>d</sup>Heart insufficiency, myocardial infarction, coronary artery disease and other cardiac disorders.

<sup>e</sup>Fever, night sweats, loss of weight.



**FIGURE 2** Choice of systemic first-line treatment in Waldenström's macroglobulinaemia. Shown are first-line treatments/ treatment combinations between 2009 and 2014 sorted by relative frequency ( $n = 139$ ). *Bendamustine-based*: bendamustine (mono), bendamustine + rituximab ( $\pm$ prednisone/dexamethasone); *chlorambucil-based*: chlorambucil (mono), chlorambucil + rituximab ( $\pm$ prednisone/mitoxantrone); *fludarabine-based*: fludarabine (mono), fludarabine + cyclophosphamide ( $\pm$ rituximab); *CHOP-based*: variations of CHOP (CHOP, CH, COP, HOP)  $\pm$  rituximab ( $\pm$ prednisone/dexamethasone). Percentages may not add up to 100% due to rounding. C, cyclophosphamide; H, doxorubicin; O, vincristine; P, prednisone

patients who received rituximab-bendamustine, bendamustine was used for a median of six cycles (interquartile range [IQR] 1.0), rituximab for a median of six cycles (IQR 2.0). Our data show a trend towards an increasing use of rituximab-bendamustine in course of the observation period (data on file). However, more than 60% of patients were treated with this combination already in 2009. Overall, other treatments were assigned to 15% of patients ( $n = 21$ ). These treatments were based on chlorambucil (4%,  $n = 6$ ) or cyclophosphamide/doxorubicin/vincristine/prednisone (CHOP; 4%,  $n = 6$ ) or fludarabine (5%,  $n = 7$ ), all of them mainly combined with rituximab. Rituximab monotherapy was used in two patients (1%). Due to rounding, individual percentages presented here may not add up to 100%.

### 3.2.2 | Second-line treatment

Second-line treatment was documented for 19% of patients ( $n = 26$ ) at the time of analysis, while 13% ( $n = 18$ ) had died prior to receiving a second-line treatment. The remainder were either still in first-line treatment (potentially receiving more lines of treatment) or had been lost to follow-up after first-line treatment. From 2010 to 2017, patients most frequently received therapies based on bendamustine (31%,  $n = 8$ ) as second-line treatment, particularly rituximab-bendamustine (23%,  $n = 6$ ). Seven patients (27%) were treated with a regimen based on CHOP (mainly plus rituximab, R-CHOP), five

**TABLE 2** OS, PFS and best response since start of first-line treatment

Characteristic	Patients with WM ( $n = 139$ )	
Best response	<i>n</i>	%
CRu <sup>a</sup>	24	17.3
PR	82	59.0
SD	13	9.4
PD	6	4.3
Unknown	14	10.1
Progression-free survival	<i>n</i>	%
Events	37	26.6
Median PFS <sup>b</sup>	<b>Months</b>	<b>95% CI</b>
	NA	NA
Survival rate	%	<b>95% CI</b>
12 months	91.5	85.2 to 95.2
24 months	86.5	79.1 to 91.4
36 months	82.5	74.4 to 88.3
Overall survival	<i>n</i>	%
Events	25	18.0
Median OS	<b>Months</b>	<b>95% CI</b>
	NA	NA
Survival rate	%	<b>95% CI</b>
12 months	95.5	90.3 to 98.0
24 months	90.0	83.3 to 94.0
36 months	87.1	79.8 to 91.9
Median duration of observation	<b>Months</b>	<b>95% CI</b>
	60.3	59.5 to 61.1

Note: Some percentages might not add up to 100% due to rounding. Abbreviations: CI, confidence interval; CRu, unconfirmed complete response; NA, not applicable; OS, overall survival; PD, progression; PFS, progression-free survival; PR, partial response; SD, stable disease; WM, Waldenström's macroglobulinaemia.

