The Rory Morrison Registry

Second UK Waldenström's Macroglobulinaemia Registry Report

2021

WMUK

The UK charity for **Waldenstrom's macroglobulinaemia**

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Executive summary

Background

- Waldenström's macroglobulinaemia (WM) is a rare form of lymphoma. In the UK, WM is diagnosed in about 400 people each year, and about 4,000 people are currently living with the condition.
- In the past, WM was treated with a variety of chemotherapy regimens. However, recently there have been new regimens developed for the condition, and novel therapies such as Bruton's Tyrosine Kinase (BTK) inhibitors like ibrutinib.
- To understand the impact of these new treatments, as well as the broader picture of what life with WM is like for patients in the UK, the charity Waldenström's Macroglobulinaemia UK (WMUK) set up a patient registry to collect real world data.
- This registry was named the Rory Morrison Registry, after the beloved BBC presenter and WM patient.
- The Rory Morrison Registry published its first report in 2018, six months after the Registry was rolled-out nationally.
- This Second Report from the Registry provides updated data and further insights on diagnosis, treatment and outlook for people living with WM.

Patients in the Registry

- The Rory Morrison Registry is one of the largest of its kind in the world. On the data cut-off date of 1st September 2020, the Registry held data from 926 patients, including 802 with confirmed WM, and the remainder with other IgM-related conditions.
- Data for over half of the patients in the Registry have been submitted by just one hospital, University College Hospital in London. Seven other hospitals account for another third of patients in the Registry.
- Patients should be aware that the data in the report might not always reflect their experience. WM is a very variable disease, and it is always difficult to extrapolate findings from a whole group of people to one individual person.
- In addition, the data in the report may be biased towards patients seen at larger specialist centres in urban areas, and the treatment practices of these hospitals.

Diagnosis

- WM has been historically seen as a 'disease of old white men', but the data in the Registry challenges this view. A third of patients are diagnosed under the age of 60, and almost 40% are women. 10% of patients are from a non-White or mixed-race background, but some ethnic groups are underrepresented in the Registry compared to the wider population.
- Among the patients in the Registry, there is a roughly equal split between patients who were diagnosed with symptoms and without symptoms.
- According to the 2009 international prognostic scoring system for Waldenström's macroglobulinaemia (IPSSWM[1]) , 34% of the WM patients in the Registry are in the low-risk category, 28% are in the intermediate category, and 38% are in the high-risk category. However, the IPSSWM score is based upon measurements at diagnosis, not at first treatment. This reduces their utility, as scores are likely to change over time. The Registry plans to use the 2019 revised IPSSWM[2] going forward.

Watch and wait

- WM patients can remain on active surveillance (commonly known as 'watch and wait') for many years after their initial diagnosis. Some patients in the Registry have been on 'watch and wait' for 10 years or more, including some patients diagnosed with symptoms.
- Given the lack of evidence that treating someone as soon as they are diagnosed extends their lifespan or improves quality of life, 'watch and wait' is the preferred option for patients diagnosed without symptoms. This ensures that treatment and its associated side-effects are delayed until absolutely necessary.

First-line treatment

- As expected, symptomatic patients start their first treatment sooner than those who do not have symptoms at diagnosis. By five years after diagnosis, 97.3% of patients diagnosed with symptoms have received their first treatment, compared to 83.6% of patients who were asymptomatic at the time of diagnosis.
- The decision to start treatment should be made by experienced clinicians in collaboration with patients, as every patient's situation and perspective is unique.
- Hyperviscosity and fatigue are by far the most common symptoms recorded as indications for first-line therapy in WM patients in the Registry.
- The data indicates that there is no standard first-line treatment for WM patients in the Registry, though dexamethasone- rituximab- cyclophosphamide (DRC) and bendamustine-based therapies are popular options.
- In recent years, a greater consensus is emerging on how WM should be managed. This can be seen in the treatment received by WM patients in the Registry: in the last five years treatment has become more streamlined, with a narrower range of treatments being used.
- Most WM patients respond well to their first-line treatment, with 70% of patients having a partial response or better (more than 50% reduction in IgM levels). This illustrates how WM is often a predictable and 'obedient' disease which responds well to treatment.

Second-line and subsequent therapies

- Half of WM patients in the Registry who have started their second-line therapy began this treatment within one year of completing their first-line therapy.
- Ibrutinib has become the leading second-line therapy choice for patients in the Registry, since it became available to WM patients on the NHS through the Cancer Drugs Fund in 2017. For most patients, their disease responds well to ibrutinib, and they can continue to take the drug for years.
- Looking at all second-line treatments, for most WM patients their disease responds well to therapy, with almost 70% of patients in the Registry having a partial response or better.
- As WM is often a slow-growing disease which responds well to treatment, patients may receive multiple lines of therapy over time – with some patients in the Registry receiving five or more different treatments.

Outlook for people with WM

- Survival rates for WM patients in the Registry are good compared to other lymphomas.[3]
- Recent studies suggest median survival rates close to 14-16 years after diagnosis,[4] and the data from the Registry is in line with this.
- Most patients who have submitted data to the Registry report a good quality of life, but for some, WM is having a significant effect on their lives. For example, a significant proportion of patients report symptoms of anxiety and depression and poor overall health.
- The management of WM needs to be optimised for individual patients, to strike the right balance between controlling the disease effectively and maintaining a good quality of life.

Conclusions

- We hope the Second Registry Report provides healthcare professionals with insights to improve the care of people living with WM, to continue building on the significant improvements in patient care over recent years.
- We hope too that commercial partners will find this report helpful as they seek to gain approval for their therapies within the NHS. We also hope that it will help to ensure commissioning bodies such as NICE are better equipped in their decision-making processes as they appraise promising new therapies.
- Patients can help improve the Registry by checking with their doctor whether their hospital is signed up to submit clinical data, and by completing Quality of Life questionnaires if asked. Patients can email registry@wmuk.org.uk to sign up to receive Quality of Life questionnaires.
- We would like to thank all patients and clinicians who submitted data to the Registry for their valuable contribution.

