Treatment and outcome patterns in European patients with Waldenström's macroglobulinaemia: a large, observational, retrospective chart review

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Summary

Background Treatment options for Waldenström's macroglobulinaemia are heterogeneous, and no well established treatment standards exist. Although guidelines from the Eighth International Workshop on Waldenstrom's Macroglobulinemia were published in 2016, inconsistent awareness and budget constraints have prevented their widespread implementation, and real-life treatment patterns might differ across health-care systems. We aimed to generate information about treatment and outcome patterns for patients with Waldenström's macroglobulinaemia outside of clinical trials.

Methods In this large, observational, retrospective chart review, academic and community physicians in ten European countries were invited to retrospectively complete electronic records for patients with symptomatic Waldenström's macroglobulinaemia who had begun treatment after Jan 1, 2000, and before Jan 1, 2014, and had available clinical and biological data. The primary endpoints were reasons for treatment initiation, treatment choices, progression-free survival, and overall survival. We assessed the variables that affected choice of front-line therapy, progression-free survival, and overall survival in multivariate analyses.

Findings Electronic records were reviewed for 454 eligible patients. The most frequent reasons for starting front-line treatment were anaemia (in 328 [72%] patients) and constitutional symptoms (in 264 [58%] patients). Choice of therapy varied between front-line, second-line, and third-line approaches; age; and type of institution. In the front-line setting, 193 (43%) of 454 patients received monotherapy, 164 (36%) received chemoimmunotherapy, and 95 (21%) received other combination regimens (data on front-line treatment were missing for one patient, and another patient received only steroids). After front-line treatment, median progression-free survival was 29 months (95% CI 25–31), median overall survival was not reached (not reached–not reached), and 10-year overall survival was 69% (62–74). In multivariate analyses, patients who were high risk according to the International Prognostic Scoring System for Waldenström Macroglobulinemia had significantly worse progression-free survival and overall survival than did those who were low risk. Additionally, progression-free survival was shortened in patients treated with monotherapy compared with those treated with chemoimmunotherapy or other combination therapies and in those treated at an academic institution compared with those treated in the community. Constitutional symptoms (excluding fatigue) were associated with worsened overall survival.

Interpretation This large observational dataset should inform and help set guidelines, and improve understanding of treatment practices and outcomes, for European patients with Waldenström's macroglobulinaemia.

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Introduction

Waldenström's macroglobulinaemia is a rare, indolent B-cell lymphoma that is characterised by infiltration of IgM-producing, clonal lymphoplasmacytic cells into the bone marrow. The estimated age-adjusted incidence of Waldenström's macroglobulinaemia in Europe is 7·3 per 1 million men and 4·2 per 1 million women.[1,2] Patients with Waldenström's macroglobulinaemia can remain asymptomatic for years, during which time a watch-and-wait approach is recommended. Treatment is generally started when patients develop cytopenias, bulky adenopathy, organomegaly, constitutional symptoms (eg, fever and fatigue), or IgM-related symptoms (eg, neuropathy and blood hyperviscosity due to elevated serum immunoglobulin concentrations).[1,3,4] Mortality varies, and causes of death in patients who have Waldenström's macroglobulinaemia include disease-related events—such as disease progression, transformation to high-grade lymphoma, or infections—and causes unrelated to Waldenström's macroglobulinaemia, such as cardiac issues.[5,6]

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Research in context

Evidence before this study

We searched for articles indexed in PubMed from inception to Jan 1, 2016, using the search terms "Waldenström's macroglobulinaemia" and "Waldenström's macroglobulinemia", both alone and in conjunction with "review", "chart review", and "outcomes". We additionally considered abstracts and presentations from international congresses. Waldenström's macroglobulinaemia is a rare, indolent B-cell lymphoma, with wide heterogeneity in its treatment in clinical practice. It usually occurs in the elderly patient population. With few prospective phase 3 clinical trials, and in the absence of a large prospective registry, it has been difficult to define treatment standards and to identify frequently used or feasible treatment regimens for this rare disease.

Added value of the study

To our knowledge, this study is the first to investigate the treatment landscape for patients with Waldenström's macroglobulinaemia in Europe. We analysed a comprehensive dataset covering ten European countries over a period of 14 years (2000–14) to obtain detailed information regarding the clinical presentation of Waldenström's macroglobulinaemia, reasons for initiation of treatment, treatment practices, and treatment outcomes.

Implications of all the available evidence

This large, observational dataset should improve understanding of treatment practices and outcomes for Waldenström's macroglobulinaemia outside of the clinical trial setting. It should also highlight the need for, and inform, treatment standards for the disease that are feasible and applicable across countries. Future surveys might allow investigation of the effect of potential therapies or combinations of novel drugs on the survival of patients with Waldenström's macroglobulinaemia, as well as their long-term outcomes in the real-world setting.

Although a general consensus exists on the diagnosis of Waldenström's macroglobulinaemia and when to begin treatment, there is wide heterogeneity in the approaches and regimens used to treat patients, even in international guidelines.[7–9] Because of the low incidence of the disease, few large randomised studies to define treatment standards have been conducted.[10–13] Systemic treatment options include rituximab alone or in combination with alkylating agents, such as chlorambucil; proteasome inhibitors, such as bortezomib; nucleoside analogues, such as fludarabine; and, more recently, the Bruton's tyrosine kinase inhibitor ibrutinib.[1,3,4,13,14] Choice of therapy after relapse depends on the duration of response to primary treatment. Unlike other closely related lymphomas, the efficacy of maintenance therapy for Waldenström's macroglobulinaemia is unclear, although improved outcomes were reported in an observational study[15] of rituximab maintenance therapy. Retreatment with the primary regimen is recommended for patients whose response lasted at least 12 months, whereas treatment with a different regimen is preferred after a short remission (<12 months).[1,3,4,14] Autologous stem-cell transplantation might be an option for younger patients and those with chemosensitive disease.[1,3] Additionally, although the role of *MYD88* and *CXCR4* mutations in the clinical presentation and prognosis of Waldenström's macroglobulinaemia is still an open research question, outcomes in patients with these mutations suggest that future treatment options could be tailored to mutational status and that existing risk scores might be adjusted to incorporate the findings of mutational analyses.[3,16,17]