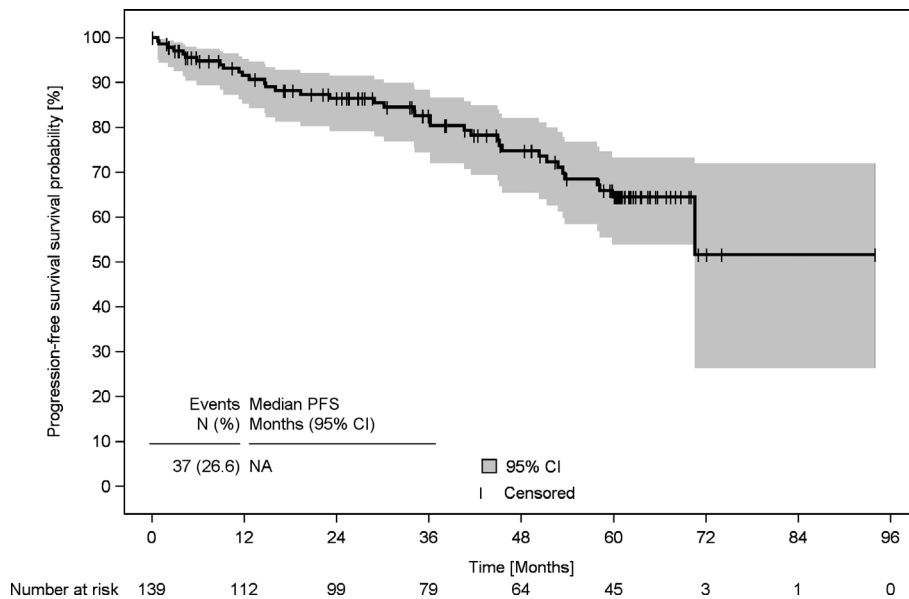
<sup>a</sup>Assessment by study sites, no evaluation by the criteria used in clinical trials.

<sup>b</sup>Assessment by study sites and not according to response criteria used in clinical trials.

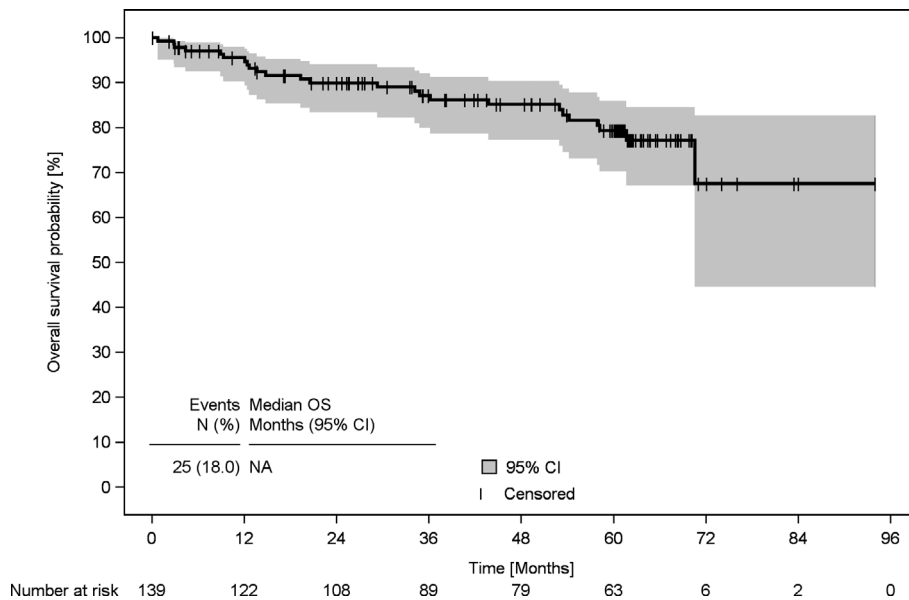
patients (19%) received fludarabine monotherapy or in combination with other substances. Ibrutinib, approved in October 2014, was prescribed to three patients (12%). Since a total of five patients had been recruited after the approval date of ibrutinib, this corresponds to a prescription rate of 60%. One patient (4%) received chlorambucil, two patients (8%) another treatment option: dexamethasone/high-dose cytarabine (Ara-C)/cisplatin (DHAP) combined with rituximab or a cyclophosphamide-/etoposide-based chemotherapy with rituximab.

### 3.3 | Sequential treatment

The three most frequently used sequences for patients proceeding from first-line to second-line treatment were: bendamustine-based



**FIGURE 3** Progression-free survival of patients with Waldenström's macroglobulinaemia since start of first-line treatment. Progression-free survival of patients with WM who had been enrolled at the beginning of their first-line treatment ( $n = 139$ ). CI, confidence interval; NA, not applicable; PFS, progression-free survival; WM, Waldenström's macroglobulinaemia



**FIGURE 4** Overall survival of patients with Waldenström's macroglobulinaemia since start of first-line treatment. Overall survival of patients with WM who had been enrolled at the beginning of their first-line treatment ( $n = 139$ ). CI, confidence interval; NA, not applicable; OS, overall survival; WM, Waldenström's macroglobulinaemia

therapy followed by (a) a bendamustine-based treatment (23%,  $n = 6$ ), or (b) a CHOP-based treatment (23%,  $n = 6$ ), or (c) a fludarabine-based treatment (15%,  $n = 4$ ).

### 3.4 | Best response, PFS and OS

Outcome data are displayed in Table 2. The objective response rate for patients encompassing any positive response was 76%, with unconfirmed complete response (CRu) of 17%. For 13 patients (9%), stable disease has been reported, whereas for 6 patients (4%), progressive disease has been documented as the best response achieved during first-line treatment.