Foreword

Prof. Dr. Christian Buske

Despite the fact that Waldenström's macroglobulinaemia is a rare lymphoma subtype, tremendous progress has been made in understanding the biology and the genetics which affect treatment outcome in recent years. Also based on this, we have seen substantial progress in treatment, with the emergence of chemotherapy-free approaches such as the BTK inhibitors and new exciting therapies at the horizon such as BCL-2 inhibition or use of CAR-T cells. Thus, we can proudly say that Waldenström's macroglobulinaemia has developed as a pacemaker for new developments in indolent lymphoma.

However, we have to state that there is still no standard treatment for this disease, and treatment ranges from watch & wait to intense chemotherapy. Why is this? Because our patients are so heterogenous, the disease itself is heterogenous, and we know well that our treatment approaches have to fit into the social environment of the individual patient.

Surprisingly, and despite all the well-controlled clinical trials in Waldenström's macroglobulinaemia, there is a major lack of real-world data on how patients with Waldenström's macroglobulinaemia are diagnosed, treated, and actually benefit from therapies. But we urgently need these data, as this information is of utmost importance for optimising clinical management of WM patients outside the often "artificial" world of controlled clinical studies.

Registries are vital for collecting real-world data. However, we face the situation that there are hardly any well-organised registries for Waldenström's macroglobulinaemia worldwide. This is why we indeed must applaud all the colleagues who worked hard to initiate the Rory Morrison Registry, which is a wonderful example of how fast such a registry is able to collect data of excellent quality. So far, the registry has succeeded to include over 1,000 patients, which qualifies the Rory Morrison Registry as one of the largest of its kind worldwide. It is unique within the European Consortium for Waldenström's Macroglobulinemia (ECWM), the largest existing consortium for this lymphoma subtype. Surely, it will help us to understand the treatment landscape for Waldenström's macroglobulinaemia based on prospectively collected data. Importantly, the Registry also provides patient reported outcome surveys and with this includes the perspective of the patients themselves. This is a major asset of this registry, because the patient counts at the end!

It only remains to say congratulations! A great achievement and a big step forward in optimising our clinical care for Waldenström's macroglobulinaemia.

Prof. Dr. Christian Buske

Coordinator, European Consortium for Waldenström's Macroglobulinemia (ECWM)
President, German Lymphoma Alliance (GLA)
Medical Director, Comprehensive Cancer Center Ulm
University Hospital Ulm

Introduction

Dr. Shirley D'sa

Waldenström's macroglobulinaemia (WM) is a rare and unique form of B cell non-Hodgkin's lymphoma (NHL) characterised by an accumulation of malignant B cells and plasma cells that together form lymphoplasmacytic lymphoma (LPL).

A hallmark of WM is the production and secretion of an IgM monoclonal protein* by the plasma cell fraction of the LPL cells. The presence of the IgM sets this disease aside from most forms of B cell NHL in terms of biological behaviour and assessing response to treatment. Excess IgM can lead to a range of symptoms due to the physical, chemical or immunological properties of the protein, such as targeting 'self' tissues and organs, high blood viscosity, bleeding problems and a range of immune derangements.

WM can present with a vast array of symptoms, including lymphoma-related problems due to the 'occupation' of tissues, resulting in low blood counts, immune deficiency and enlargement of the lymph nodes or soft tissues. However, many patients are asymptomatic when diagnosed, and do not require treatment for many years.

For most people their disease responds well to initial treatment. However, despite a range of advancements in the science underpinning the disease and the advent of new therapies, there is still much to learn about the best way to manage WM. The optimal selection and sequencing of therapies and management of adverse effects requires improvement, so that we do not slash and burn our way through available treatments and induce cumulative immunosuppression. Many promising new therapies are beyond the scope of provision within the UK's National Health Service (NHS) due to cost. Not being able to deliver effective new therapies is an impediment to better clinical outcomes and a huge frustration for all concerned.

Commissioning bodies such as the UK's National Institute of Health and Care Excellence (NICE) consider randomised controlled trials (RCTs) to be the source of the highest quality evidence on a treatment's effectiveness compared to other options. However, it is not always possible to perform RCTs for a variety of practical or ethical reasons, especially in rare diseases. In some settings, RCTs do not provide estimates of treatment outcomes of particular interest to NICE, that are generalisable, or available within appropriate time scales for technology appraisals.[5]

As a result, Real-World Data (RWD) are increasingly used to supplement other types of information across NICE programmes. RWD is a term used to describe data generated from sources that relate to everyday clinical practice, such as patient-generated data (including validated questionnaires), observational data from registries and electronic health record systems (EHRS). Although the NHS is a mine of clinical information, it is not uniformly or systematically collected in a way that advances clinical practice in rare diseases.

In order to capture RWD from WM patients in the UK, including diverse complications, disease characteristics, prescribing habits and clinical outcomes, the web-based Rory Morrison Registry (RMR)

* A few cases occur with a different protein (IgG) or no protein but it is still the same disease in terms of the underlying cells involved (LPL). The treatment and expected outcome of non-IgM LPL is the same, except for their frequent exclusion from clinical trials. For the remainder of this report, we will refer to the protein as IgM for simplicity.

was developed using generous funds donated to the Waldenström's macroglobulinaemia UK (WMUK) registered charity.

A consortium of clinicians and patients developed a comprehensive list of important data items, secured ethical approval and established a dedicated Review Committee to ensure high quality data entry and compliance with data protection laws. The data fields have evolved over time to take account of novel treatments. They have also been refined as more cases have been added, totalling almost 1,000 registrants at the time of writing.

To capture all-comers across the United Kingdom, including less internet-aware / engaged patients, approval was obtained from the NHS's Health Research Authority's Confidentiality Advisory Group and Research Ethics Committee to enter anonymised data without patient consent. The approval was future-proofed for the introduction of the EU's General Data Protection Regulation (GDPR) in May 2018 which was codified into UK law through the UK Data Protection Act 2018 (DPA) and includes a robust opt-out mechanism, Fair Processing and Privacy Notices. Following the departure of the UK from the EU, any new regulations will be appropriately addressed.