See Online for appendix

Understanding the treatment landscape of Waldenström's macroglobulinaemia is a key unmet need for this rare disease, and better understanding of practice patterns and uptake of new therapeutic concepts might lead to better allocation of health resources. To date, population-based studies in Waldenström's macroglobulinaemia have used sources such as the Surveillance, Epidemiology, and End Results database,[5] or have been based on single-country experiences.[18] Many of these analyses have lacked essential information, such as response to therapy, disease progression, or performance status. For instance, the Swedish Cancer Registry[19] reported survival trends in Waldenström's macroglobulinaemia but did not provide information about treatment practices, whereas the Greek Myeloma Study Group[20,21] mainly focused on reporting changes in survival of patients with Waldenström's macroglobulinaemia treated before and after 2000.

To address this knowledge gap, we compiled extensive datasets describing patients with Waldenström's macroglobulinaemia who were treated in academic or community centres in ten European countries over the course of 14 years. The datasets include patient characteristics, treatment choices, and information about disease progression and patient survival, which we analysed to assess differences in treatment and outcomes for patients with Waldenström's macroglobulinaemia.

Methods

Study design and participants

We completed a large, observational, retrospective chart review of patients who presented with Waldenström's macroglobulinaemia at 71 sites across ten European countries: Austria, France, Germany, Greece, Italy, Poland, Spain, the Czech Republic, the Netherlands, and the UK (appendix pp 2–4). Patients were eligible for inclusion if they had a confirmed diagnosis of Waldenström's macroglobulinaemia according to criteria of the Second International Workshop on Waldenström's macroglobulinemia,[2] symptomatic disease requiring treatment, and complete clinical and biological data

available at the time of initial therapy or diagnosis. Additionally, patients had to have been diagnosed with Waldenström's macroglobulinaemia and have begun front-line treatment (excluding maintenance therapy) after Jan 1, 2000, and before Jan 1, 2014. The baseline clinical and biological data we collected included complete blood count; serum concentrations of β-2 microglobulin, albumin, IgM, and monoclonal protein; and evaluations of lymphadenopathy, splenomegaly, and bone marrow infiltration. Each site's institutional review board ensured appropriate consent was provided before the study.

Academic and community physicians were selected by the European Consortium for Waldenstrom's Macroglobulinemia through individual country coordinators, and were asked to retrospectively complete anonymised electronic records for patients with Waldenström's macroglobulinaemia who had been treated at their institutions within the 14-year study period. Between Dec 11, 2014, and Jan 31, 2015, physicians completed a questionnaire for each patient, which was designed by Genactis (London, UK), who also did data collection and management.

Outcomes

The primary outcomes were reasons for treatment initiation, choice of treatment regimen, progression-free survival, and overall survival. Progression-free survival was defined as the time between start of front-line, second-line, or third-line treatment and physician-documented disease progression or death. Patients who did not have documented disease progression after initiation of their second-line or third-line treatment or a recorded date of death were censored on the date of their last recorded hospital contact. Overall survival was defined as the time between start of front-line treatment and death, and patients without a recorded date of death were censored on the date of last contact.

Procedures

Data extracted from the completed chart reviews included patient demographics, disease characteristics, reasons for starting treatment, choice of treatment in each line of therapy, patient outcomes, type of treating institution (academic or community), and incidence of other cancers before and after diagnosis and treatment. Patient and disease characteristics of interest were constitutional symptoms, including clinically relevant fatigue and fever;[22] age; sex; International Prognostic Scoring System for Waldenström Macroglobulinemia (IPSSWM) risk score; β-2 microglobulin concentration; cytopenias, including anaemia, thrombocytopenia, and neutropenia; organomegaly, including lymphadenopathy; and IgM-related symptoms.

Statistical analysis

We analysed overall and progression-free survival using the Kaplan-Meier method to appropriately take into account the censored observations.[23] The Cox proportional-hazards model was used to identify baseline and prognostic variables that might be associated with the survival outcomes.[24] We did multivariate analysis using the Cox proportional-hazards model, with inclusion of a missing category for variables with missing values, to generate hazard ratios (HRs), 95% CIs, and p values. The models were built with a stepwise selection procedure in SAS software version 9.3: each variable was entered into the model if its p value was less than 0·20 and remained in the model if its p value was less than 0·05 (appendix p 5). Multivariate logistic regression, performed with a similar stepwise selection procedure, was used to assess variables associated with the use of chemoimmunotherapy, monotherapy, or other combination regimens.

Summary statistics are descriptive for demographics, clinical characteristics, and treatment patterns. For continuous data, medians and IQRs are presented. For categorical data, frequencies and percentages are presented. No adjustments were made for multiplicity; the results of significance testing should be considered as hypothesis-generating only. Statistical analyses were done with SAS software, version 9.3.

Role of the funding source

The funder of the study was involved in study design, compilation of data, and statistical analysis, and provided editorial support to the authors. All authors had full access to all the data. The corresponding author had final responsibility for the decision to submit for publication.

Results

We reviewed retrospectively completed electronic records for 454 patients who were diagnosed with Waldenström's macroglobulinemia and commenced front-line treatment over a 14-year period in Austria (n=19), France (n=92), Germany (n=66), Greece (n=27), Italy (n=56), Poland (n=21), Spain (n=60), the Czech Republic (n=16), the Netherlands (n=25), and the UK (n=72; appendix pp 2–4). All patients had a progression event after front-line therapy, and all patients for whom subsequent therapy was documented were included in the analyses of second-line and third-line outcomes.