Median duration of observation was 60.3 months (95% confidence interval [CI] 59.5-61.1). For both OS and PFS, the median was

not reached. Three-year PFS of patients was 83% (95% CI 74%-88%; Table 2 and Figure 3), 3-year OS was 87% (95% CI 80%-92%; Table 2 and Figure 4).

At data cut-off, 25 patients (18%) had died, 18 (13%) were still being observed, 36 (26%) were lost to follow-up and 60 (43%) were alive at the end of the individual 5-year observation period.

## 4 | DISCUSSION

Waldenström's macroglobulinaemia is a rare haematological disorder for which only little prospective phase III evidence on its management exists and thus a clear standard of care for first-line treatment is lacking. We present prospective real world data on treatment and survival of patients with WM outside a clinical trial setting in Germany.

We show that rituximab-bendamustine was by far the most frequently used first-line treatment (81%). Second-line treatment was more heterogeneous and was mainly based on bendamustine, CHOP, fludarabine or ibrutinib which was approved 5 years after the start of this study. Three-year PFS and 3-year OS were 83% (95% CI 74%–88%) and 87% (95% CI 80%–92%), respectively.

Strengths of this study are the prospective, longitudinal design and the non-selected participation of haematologists/oncologists across Germany recruiting into a large study cohort. This allows the analysis of smaller subsets of patients, such as the WM patient population. Nonetheless, there are limitations. In the TLN, only patients with WM who received systemic treatment had been included and not those with a watch-and-wait approach and no systemic treatment at all. Therefore, characteristics of our cohort are not representative of the whole WM patient population. Since data on the time of diagnosis were documented retrospectively, the median time between diagnosis and start of first-line treatment may be underestimated, because patients with a long period of time until start of treatment may be underrepresented in the TLN: not all participating centres were possibly aware of the inclusion of such patients as soon as the need for treatment arose and therefore did not consider them for inclusion into the registry in the same way as patients for whom systemic treatment started close to diagnosis. Some prognostic factors for calculating the ISSWM, such as beta-2 microglobulin and platelet count, had not been documented within the TLN. Since WM is a rare disorder, the number of patients included into this analysis is rather small compared to more common types of lymphomas and percentages provided in the results section should be interpreted with some caution. There were no specifications as to the timing, frequency or criteria of tumour assessment. Thus, clinical PFS data could be considered as the best clinical approximation, but might not be identical to the PFS determined in prospectively RCTs. The same holds true for data on CRu.

Our data show that the vast majority of patients with WM in German routine practice received first-line treatment with rituximab-bendamustine, with six cycles in median. This is in accordance with former and current guidelines recommending four to six cycles of rituximab combined with bendamustine as one primary first-line treatment option for 'medically fit' patients (in addition to plasmapheresis in case of hyperviscosity).<sup>1,37–39</sup> In a randomised phase III study, patients with rituximab-bendamustine in first-line had longer PFS and OS than those who underwent therapy with R-CHOP.<sup>14</sup> Since rituximab-bendamustine has been associated with a prolonged PFS and time-to-next therapy, deep responses (complete response + very good partial response rates), and favourable toxicity profile, this combination is currently the primary regimen of choice for previously untreated WM.<sup>39,40</sup>

Our findings on treatment patterns vary from those of the Swedish Lymphoma Registry (SLR) study on prognostic factors and treatment for WM that—to our knowledge—is the only prospective population-based study published so far.<sup>11</sup> Of 203 patients with documented systemic first-line treatment between 2000 and 2014, 153 were treated between 2007 and 2014 and mainly received

cyclophosphamide-(rituximab)-based regimens (28%, of which 6% were R-CHOP-like regimens) and chlorambucil (27%, mostly without rituximab). Only in 7% of patients rituximab-bendamustine was used.<sup>11</sup> These differences might reflect differences in patient cohorts, national guidelines and health care systems between Sweden and Germany.

Among the existing retrospective, mainly population-based studies on treatment and outcome patterns of patients with WM,<sup>9,24,26,27,40–44</sup> one large chart-based study also included patients from German clinical practice.<sup>9</sup> In this study, R-CHOP and rituximab-bendamustine were the most frequently used chemoimmunotherapy regimens in first-line which is similar to our findings. Of the 454 patients who had been treated in European academic and community centres from 2000 to 2014, 66 patients were treated in Germany (38%,  $n = 25$  in community centres).<sup>9</sup>

In our study, second-line treatment was mostly based on bendamustine (primarily in combination with rituximab), CHOP or fludarabine. This is in line with German guidelines valid during the observation period<sup>37</sup> and similar to the results observed in the aforementioned chart-based study, with rituximab-bendamustine and cyclophosphamide-/CHOP-based regimens used most frequently for second-line chemoimmunotherapy, followed by regimens based on fludarabine.<sup>9</sup> As for ibrutinib which was used for second-line treatment in more than half of patients who had been recruited after the approval date of ibrutinib in October 2014, our data clearly show that newly licensed agents are quickly implemented into routine practice. This is even more noteworthy, as the uptake of ibrutinib for relapsed WM disease into consensus publications and guidelines took some time.