We now present the Second Registry Report with a focus on the data itself and its significance, without ignoring potential limitations, such as representativeness of the UK WM population, correcting systematic errors (bias) and improving data completion rates. Knowing that clinical data is one of the most valuable resources in the UK's NHS, we are determined to capture meaningful and powerful data in a comprehensive and longitudinal way. This project is set to run for a total of 15 years and will no doubt prove to be a highly valuable resource.

We are immensely grateful to the patients and families whose donations have made this Registry possible, and to colleagues in the WMUK RMR centres for their valuable contributions. We also acknowledge our commercial partners who have provided much needed grants to make it possible to operate the Registry through funding of personnel and running costs.

Dr Shirley D'Sa

Chief Investigator & Data Guardian, Rory Morrison Registry

Acknowledgements

We would like to thank the patients and clinical staff who participate in and submit data to the Registry. Your valuable contribution will help improve the lives of people living with WM around the world.

Waldenström's Macroglobulinaemia UK (WMUK) is a unique charitable alliance of doctors, patients and carers fighting WM. The Registry is dedicated to the memory of founder member Rory Morrison, the much-loved BBC Radio 4 broadcaster who died in 2013.

On behalf of us all at WMUK, our very special thanks go to Rory's wife, Nikki, family and friends who have continued to support the RMR over the years, including a heroic fundraising cycle ride in 2020 from John O'Groats to Land's End.

Contributors

This Second Registry Report has been compiled through a collaboration between people living with WM and expert clinicians. They have also provided their opinions and perspectives throughout the report:

Dr Harriet Scorer

Harriet was diagnosed with WM over 20 years ago. She is a qualified doctor and runs her own healthcare consultancy business. She is a patient trustee of WMUK and is part of the governance committee for the Rory Morrison Registry.

John Mordue

John was diagnosed with WM two years ago. He retired from paid employment several years ago, where he worked on large data collection projects within Adult Care Services/NHS and took a lead role in producing a number of key strategic reports. John is particularly interested in developing a better understanding of WM and using RMR data to inform best practice care, and the contribution that lifestyle factors may make to achieving better physical and mental health despite WM.

Dr Shirley D'Sa

Dr D'Sa is a founder trustee of WMUK. She is a Consultant Haematologist with a special interest in Waldenström's macroglobulinaemia and runs the largest WM clinic in the UK at University College London Hospitals (UCLH), a leading centre for WM trials in the UK. She leads WMUK's Biobank and Rory Morrison Registry projects that collect and store clinical data about WM.

Dr Dima El-Sharkawi

Dr El-Sharkawi is a Consultant Haematologist at the Royal Marsden Hospital, London, with a specialist interest in Waldenström's macroglobulinaemia. She is a trustee of WMUK and is part of the governance committee for the Rory Morrison Registry. She is an investigator on a number of clinical trials.


Dr Harriet Scorer


Dr Shirley D'Sa


Dr Dima El-Sharkawi

About Waldenström's macroglobulinaemia

What is Waldenström's macroglobulinaemia?

Waldenström's macroglobulinaemia (WM) is a rare form of lymphoma, in the family of cancers known as non-Hodgkin's lymphoma. WM is defined by lymphoplasmacytic lymphoma growing in the bone marrow, and excess protein in the blood known as monoclonal IgM.

B cells help to fight infections as part of the immune system. Some B cells do this by developing into plasma cells, whose role it is to produce antibodies. Antibodies are proteins which identify and stick to foreign objects such as bacteria, viruses, or other pathogens. There are five types of antibodies (also known as 'immunoglobulins' or Ig for short) and one of them is called IgM.

Lymphoplasmacytic lymphoma (LPL) is a cancer where cells that include both B cells and plasma cells grow out of control. These LPL cells can produce excessive amounts of identical antibodies, which are known as M (for monoclonal)-proteins or paraproteins. These antibodies are not useful to the immune system; indeed they may have harmful consequences for the body. The presence of LPL cells together with an IgM paraprotein results in the condition known as Waldenström's macroglobulinaemia.

In the UK, around 400 people are diagnosed with WM each year, and it is estimated that a total of about 4,000 people are currently living with WM. It is traditionally viewed as a disease which affects people over the age of 65, though it is seen in younger age groups too.

Diagnosis and symptoms

WM is diagnosed by blood tests looking for abnormal IgM in the blood, and a bone marrow biopsy to look for LPL cells in the bone marrow. The condition may be spotted by chance when having blood tests for other reasons.

WM often develops over a long period of time; some people have no symptoms at all when they are first diagnosed. The symptoms that do develop are related to the two defining aspects of the disease – infiltration of LPL cells into the bone marrow and other tissues, and the presence of IgM protein in the blood.

Lymphoma-related features occur because the LPL cells 'crowd-out' the normal blood stem cells in the bone marrow, preventing them from producing the normal range of blood cells that the body needs. The symptoms may include tiredness, weakness, breathlessness, recurrent infections, bruising or bleeding easily, swollen glands, fevers, night sweats, and unexplained weight loss.

Excessive amounts of IgM can cause a range of problems across the body. It can cause the blood to thicken (hyperviscosity), leading to problems with vision, shortness of breath, nosebleeds, bleeding gums, and dizziness. IgM paraproteins can also damage the nerves, particularly in the extremities of the body, causing tingling or numbness in the hands and feet (peripheral neuropathy). IgM can also cause red blood cells to stick together in the coolest parts of the body such as the tips of the hands, feet, ears and

nose, which can lead to cold-agglutinin disease. If it has so-called 'cryoglobulin' activity, the IgM itself can clump together in cool conditions and cause blockage of the circulation in small blood vessels.

Rare complications of WM include amyloidosis, Schnitzler's syndrome, and Bing-Neel syndrome. Amyloidosis is when the build-up of abnormal proteins causes problems with the kidneys and heart, first causing symptoms such as tiredness, swelling of the legs, and weight loss. Left untreated, amyloidosis can be fatal. Schnitzler's syndrome mostly appears as chronic hives on the skin, as well as fever and bone and joint pain. Bing-Neel syndrome occurs when LPL cells enter components of the central nervous system (the brain, spinal cord and spinal fluid). This may result in a wide variety of neurological symptoms, including problems with sensation and strength, seizures, reduced concentration, poor memory, and loss of hearing or sight. Such symptoms can develop slowly over many weeks and months, or more quickly.