Patient characteristics at the time of starting treatment are shown in table 1. Patients were recruited from 27 community institutions and 44 academic institutions. Most patients had either an intermediate or a high IPSSWM risk score at treatment initiation. The most common reasons for starting front-line treatment were anaemia, followed by constitutional and IgM-related symptoms; organomegaly was less frequently reported than were other symptoms. Symptoms that led to treatment initiation were largely similar across countries (appendix p 6).

Of the 454 patients who received front-line treatment, 193 (43%) received monotherapy, 164 (36%) received

	Overall (n=454)	Academic centre (n=306)	Community centre (n=148)
Age (years)	65 (57–73)	65 (56–72)	65 (59–73)
<65 years	223 (49%)	149 (49%)	74 (50%)
≥65 years	231 (51%)	157 (51%)	74 (50%)
≥75 years	77 (17%)	50 (16%)	27 (18%)
Sex			
Women	176 (39%)	123 (40%)	53 (36%)
Men	278 (61%)	183 (60%)	95 (64%)
IPSSWM risk			
Low	76/357 (21%)	57/249 (23%)	19/108 (18%)
Intermediate	142/357 (40%)	92/249 (37%)	50/108 (46%)
High	139/357 (39%)	100/249 (40%)	39/108 (36%)
β-2 microglobulin (mg/mL)*	3·4 (2·6–4·4; 370)	3·2 (2·6–4·2; 260)	3·7 (2·9–4·7; 110)
Symptoms leading to treatment initiation†			
Constitutional symptoms	264 (58%)	177 (58%)	87 (59%)
IgM-related symptoms	247 (54%)	149 (49%)	98 (66%)
Organomegaly	77 (17%)	43 (14%)	34 (23%)
Anaemia	328 (72%)	223 (73%)	105 (71%)
Thrombocytopenia	82 (18%)	58 (19%)	24 (16%)
Neutropenia	46 (10%)	36 (12%)	10 (7%)
Region			
Austria	19 (4%)	19 (6%)	0
Czech Republic	16 (4%)	16 (5%)	0
France	92 (20%)	63 (21%)	29 (20%)
Germany	66 (15%)	41 (13%)	25 (17%)
Greece	27 (6%)	27 (9%)	0
Italy	56 (12%)	40 (13%)	16 (11%)
Netherlands	25 (6%)	13 (4%)	12 (8%)
Poland	21 (5%)	21 (7%)	0
Spain	60 (13%)	60 (20%)	0
UK	72 (16%)	6 (2%)	66 (45%)

Data are median (IQR), n (%), or n/N (%) unless otherwise stated. IPSSWM=International Prognostic Scoring System for Waldenström Macroglobulinemia. *Data are median (IQR; number of patients for whom data were available). †Patients could have more than one symptom at start of treatment.

Table 1: **Patient characteristics at the time of treatment initiation**

chemoimmunotherapy, and 95 (21%) received other combination regimens (figure 1A). Data on front-line treatment were missing for one patient, and one patient received steroids only. Chlorambucil was the most frequently used monotherapy (n=123), followed by rituximab (n=28) and fludarabine (n=21). The most frequently used chemoimmunotherapy regimen was R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone or prednisolone; n=48). Regimens consisting of cyclophosphamide, prednisone, and rituximab, or dexamethasone, rituximab, and cyclophosphamide, were only used in 27 patients despite being recommended for front-line therapy.[3] Regimens consisting of bendamustine and rituximab, or fludarabine, cyclophosphamide, and rituximab, were each used in 21 patients. Other combination regimens were bortezomib and rituximab (n=17) and various other combinations without rituximab (n=78), including chemotherapy and targeted therapy approaches, without any clear preferences. Altogether, 209 (46%) patients received rituximab in the front-line setting, either as monotherapy (n=28) or in combination with other drugs (n=181).

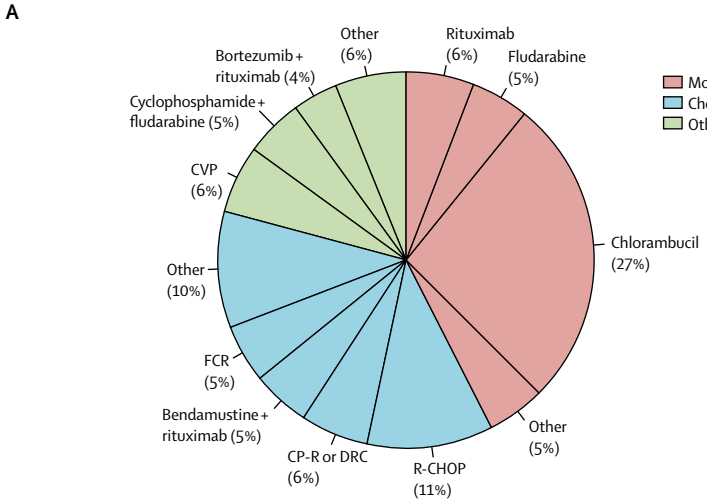
Variations in choice of therapy were observed between countries (appendix p 7). In Austria, Germany, Greece, Italy, and the Netherlands, chemoimmunotherapy was most frequently used, whereas in France and Spain, monotherapy was most frequently used. In Poland, the Czech Republic, and the UK, combination regimens were used more frequently than monotherapy and chemoimmunotherapy.