The PFS data presented here (2-year PFS of 87%; 3-year PFS of 83%) are in line with recent retrospective data in patients with WM after first-line treatment with rituximab-bendamustine revealing a 2-year PFS of 88%<sup>40</sup> and a 3-year PFS of approximately 85%.<sup>27</sup> In the phase III RCT on bendamustine plus rituximab vs R-CHOP, those patients with WM who received bendamustine plus rituximab in first-line ( $n = 22$ ) had a 3-year PFS of about 80%.<sup>14</sup> The latter finding is even more surprising, since patients treated in routine practice usually markedly differ from those selected for clinical trials<sup>30,45</sup> and results suggest that patient outcomes are worse outside a clinical trial setting.<sup>9</sup> Interestingly, in the above-mentioned retrospective chart review, PFS was shortened in patients treated in academic centres compared to those treated in community institutions, but this result might have been confounded by factors to be explored.<sup>9</sup>

Three-year OS of patients included in our analysis was 87%, a finding that agrees with results from other (retrospective and prospective) studies: in patients with WM who received any systemic first-line treatment within the period of 2000 to 2014, 3-year OS ranged from 63% to approximately 95%.<sup>9,11,26,27,41,43</sup> Notably, the lowest 3-year OS has been observed in patients with the 'highest' median age of 78 years<sup>43</sup> and the highest 3-year OS in patients of the 'youngest' median age (65 years).<sup>9</sup> With 72 years in median at start of first-line treatment, the age of our registry cohort is very similar to that of the prospective SLR cohort having a median age of 73 years.<sup>11</sup> Even

though first-line treatments differ between this study and the SLR study, both the median observation time and the 3-year OS are highly comparable: 60.3 months vs 55.5 months<sup>11</sup> and 87% vs approximately 80%.<sup>11</sup> Since patients' age has been found to be one of the strongest prognostic factors,<sup>11</sup> our data also suggest an important role of age for WM outcome.

## 5 | CONCLUSION

Since there is only little evidence from prospective phase III RCTs, the prospective data we present here provide important insights into treatment and survival of patients with WM outside a clinical trial setting in Germany. We show that bendamustine plus rituximab, with a median of six cycles, was by far the most commonly used first-line treatment corresponding to former and current guideline recommendations. Our findings indicate that a newly licensed agent like ibrutinib is quickly implemented into routine practice. Outcome data of this analysis agree with recent retrospective and prospective (observational and clinical trial) data. When patient's participation in clinical trials is not possible, real world data can help bridging the gap of evidence, especially in rare diseases.

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### CONFLICT OF INTEREST

Hans Rainer Slawik, Ute Bückner, Annette Sauer, Mark-Oliver Zahn, Natalie Wetzel, Anja Kaiser-Osterhues and Leonora Houet declare no conflict of interest concerning the topic of this publication. Wolfgang Knauf has received honoraria by Mundipharma and Janssen for talks and attendance of conferences. Wolfgang Abenhardt has received financial support from Roche, Amgen, Celgene and Gilead Sciences in the context of a lymphoma symposium. Burkhard Otremba declares stock ownership of iOMEDICO. Norbert Marschner is Chief Executive Officer of iOMEDICO and holds shares of this company.

### AUTHOR CONTRIBUTIONS

Wolfgang Knauf, Wolfgang Abenhardt, Leonora Houet, Natalie Wetzel, Anja Kaiser-Osterhues and Norbert Marschner designed the

research study. Wolfgang Knauf, Wolfgang Abenhardt, Hans Rainer Slawik, Ute Bückner, Burkhard Otremba, Annette Sauer, Mark-Oliver Zahn and Norbert Marschner performed the research. Natalie Wetzel, Leonora Houet and Anja Kaiser-Osterhues analysed the data. Anja Kaiser-Osterhues wrote the paper. All the authors critically reviewed and approved the manuscript.

### ETHICS STATEMENT

All experiments comply with the current laws in Germany, where they were performed. All procedures performed in studies involving human participants were in accordance with the ethical standards of the national research committee and with the 1964 Helsinki declaration and its later amendments. This study was approved by the responsible ethics committee and is registered at ClinicalTrials.gov (NCT00889798).

### ORIGINAL PUBLICATION

The authors confirm that this work has not been published previously. Parts of it have been presented at the German annual meeting of the DGHO German Society for Hematology and Medical Oncology eV, 2018 (poster presentation).

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