Treatment and outlook

When first diagnosed, people with WM are often not immediately started on treatment, but instead are offered regular check-ups known as 'active surveillance' or 'watch and wait'. The decision to eventually start treatment is often made in response to increasing symptoms or worsening blood test results.

Common first treatments for people with WM include rituximab in combination with chemotherapy, for example dexamethasone-rituximab-cyclophosphamide, bendamustine-rituximab, or rituximab on its own, given in cycles over four to six months. Once the disease comes back after treatment (relapse), the same treatments can be used again, or combinations including rituximab or bortezomib (a proteasome inhibitor), or ibrutinib may be suitable. Other treatment options include further chemotherapy and stem cell transplants, or new therapies via clinical trials.

Ibrutinib (either on its own or in combination with chemotherapy) continues to be explored as a potential option for treating WM. Ibrutinib is currently available through the Cancer Drugs Fund, and is due to be re-assessed by NICE in 2021 for use in the NHS for the treatment of relapsed WM.

A NICE appraisal of zanubrutinib, a next-generation BTK inhibitor, is also underway to assess the clinical and cost effectiveness of this agent for treating WM, with an expected publication date of September 2021.

WM is generally a slow-growing disease, and although it is not currently curable, it is a condition that people can live with for many years. In some rare cases it can progress into a more aggressive form of lymphoma, known as diffuse large B-cell lymphoma. This more aggressive disease can nevertheless be treated effectively in many cases.

As WM is a long-term condition, quality of life is especially important for patients. The treatments used (and the decision to treat at all) is often a balance between keeping the disease and its symptoms under control versus avoiding side-effects to maintain a good quality of life.

More information for patients about the condition is available from the WMUK website at https://www.wmuk.org.uk/about-wm/what-is-waldenstroms-macroglobulinaemia-wm [6]

Diagnosis

WMUK

The UK charity for **Waldenstrom's macroglobulinaemia**

Patients in the Registry

On the data cut-off date of 1st September 2020, there were 926 patients recorded in the Registry, making it one of the largest WM registries in the world. The number of hospitals submitting data to the Registry has increased since the 1st Registry Report was published in 2018, with most of the data submitted by just eight hospitals.

The data in the Registry is submitted by participating hospitals across the UK. Table 1 below shows the numbers of patients in the Registry on the data cut-off date of 1st September 2020, and at which hospital they are being treated. Note this does not include patients who have only returned quality of life questionnaires (see page 58).

Table 1: Patients registered per hospital

Hospital	Patients registered
Churchill Hospital, Oxford	30
Dewsbury & District Hospital, West Yorkshire	1
Epsom General Hospital, Surrey	1
Hammersmith Hospital, London	2
Kent and Canterbury Hospital	9
King's College Hospital, London	30
Manchester Royal Infirmary	2
Mount Vernon Hospital, Northwood, Middlesex	1
National Hospital for Neurology and Neurosurgery, London	34
Nevill Hall Hospital, Wales	9
Northwick Park Hospital	33
Queen Elizabeth Hospital, Birmingham	31
Royal Bournemouth General Hospital	106
Royal Marsden Hospital, London	77
Royal United Hospital, Bath	2
Southmead Hospital, Bristol	1
St James's University Hospital, Leeds	19
Stoke Mandeville Hospital, Aylesbury	4
The Christie Hospital, Manchester	11
Torbay Hospital, Torquay	14
University College Hospital, London	507
University Hospital of Wales, Cardiff	1
University Hospitals Plymouth NHS Trust	1
All hospitals	**926**

More than half of the patients (507 of 926) are being treated at University College Hospital London. Seven other hospitals account for more than a third (341) of patients in the Registry: Churchill Hospital in Oxford, Queen Elizabeth Hospital in Birmingham, Royal Bournemouth General Hospital, and the rest in London: King's College Hospital, National Hospital for Neurology and Neurosurgery, Northwick Park Hospital, and the Royal Marsden Hospital. Higher data entry is associated with the existence of specialist WM Clinics.

Nine hospitals have only registered one or two patients into the Registry. One reason for this might be because they have only recently started contributing data. For example, patients from Dewsbury & District Hospital, Epsom General Hospital, Southmead Hospital Bristol, University Hospital of Wales in Cardiff, and University Hospitals Plymouth NHS Trust are included for the first time since the first Registry report was published in 2018.

Patients in the Registry are attributed to one hospital, but they may have been treated at more than one centre. For example, they could have been diagnosed in their local hospital and referred for treatment or a 'second opinion' at a more specialist centre elsewhere. This could introduce bias into the data, as patients with more severe cases of WM could be more likely to be referred to specialist centres for treatment. Mechanisms are in place to avoid double-counting patients.

This is by no means an exhaustive list of every hospital treating WM patients in the UK; in fact, virtually all hospitals will have at least a handful of WM patients under their care.

In general, there is interest and enthusiasm from hospitals for submitting data to the Registry but the capacity to do so is a limiting factor at many sites. As well as the time and resource needed to begin participating in the project (regulatory procedures, data sharing agreements, personnel to oversee the process), submitting data to the Registry is a time-consuming task. Some hospitals may have the means to do this, but other hospitals which only see one or two WM patients a year struggle to muster the resources needed.

With 926 patients, the Rory Morrison Registry is very large and detailed compared to other WM registries elsewhere in the world.

Patient perspective

"*It is encouraging to see an increase in numbers of people who are now enrolled on the Registry. However, consideration needs to be given to ensuring the Registry proportionally reflects the WM population. 13 hospitals (mostly specialist units) report on 910 people and a further 10 hospitals report on 16 people. We need to know more about the patient journeys of people linked to non-specialist services.*"

John Mordue

Clinical perspective

"*In a short space of time, we have a large database of patients and are able to assess their outcomes. This will give us all a better understanding of WM, its treatment both in terms of efficacy and side effects, and the impact the disease and its treatment is having on patients.*"

Dima El-Sharkawi

Demographics

The data on patients in the Registry challenges the view that WM is predominantly a disease of old white men, and instead shows diversity across age, sex, and ethnicity.