Community institutions predominantly used monotherapy approaches, whereas academic institutions predominantly used chemoimmunotherapy (figure 1A). Patients who received monotherapy at community institutions were more likely to be treated with chlorambucil (41% [61/148] *vs* 20% [62/306]) and less likely to be treated with rituximab (3% [5/148] *vs* 8% [23/306]) than were those who received monotherapy at academic institutions. Patients aged 65 years or older were more likely to receive monotherapy than were patients younger than 65 years (figure 1A).

In multivariate analyses, we noted an association between institution type and geographical region and whether or not patients received chemoimmunotherapy over monotherapy or other combination therapy (appendix p 8). Serum β-2 microglobulin concentration, percentage of bone marrow infiltrated by lymphoplasmacytic cells, and the presence of IgM-related symptoms (primarily symptomatic hyperviscosity and elevated IgM in serum) were also associated with the selection of chemoimmunotherapy over monotherapy. Geographical region, β-2 microglobulin concentration, percentage of bone marrow infiltration, and IgM-related symptoms were all significant factors in the selection of monotherapy over other combination therapies or chemoimmunotherapy.

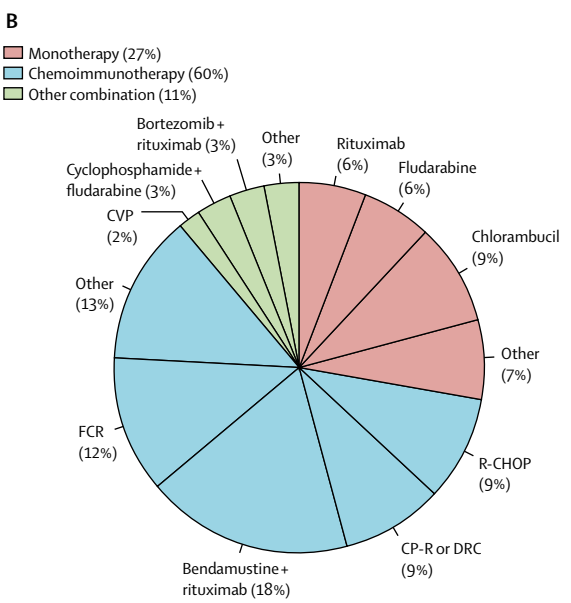
Median follow-up in the entire population was 87 months (IQR 63–123), and median overall survival was not reached (95% CI not reached–not reached). Estimated 5-year overall survival was 87% (83–90) and estimated 10-year overall survival was 69% (62–74) (figure 2). Median overall survival was not reached (not reached–not reached) for patients with either low-risk or intermediate-risk IPSSWM scores and was 120 months (107–not reached) for patients with high-risk IPSSWM scores. In multivariate analyses, only constitutional symptoms (excluding fatigue) and IPSSWM risk level were independent factors significantly associated with decreased overall survival (table 2).

Median progression-free survival for the entire population that received front-line therapy was 29 months (95% CI 25–31), and estimated progression-free survival was 82% (78–85) at 10 months, 63% (58–67) at 20 months, and 46% (41–51) at 30 months; 5-year progression-free survival was 13% (10–16; figure 3). Median progression-free



Front-line use by treatment centre type and age

	Overall (n=454)	Academic institution (n=306)	Community institution (n=148)	Age <65 years (n=223)	Age ≥65 years (n=231)
Monotherapy	193 (43%)	114 (37%)	79 (53%)	79 (35%)	114 (49%)
Chemoimmunotherapy	164 (36%)	135 (44%)	29 (20%)	90 (40%)	74 (32%)
Other combination	95 (21%)	55 (18%)	40 (27%)	52 (23%)	43 (19%)



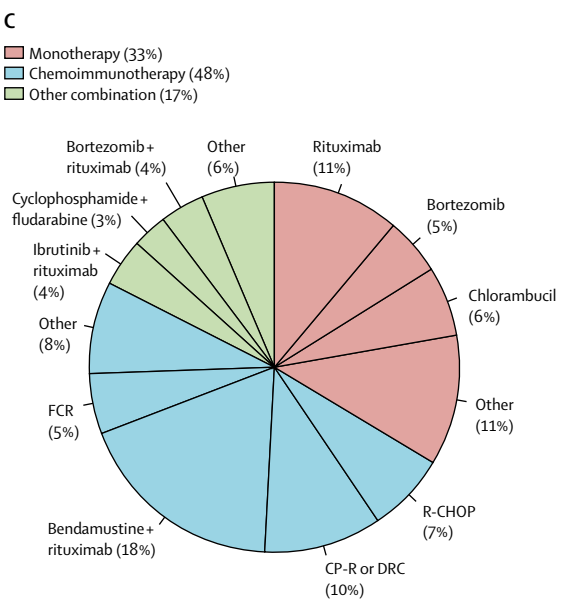


Figure 1: **Treatment choices in patients with Waldenström's macroglobulinaemia**
(A) Front-line setting (n=454). (B) Second-line setting (n=397). (C) Third-line setting (n=160). R-CHOP=rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. CP-R=cyclophosphamide, prednisone, and rituximab. DRC=dexamethasone, rituximab, and cyclophosphamide. FCR=fludarabine, cyclophosphamide, and rituximab. CVP=cyclophosphamide, vincristine, and prednisone. *One patient received steroids and data were missing for one patient.

survival was 37 months (31–45) for patients with low-risk IPSSWM scores, 27 months (22–32) for patients with intermediate-risk IPSSWM scores, and 23 months (18–29) for high-risk IPSSWM scores. Median progression-free survival was similar between patients who received chemoimmunotherapy (31 months [95% CI 27–35]) and those who received combination therapy (29 months [24–36]), but was lower for patients who received