Top-level diagnosis

Of the 926 patients in the Registry, 802 (86.6%) have confirmed WM. 124 patients (13.4%) have IgM-related conditions which do not meet the criteria for WM. These could include monoclonal gammopathy of undetermined significance (MGUS).

Of the 802 WM patients in the registry, Table 2 below shows that there is a roughly equal split between patients who had symptoms (symptomatic) or no symptoms (asymptomatic) at the time of diagnosis.

People may be diagnosed without symptoms because of a blood test taken for another reason, which could accidentally reveal features of WM, such as IgM paraprotein or reduced numbers of blood cells.

Table 2: Patients with a diagnosis of WM: diagnosis

		Patient counts	Percentage
WM diagnosis	Asymptomatic	363	45.3%
	Symptomatic	398	49.6%
	Unspecified	41	5.1%
	Total number of patients with WM	**802**	

Age and gender

Table 3 (overleaf) outlines the spread of WM patients in the Registry across gender and age. The percentages shown in the male and female columns are the percentage of men or women diagnosed in that age group. For example, 14.0% of men diagnosed with WM are aged 55-59, and 11.0% of women are diagnosed aged 55-59.

The gender split of the patients in the Registry is a male-to-female ratio of 1.6 : 1, with 61.2% of patients being male and 38.8% female.

The peak age for WM diagnosis in the Registry is between 60 and 69, representing more than a third of all patients (35.3%). However, a significant proportion of patients are younger, with a third of patients diagnosed under the age of 60

These findings challenge the perception of WM as a disease of old men; WM affects people of all ages, both male and female. However, we should acknowledge that this could be because the Registry is skewed towards patients from specialist centres (see page 13). Younger patients might be more likely to be referred to specialist centres because of their perceived rarity.

Throughout the rest of this report, we will be highlighting the differences and similarities in the experiences of people with WM, and the implications for their care.

Table 3: Patients with a diagnosis of WM: age and gender

		Gender		
		Male	**Female**	**All patients**
Age at diagnosis / years	25-29	0 (0.0%)	2 (0.6%)	**2** (0.3%)
	30-34	2 (0.4%)	2 (0.6%)	**4** (0.5%)
	35-39	14 (2.9%)	14 (4.5%)	**28** (3.5%)
	40-44	20 (4.1%)	9 (2.9%)	**29** (3.6%)
	45-49	27 (5.5%)	19 (6.1%)	**46** (5.8%)
	50-54	37 (7.6%)	29 (9.4%)	**66** (8.3%)
	55-59	68 (14.0%)	34 (11.0%)	**102** (12.8%)
	60-64	86 (17.7%)	56 (18.1%)	**142** (17.8%)
	65-69	85 (17.5%)	54 (17.4%)	**139** (17.4%)
	70-74	50 (10.3%)	37 (11.9%)	**87** (10.9%)
	75-79	48 (9.9%)	29 (9.4%)	**77** (9.7%)
	80-84	31 (6.4%)	20 (6.5%)	**51** (6.4%)
	85-89	16 (3.3%)	4 (1.3%)	**20** (2.5%)
	90-94	3 (0.6%)	1 (0.3%)	**4** (0.5%)
	Unspecified	4	1	**5**
	All patients	**491**	**311**	**802**

Figure 1 below shows the distribution of patients by gender and age, as a percentage of the male and female patients in the Registry.

Note that the bars which are the same height for men and women indicate there are the same *percentage* of men and women diagnosed in that age group, not the same numbers. For example, 17.5% of men and 17.4% of women with WM were diagnosed at 65-69 years old, so the height of the orange

Figure 1: Gender and age at diagnosis (n=797)

and purple bars above '65-69' is almost the same. However, more men are diagnosed than women, so in reality 85 men and 54 women were diagnosed in this age group.

Overall, the percentages of male and female patients are mostly equal across the different age groups, with a few minor exceptions.

Ethnicity

Table 4 below shows the ethnicity of patients with WM in the Registry. WM has been previously assumed to be a disease that mostly affects White people; however, that possibly reflects where most of the research into the disease has taken place (Scandinavia, Western Europe, and the USA).

Of the patients with an ethnicity recorded in the Registry, about 10% are non-White or mixed ethnicity. However, if we compare this to the most recent census in England and Wales in 2011,[7] certain ethnic groups appear to be underrepresented in the Registry compared to the wider population. 5.8% of patients identify as 'Asian / Asian British', which is less than was reported in the 2011 census (7.5%). Similarly, 1.8% of WM patients in the Registry identify as 'Black African / Caribbean / Black British', compared to 3.4% in the 2011 census.

Further consideration needs to be given to these findings to develop a better understanding of the factors which are leading to this underrepresentation of certain ethnic groups in the Registry data.

Table 4: Ethnicity of patients with a diagnosis of WM

		Data	
		Count	**Percentage**
Ethnicity	Asian / Asian British	39	5.8%
	Black African / Caribbean / Black British	12	1.8%
	White	611	90.1%
	Mixed / multiple background	4	0.6%
	Other ethnic group	12	1.8%
	Unspecified	124	
	All patients	**802**	

Patient perspective

"Data made available for this report allows for a much more detailed focus on the age and gender profile of people in the Registry. Over 30% of people are aged under 60,10% are from non-white ethnic groups, and 39% are female. However, the proportion of people from minority ethnic groups appear to fall below the population at large, something which requires further consideration.

It might be timely to consider whether there is now greater awareness of WM at a primary care level, so leading to earlier diagnosis. The fact that 45% of people are asymptomatic does invite reflection on what factors led eventually to diagnosis and if these were mostly indicators in medical tests e.g. reducing platelet levels. It would also be interesting to learn more about whether these indicators are the same across gender, age, and ethnic groups."

John Mordue

Clinical perspective

"Accepting that there may be bias in data entry in the Registry, the data does show that WM can affect patients of any sex and ethnicity and does affect younger patients too. What will be interesting to understand from the Registry in the future is whether there are differences in outcomes for patients based on these demographics."