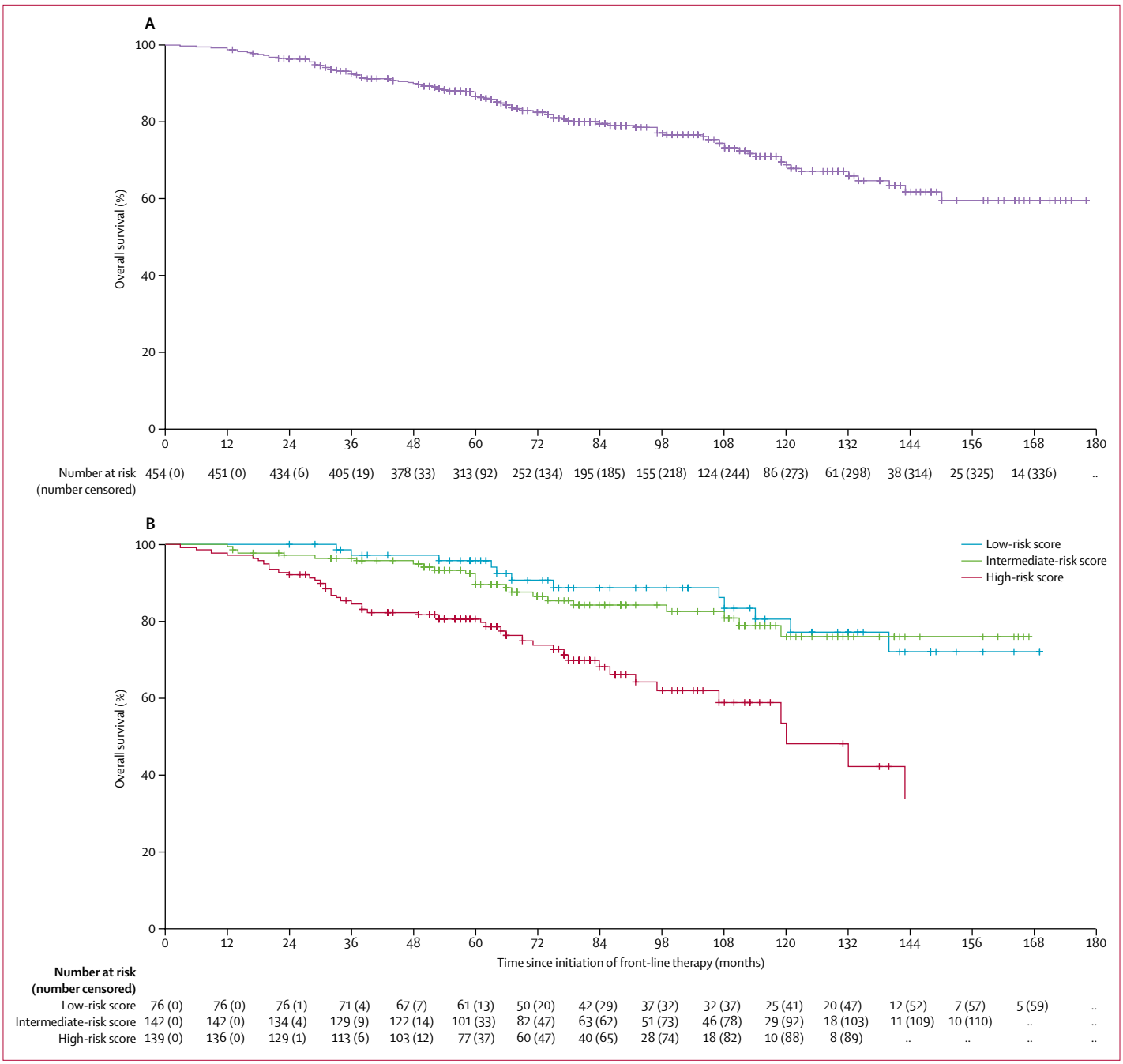


Figure 2: **Kaplan-Meier curves showing overall survival for all patients (A) and by IPSSWM risk score (B) after initiation of front-line therapy**
IPSSWM=International Prognostic Scoring System for Waldenström Macroglobulinemia.

monotherapy (24 months [21–29]). In multivariate analyses, IPSSWM risk score, type of institution, and treatment type were independent variables significantly associated with progression-free survival (table 2). Among these variables, a higher IPSSWM risk score was the only disease-related variable that was significantly associated with shortened progression-free survival; all other factors associated with shortened progression-free survival, including type of institution and type of therapy, were non-disease related. Unlike overall survival, both high versus low and intermediate versus low IPSSWM risk scores were significantly associated with worsened progression-free survival in the multivariate analysis (table 2).

Of the 397 patients who progressed after front-line treatment and initiated second-line therapy, 238 (60%)

received chemoimmunotherapy, 107 (27%) received monotherapy, and 44 (11%) received other combination regimens (data on second-line treatment were missing for seven patients, and one patient received steroids only; figure 1B). Chlorambucil was the most frequently used second-line monotherapy (n=34), followed by rituximab (n=25) and fludarabine (n=22). Regimens based on bendamustine and rituximab were most commonly used for second-line chemoimmunotherapy (n=70), and bortezomib-containing regimens (with or without rituximab or cyclophosphamide) were the most frequently used other combination regimens (n=15).

Of the 160 patients who progressed to third-line treatment, 52 (33%) received monotherapy, 76 (48%) received chemoimmunotherapy, and 27 (17%) received other combination regimens (data on third-line treatment were missing for four patients, and one patient received steroids only; figure 1C). The most frequently used monotherapy in the third-line setting was rituximab (n=18); regimens based on bendamustine and rituximab were the most frequently used chemoimmunotherapy (n=29), and the most frequently used other combination therapy was rituximab with either bortezomib (n=6) or ibrutinib (n=6).