Dima El-Sharkawi

Associated conditions at time of diagnosis

WM often goes hand-in-hand with a range of associated conditions – the most common of which is peripheral neuropathy.

Along with the symptoms that can lead to a diagnosis of WM in its typical form, many of the WM patients in the Registry have associated conditions at the time of their diagnosis that are fundamentally related to the WM disease and cause distinctive clinical features. These conditions result from abnormal properties of the paraprotein, apart from Bing-Neel syndrome which is caused by WM cells. It is unclear why these complications occur in some patients but not others.

Table 5 (overleaf) summarises the associated conditions in WM patients in the Registry. They include:

- **Amyloidosis** – the build-up of abnormally folded light chains (part of the IgM paraprotein structure) in the body's organs. Amyloidosis initially causes symptoms including tiredness, swelling of the legs, and weight loss, and can lead to organ failure in serious cases.
- **Peripheral neuropathy** – damage to the nerves which can lead to numbness, tingling, or pain in the feet or hands, and problems with balance or muscle weakness. In WM, this damage can be caused by inflammatory effects of IgM or the build-up of IgM in nerve tissue.
- **Autoimmune haemolytic anaemia** – where the body's altered immune system mistakenly targets and destroys red blood cells, leading to anaemia (weakness and pale appearance).
- **Immune thrombocytopenia purpura** – where the immune system mistakenly destroys platelets, which would normally help the blood to clot. This leads to symptoms like easy bruising, rashes that look like pin pricks, and bleeding from gums and nose.
- **C1-esterase deficiency** – C1-esterase helps control the immune system. A lack of C1-esterase can lead to severe swelling of the hands, feet, and face.
- **Pure red cell aplasia** – this is where the bone marrow stops producing red blood cells (without any reduction in other blood cells). It can lead to symptoms of anaemia such as fatigue and pale appearance.
- **Cryoglobulinaemia** – this is a condition where proteins in the blood become clumped together at low temperatures, such as in the body's extremities. This clumping can block blood vessels and prevent the flow of blood to the hands or feet. This can cause skin ulceration, kidney damage and joint inflammation.
- **Schnitzler's syndrome** – symptoms include chronic hives, repeated fevers, and joint pain.

- **Bing-Neel syndrome** – this is reported to occur in 1% of people with WM, and is caused by the infiltration of the lymphoma cells into the central nervous system. It causes a range of symptoms including problems with sensation and strength, seizures, reduced concentration, poor memory, and loss of hearing or sight.

Table 5: Associated conditions at time of diagnosis of WM

Associated conditions	Presence of the condition			
	No	Yes	Unspecified	Rate
Amyloid	352	14	32	3.8%
Peripheral neuropathy	289	78	31	21.3%
Autoimmune haemolytic anaemia	347	17	34	4.7%
Immune thrombocytopenia purpura	363	3	32	0.8%
C1-esterase deficiency	364	1	33	0.3%
Pure red cell aplasia	365	1	32	0.3%
Cryoglobulinaemia	350	16	32	4.4%
Schnitzlers syndrome	360	6	32	1.6%
Bing Neel Syndrome	175	8	215	4.4%

The most common condition associated with WM is peripheral neuropathy, present in 21.3% of the 398 WM patients diagnosed with symptoms. All other conditions are present in less than 5% of WM patients diagnosed with symptoms. The Registry has only recently started collecting information on Bing-Neel syndrome, which explains why there are a large number of patients (215) with 'unspecified' Bing-Neel syndrome status.

Patient perspective

"It is very useful to have information available through the Registry on the prevalence of associated conditions and how likely these are to occur in any one person with WM. It is also very useful to have details of the symptoms people might experience.

It would seem that a greater understanding may need to be developed around the factors which lead to associated conditions, and how they can best be managed."

John Mordue

Clinical perspective

"There are many associated conditions that can complicate WM, and individually these complications are rare. So it is only by grouping large patient numbers in registries such as this that we will be able to reflect on how they are managed across the country and understand outcomes."

Dima El-Sharkawi

IPSSWM

Patients in the Registry show a range of IPSSWM scores. However, the scores were based upon measurements taken at diagnosis, not at first treatment, reducing their usefulness. In addition, the different IPSSWM risk categories were based upon treatment regimens that have since been superseded by new therapies. Going forward, the Registry will collect information on the revised (2019) IPSSWM score.

The international prognostic scoring system for Waldenström's macroglobulinaemia (IPSSWM) was described by an international group of WM specialists.[1] It was derived from an analysis of 587 patients with WM and published in 2009. In this group, five parameters were found to be most influential in defining three risk categories that correlated with survival:

- advanced age (>65 years),
- haemoglobin less than or equal to 115 g/L (a marker of moderate anaemia)
- platelet count less than or equal to 100 × 109/L (moderate lowering of blood cells that clot the blood)
- β2-microglobulin more than 3 mg/L (a measure in the blood of a protein that associates with the overall burden of LPL disease)
- serum monoclonal protein concentration more than 70 g/L (a very high level of IgM paraprotein)

Patients who meet 0 or 1 of these criteria are considered low risk; those who meet 2 or whose age is over 65 are intermediate risk; and those who meet more than 2 are considered high risk. Of the five criteria, age has the largest effect: patients older than 65 are classified as intermediate or high risk, depending on other criteria.

The IPSSWM was originally designed to adapt treatment according to prognosis and facilitate comparison in clinical trials. It aimed to predict overall survival, related to death from any cause (not just WM), from the start of first treatment. One way of measuring survival is through five-year survival rates – the percentage of people who survive five years or more. In the original description of IPSSWM,[1] five-year survival rates for the low-, intermediate-, and high-risk groups were 87%, 68%, and 36% respectively.

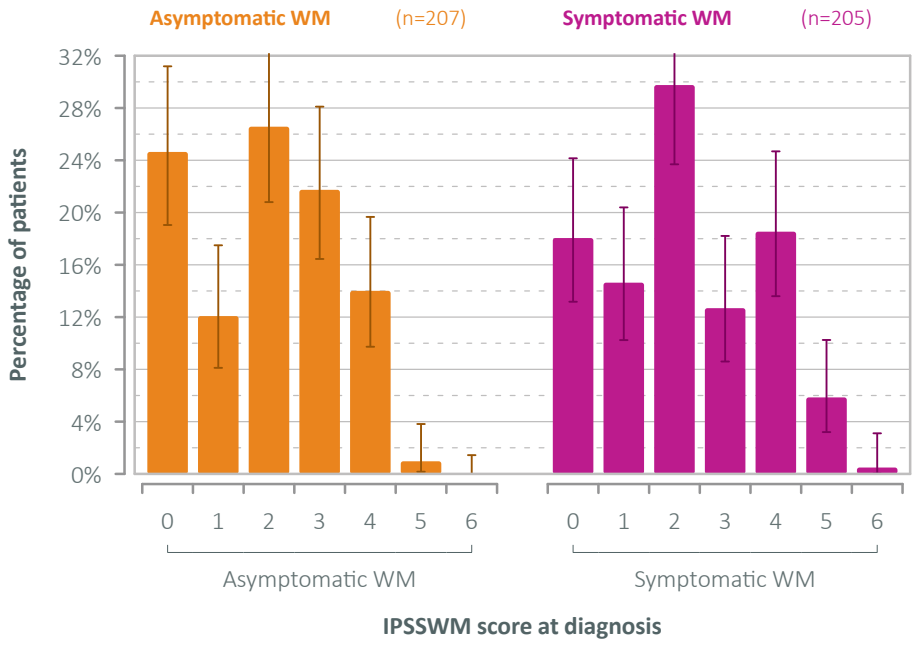
Table 6 and Figure 2 (overleaf) show the IPSSWM scores for WM patients in the Registry. One of the patient records has a score of 6, which is likely a data entry error. Of the 424 WM patients in the Registry with complete IPSSWM scores at diagnosis, 146 (34%) have a score of 0 or 1, and are in the low-risk category. 119 (28%) are in the intermediate category, and 159 (38%) are in the high-risk category.

There are no significant differences in the ISSPWM scores for patients diagnosed symptomatically or asymptomatically.

Table 6: IPSSWM at diagnosis of WM

IPSSWM at diagnosis	WM diagnosis: Asymptomatic	Symptomatic	Unspecified	All patients
0	51	37	3	**91**
1	25	30	0	**55**
2	55	61	3	**119**
3	45	26	4	**75**
4	29	38	1	**68**
5	2	12	1	**15**
6	0	1	0	**1**
Unspecified	156	193	29	**378**
All patients	**363**	**398**	**41**	**802**

Figure 2: IPSSWM score at diagnosis of WM



There are a few reasons why the IPSSWM scores are no longer useful for the Registry. Firstly, the scores are based upon assessment at diagnosis, not at the time of first treatment. This reduces its utility, as the IPSSWM was originally designed to help make treatment decisions. Patients may spend many years on active surveillance, or 'watch and wait' before commencing treatment, by which point the measures used in the IPSSWM criteria may have changed since diagnosis. Unfortunately most non-specialist clinicians would not be in the habit of calculating the score, so data are often missing, especially for the β2-microglobulin measure.

The IPSSWM is not currently used to stratify treatment. This is largely because survival rates for WM have improved thanks to newer treatment regimens which became available after the score was published. In addition, the identification of recurrent WM mutations in the MYD88 and CXCR4 genes in 2012 and 2014[8,9] have added to our knowledge of factors which affect survival rates.

In 2019, a new revised IPSSWM was developed.[2] The revised IPSSWM uses updated criteria, and is based upon updated survival data which takes into account changes to treatment, such as rituximab for first-line therapy, proteasome inhibitors such as bortezomib, and BTK inhibitors like ibrutinib, which weren't in common use at the time the original IPSSWM was developed. The WM Registry has been adjusted to incorporate the revised IPSSWM going forwards.

Patient perspective

"New therapeutic approaches require an updated approach to risk assessment and response. It is very useful for patients to have an understanding of how risk is assessed and what the outcomes may be if treatment is either delayed or implemented. It may be particularly helpful for asymptomatic patients who score intermediate- to high-risk to understand why treatment may be beneficial when they have no apparent symptoms. Further data on quality of life, submitted by patients, could make a very significant addition to improving knowledge in this area."

John Mordue

Clinical perspective

"Prognostic scores can provide clinicians with information that we can share with patients regarding their likely outlook based on current therapy. However, this is based on population data and does not definitely reflect what will happen for the individual. They also may not be as useful after new therapies are introduced (such as BTK inhibitors), so it is always important to constantly reassess whether there are better prognostic scores available. At present these scores do not help us decide which is the best treatment to give, but updated scores like the revised IPSSWM may help in the future."

Dima El-Sharkawi

Treatment

WMUK

The UK charity for **Waldenstrom's macroglobulinaemia**

Numbers on 'watch and wait'

Many people diagnosed with WM will go onto 'watch and wait' instead of starting treatment immediately. The time that people can be on 'watch and wait' for is variable, but many patients can remain under active surveillance for five or ten years or more.

Many people diagnosed with WM will not start treatment immediately, but instead have regular check-ups for symptoms. This is known as 'active surveillance', or 'watch and wait'. As WM is often a slow-growing disease, it is a safe strategy which means people diagnosed with WM can avoid the side-effects that treatment can bring.

Even for people who are diagnosed with symptoms, 'watch and wait' might still be a suitable strategy if those symptoms are not severe enough to warrant urgent treatment.

In the Registry, patients are defined as being on 'watch and wait' for the period between their diagnosis of WM and their first recorded treatment.

Of the 802 patients with a diagnosis of WM in the Registry, 248 (30.9%) did not receive any treatments before the data cut-off on 1st September 2020. We can say these people are currently on 'watch and wait' (on the 1st September 2020). Note this number does not include patients who have been on 'watch and wait' in the past but who have since received treatment for WM.

175 of the 383 people diagnosed with WM without any symptoms (asymptomatic) are currently on watch and wait, as are 60 of the 398 people diagnosed with symptoms. In total, 150 patients currently on watch and wait have been so for five years or more. 73 of these 150 have been on watch and wait for 10 years or longer, including 21 WM patients who were initially diagnosed with symptoms.