We analysed treatment patterns between front-line and second-line regimens to predict the type of second-line regimen a patient would be most likely to receive in view of the type of front-line therapy used. Patients who received front-line chemoimmunotherapy were most likely to receive the same type of treatment in the second-line setting: 99 (74%) of 133 patients who received front-line chemoimmunotherapy went on to receive second-line chemoimmunotherapy. Patients who initially received other combination regimens were also likely to receive chemoimmunotherapy in the second-line setting (55 [67%] of 82 patients; only eight [10%] patients received a combination other than chemoimmunotherapy in the second-line setting). Although 83 (48%) of 172 patients who received front-line monotherapy went on to receive second-line chemoimmunotherapy, a substantial proportion (69 [40%] patients) continued to receive monotherapy in the second-line setting. Patients who were initially treated with rituximab monotherapy received various second-line regimens, with no clear pattern.

Median follow-up for the 397 patients who received second-line therapy was 32 months (IQR 5–not reached), and median progression-free survival was 23 months (95% CI 20–26). Estimated progression-free survival was 78% (72–82) at 10 months, 54% (48–60) at 20 months, and 37% (31–43) at 30 months (appendix p 9). Median follow-up for the 160 patients who received third-line therapy was 24 months (IQR 4–not reached), and median progression-free survival was 16 months (95% CI 10–18). Estimated progression-free survival was 60% (50–68) at 10 months, 35% (25–44) at 20 months, and 22% (14–31) at 30 months (appendix p 9).

	n	HR (95% CI)	p value
Progression-free survival			
IPSSWM risk	..	..	<0·0001*
Comparison with low risk	76	1·00 (ref)	..
Intermediate	142	1·61 (1·21–2·14)	0·0010
High	139	1·89 (1·42–2·52)	<0·0001
Missing	97	1·31 (0·96–1·78)	0·084
Comparison with intermediate risk	142	1·00 (ref)	..
High	139	1·18 (0·93–1·49)	0·18
Type of institution			
Academic	306	1·00 (ref)	..
Community	148	0·67 (0·54–0·82)	0·00010
Treatment type	..	..	0·0080*
Comparison with chemoimmunotherapy	164	1·00 (ref)	..
Combination therapy	95	0·99 (0·76–1·29)	0·95
Monotherapy	193	1·34 (1·08–1·67)	0·0070
Missing	2	3·44 (0·84–14·00)	0·085
Comparison with combination therapy	95	1·00 (ref)	..
Monotherapy	193	1·36 (1·06–1·74)	0·017
Overall survival			
Constitutional symptoms (excluding fatigue)			
No	310	1·00 (ref)	..
Yes	144	2·25 (1·52–3·35)	<0·0001
IPSSWM risk	..	..	0·00020*
Comparison with low risk	76	1·00 (ref)	..
Intermediate	142	1·03 (0·51–2·10)	0·93
High	139	2·89 (1·51–5·54)	0·0010
Missing	97	1·75 (0·88–3·49)	0·11
Comparison with intermediate risk	142	1·00 (ref)	..
High	139	2·80 (1·67–4·69)	<0·0001

IPSSWM=International Prognostic Scoring System for Waldenström's Macroglobulinemia. *Overall p value.

Table 2: **Multivariate analysis of progression-free and overall survival for 454 patients who received front-line treatment**

To understand the occurrence of other cancers in patients with Waldenström's macroglobulinaemia, we collected data on the presence of cancers before and after diagnosis of Waldenström's macroglobulinaemia (appendix p 10). 31 (7%) of 454 patients had other cancers before diagnosis. The majority of these were skin cancers (n=13) and solid tumours (n=15). After diagnosis of Waldenström's macroglobulinaemia, 56 (12%) of 454 patients had new cancers, including solid tumours (n=26), skin cancers (n=12), and transformation to non-Hodgkin lymphoma (n=15). Most patients who developed a second primary cancer had a median latency of 4 years (IQR 3–6). Although we did not observe an association between choice of treatment and incidence of secondary cancer, our dataset did not allow this association to be rigorously investigated because the data were confounded with multiple combinations and regimen sequences.

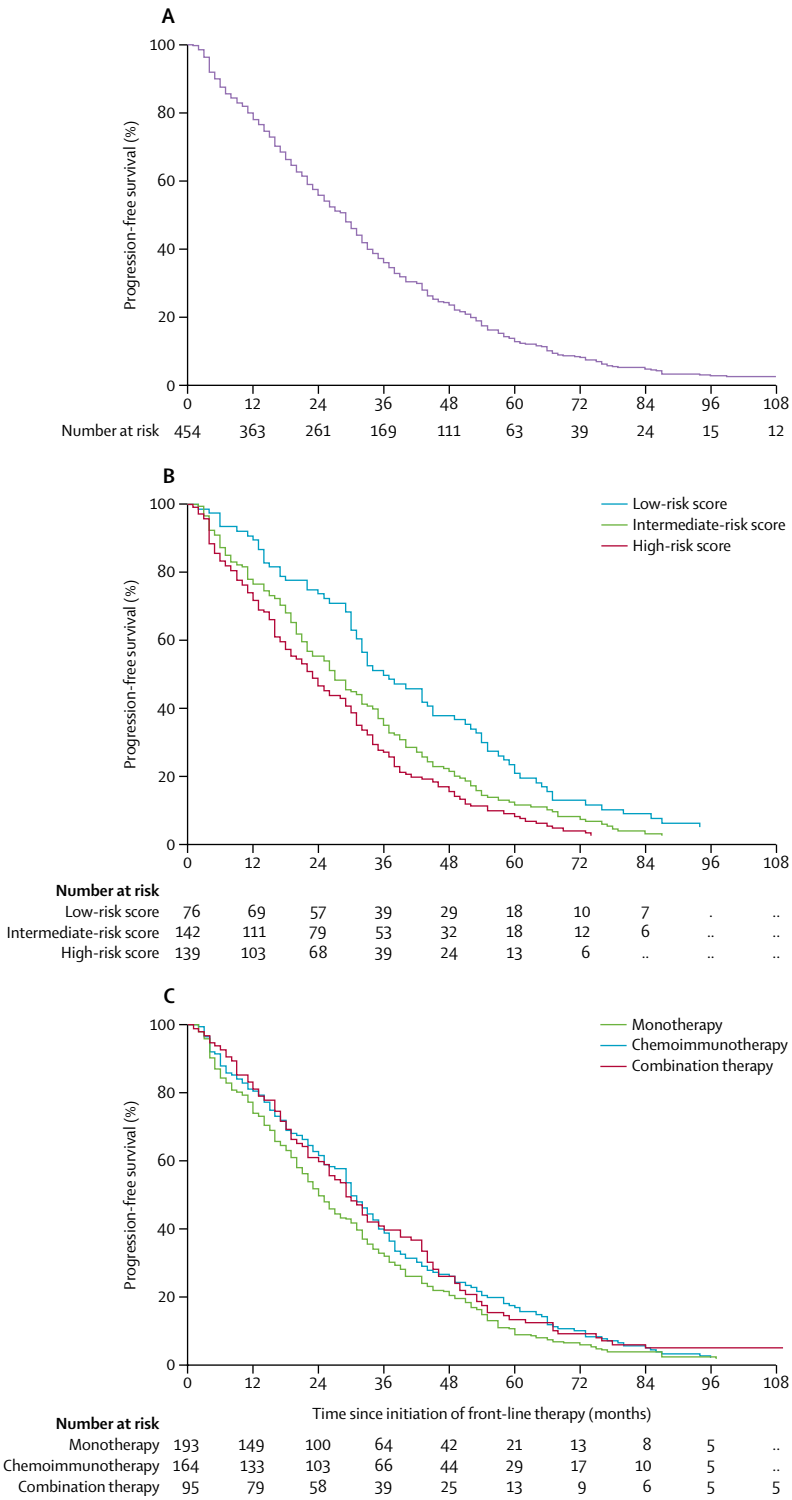


Figure 3: **Kaplan-Meier curves showing progression-free survival for all patients (A) and by IPSSWM risk score (B) and regimen type (C)**

Given that all events are shown, the number censored for each timepoint is zero. IPSSWM=International Prognostic Scoring System for Waldenström Macroglobulinemia.

Discussion

In this study, we describe the treatment of Waldenström's macroglobulinaemia in Europe over a 14-year period (2000–14). We showed that anaemia and constitutional symptoms were the most frequent reasons for initiating therapy, and that monotherapy was most commonly used in the front-line setting, with fewer patients receiving chemoimmunotherapy or other combination regimens. With a median follow-up of 87 months (IQR 63–123) for patients in the front-line setting, median overall survival was not reached (95% CI not reached–not reached) and median progression-free survival was 29 months (25–31). High-risk IPSSWM was associated with significantly shortened progression-free and overall survival in multivariate analyses. Additionally, shortened progression-free survival was associated with treatment at an academic institution and use of monotherapy, and worsened overall survival was associated with constitutional symptoms excluding fatigue. These findings are particularly relevant in lymphoma subtypes such as Waldenström's macroglobulinaemia, for which large prospective registry data are missing and prospective phase 3 clinical trials are uncommon. Given that Waldenström's macroglobulinaemia is rare, patients are often referred to large academic institutions; however, more than a third (38%) of the institutions included in our study were community hospitals, underlining the importance of real-world data because, in practice, Waldenström's macroglobulinaemia is managed in both academic and community hospitals.

Our data show that the treatment landscape in Waldenström's macroglobulinaemia is heterogeneous. Despite US and European guidelines recommending front-line chemoimmunotherapy for these patients[1,25] (particularly a regimen consisting of dexamethasone, rituximab, and cyclophosphamide), this strategy was not widely used in our study, and was especially uncommon in community-based practice. Monotherapy is still widely used as front-line treatment; more than a third of patients in our study were treated with monotherapy, mostly chlorambucil. Front-line chlorambucil monotherapy is recommended for older or non-fit patients,[26,27] but less than 20% of the population in our study was aged 75 years or older. The proportion of patients receiving chlorambucil monotherapy did not change substantially between the front-line and second-line settings, indicating that this treatment is generally considered adequate by physicians for treatment of many patients with Waldenström's macroglobulinaemia despite the introduction of highly efficient and well tolerated rituximab-containing combination regimens. We did not observe a clear advantage for chemoimmunotherapy over other, chemotherapy-only combination regimens (p=0·95), suggesting that less intensive therapies might be effective in real-life settings, although this hypothesis needs to be investigated. These results are inconsistent

with those from well controlled clinical trials[28,29] that showed superiority for chemoimmunotherapy over chemotherapy alone for the treatment of Waldenström's macroglobulinaemia. These differences might be, in part, due to the retrospective design of our study, in that there were no stringent inclusion criteria in our study to limit inclusion of patients with advanced disease or age, the exclusion of whom could lead to superior outcomes in clinical trials.

One reason for the choice of monotherapy instead of chemoimmunotherapy might be the concern that combination regimens can be too toxic for elderly patients, who often present with comorbidities.[26] This assumption is supported by our observation of increased use of monotherapy in older patients relative to younger patients. Other reasons for treatment selection might be accessibility of drugs, financial constraints, or the convenience of oral medications (eg, chlorambucil) versus the need for inpatient administration—which might also necessitate long transportation times to a treatment centre. However, these reasons only go part way to explaining the large heterogeneity in treatments because countries that have broad access to therapies, such as France and Germany, showed different treatment patterns in this study. Of note, estimates for the use of rituximab monotherapy were smaller than were estimates from the USA (50–60% in previous studies[30,31]) despite data from independent groups showing that rituximab monotherapy has substantial anti-lymphoma activity with few toxic effects.[32–35] Although monotherapy was the most widely used treatment, our chart review also showed that combination regimens without rituximab were still widely used, reflecting the slow dissemination and uptake of consensus publications and guidelines in clinical practice. Treatment was rarely adapted to the primary symptom that triggered start of treatment, although the presence of IgM-related symptoms was associated with use of monotherapy.

In this study, median progression-free survival with front-line chemoimmunotherapy was considerably shorter than that observed in clinical trials of rituximab-containing combinations for Waldenström's macroglobulinaemia. For example, in clinical trials of R-CHOP (n=34) and bendamustine plus rituximab (n=22), the median time to treatment failure was 63 months and the median progression-free survival was 70 months.[28,29] However, in our study, R-CHOP (n=50) and bendamustine plus rituximab (n=23) were the most frequently used chemoimmunotherapy regimens in the front-line setting, and median progression-free survival with any chemoimmunotherapy regimen was about 31 months. These findings highlight the difference between results obtained with selected patients in controlled prospective trials versus non-selected patients outside of clinical trials, and suggest that patient outcomes might be poorer outside the setting of clinical trials. Additionally, in our study, the type of treating institution was associated with progression-free survival in the front-line setting, with improved progression-free survival for patients treated in community-based settings versus those treated in academic institutions. However, this observation is difficult to interpret and might have been affected by numerous confounding factors.

Although we did not identify any significant differences in progression-free survival at the country level in multivariate analyses, we did observe an empirical difference in progression-free survival between the UK and Germany. One possible explanation for this observation is that a greater proportion of patients in Germany received chemoimmunotherapy than did those in the UK. It should also be noted that the country variable was a significant factor in all pairwise comparisons of treatment choice in the multivariate analysis, and the type of therapy was significantly associated with progression-free survival. These findings might suggest that, although we observed differences in the predominant type of therapy used across countries, our analysis might not have been sufficiently powered to detect these differences in progression-free survival.

The progression-free survival we report here reflects data from clinical practice, including a mix of therapies in non-selected and elderly patients who might have been ineligible for dose-intensive treatments. The same holds true for our analyses of overall survival. Patients with Waldenström's macroglobulinaemia typically live for a long time after diagnosis, with 5-year overall survival in this study of 87% (95% CI 83–90) after front-line treatment. However, Waldenström's macroglobulinaemia is a biologically heterogeneous disease, as reflected by the significant prognostic differences in progression-free survival and overall survival across IPSSWM risk groups shown in our study, although we were unable to confirm a separation of overall survival between low-risk and intermediate-risk patients. The scoring system and many of the guidelines for treatment of Waldenström's macroglobulinaemia were established before targeted therapy became available—and before the widespread use of newer drugs, such as Bruton's tyrosine kinase inhibitors, proteasome inhibitors, immunomodulatory drugs, *BCL2* inhibitors, and monoclonal antibodies—and therefore might need to be reassessed. Furthermore, patients with wild-type *MYD88* have been shown to have poor overall survival compared with patients with mutated *MYD88*,[36] so *MYD88* and *CXCR4* mutational status might need to be considered in future scoring systems and treatment guidelines.

Our study provides information about the clinical presentation of Waldenström's macroglobulinaemia at treatment initiation, reasons for starting treatment, choices of treatment regimens, and how these treatments translated into progression-free and overall survival for patients in different countries across Europe. Although limited by its retrospective design, this chart review extends previously reported data from population-based

analyses,[18–21] which often have limited access to information about treatment choices and efficacy data and focus on a narrower patient population. In the absence of a prospective registry of patients with Waldenström's macroglobulinaemia, such surveys are essential to understanding how this disease is treated in practice and with what results, and what needs to be improved in particular regions or countries. Furthermore, surveys might help define treatment standards that are feasible and applicable to most countries. Ibrutinib—the first and only treatment approved by the US Food and Drug Administration and the European Medicines Agency for use in Waldenström's macroglobulinaemia—heralds a major change in treatment options for patients with this disorder. Future chart reviews would allow investigation of how novel drugs or drug combinations might affect existing treatment patterns, and could provide evidence of the effectiveness of new therapies for Waldenström's macroglobulinaemia in clinical practice.

Contributors

TG, EB, CB, MAD, and EK were responsible for study design. TG, EB, CB, and MC contributed to data analysis and interpretation. CB, SS, EK, AT, RG-S, LB, XL, WW, RH, MCM, and MAD retrospectively reviewed patient records and contributed to data collection. MC confirmed data accuracy and compiled data for summation and analysis. CB, EB, and TG contributed to the first draft of the manuscript and final manuscript writing. All authors carefully reviewed the manuscript and approved the final version.

Declaration of interests

EK reports personal fees from Janssen, Takeda, Genesis Pharma, Prothena, and Amgen. AT reports personal fees from Janssen, AbbVie, Gilead, and Roche. RG-S reports honoraria as a speaker from Janssen, Takeda, and Amgen, as well as a direct grant for research support from Hospira, now belonging to Pfizer. WW reports grants and personal fees from Janssen, Celgene, Amgen, Novartis, Takeda, and Gilead, as well as personal fees from Roche. RH received grants, personal fees, and non-financial support from Amgen, Takeda, Janssen, Celgene, Novartis, and Bristol-Myers Squibb. EB reports other from Pharmacyclics LLC, an AbbVie company. MC reports other from Pharmacyclics LLC and Johnson & Johnson, stock ownership with AbbVie and Johnson & Johnson, and employment with Pharmacyclics LLC. TG reports personal fees from and employment with Pharmacyclics LLC, an AbbVie company. MAD reports personal fees from Amgen, Takeda, Janssen, and Celgene. MCM, CB, SS, LB, and XL declare no competing interests.

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