Patient perspective

"*It's important and reassuring to know that watch and wait is a reasonable management option for many WM patients. It should be seen more as active surveillance rather than not being offered the best treatment.*"

Harriet Scorer

Clinical perspective

"*Watch and wait is an anxious period for patients, which can span many years. The presence of symptoms in patients in the Registry who nevertheless stayed on watch and wait demonstrates that a careful review of symptoms between the patient and their clinician, their impact on the patient, and changes over time, are crucial to avoid hasty treatment. Avoiding premature treatment defers the risk of side effects until treatment is absolutely necessary – by which time, further developments in the field may uncover treatments that are more effective or less toxic.*

The decision to defer treatment should be made on an individual basis following careful clinical evaluation of the patient. Some symptoms may not be clearly attributable to WM and may require further

observation to help clarify the situation before the commitment to treatment is made. A useful tool for me is to ask myself: why should I start treatment today, rather than next week or in a month or 3 months? Will it make a difference to the patient's well-being, or can we afford to watch a little bit longer? That is not to say that patients must become unwell before starting treatment – that is not right either. There is a careful balance to achieve here."

Shirley D'Sa

Time to first treatment

WM patients who are asymptomatic when diagnosed tend to wait longer to start treatment than those diagnosed with symptoms. There is no apparent sex discrimination with regards to when treatment for WM starts.

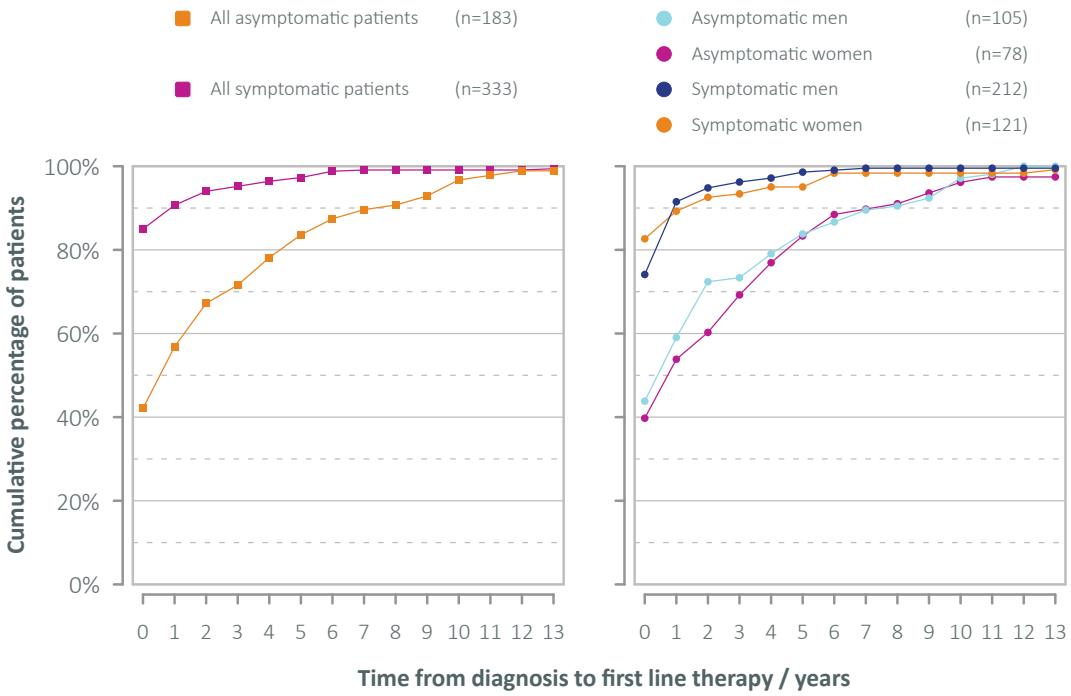
Many people diagnosed with symptoms do not start treatment straight away, but instead go on 'watch and wait'. Figure 3 below shows how long people in the Registry diagnosed with WM typically wait before they begin their first treatment.

The graphs show the cumulative percentage, or a 'running total', of patients who have started their first treatment in the years after diagnosis, up to the maximum of 100% of patients.

It shows that people who are diagnosed with symptoms tend to start their first treatment sooner than those who are diagnosed without symptoms (asymptomatic). By five years after diagnosis, 97.3% of patients diagnosed with symptoms (purple line on graph) have received their first treatment, compared to 83.6% of patients who were asymptomatic at the time of diagnosis (orange line on graph).

The figure on the right shows that there is little difference between when men and women receive their first treatment, regardless of whether they were diagnosed with symptoms or without.

Figure 3: Time from diagnosis to first-line therapy



Patient perspective

"WM seems to present and behave differently in different people. There is no set time from diagnosis to needing treatment and it is important to take into account all aspects of the disease when making treatment decisions.."

Harriet Scorer

Clinical perspective

"When it comes to starting first-line therapy, men and women appear to follow a similar path, despite the condition having a higher prevalence in men. This is unsurprising from the biological perspective, as there are no apparent differences in inherent behaviour of the disease between the sexes. Ultimately, the decision to treat lies with the clinician in conjunction with the patient. Listening to the patient and individualising the decision is crucial, as people have unique health and psychological circumstances."

Shirley D'Sa

Indications for first treatment

The symptoms which trigger first-line treatment in WM may be subdivided into paraprotein- and lymphoma-related features, each present in about half of WM patients. Hyperviscosity and fatigue are by far the most commonly recorded indications for first treatment in WM patients in the Registry.

When patients in the Registry start their first treatment, the symptoms which triggered the decision (also known as indications for treatment) are recorded. In the Registry there are three broad categories: **paraprotein-related**, **lymphoma-related**, and **B-symptoms.**

- **Paraprotein-related features** include:
  - peripheral neuropathy (tingling, numbness, or pain in the hands or feet);
  - hyperviscosity (thickening of the blood, leading to problems with vision, shortness of breath, nosebleeds, bleeding gums, and dizziness);
  - amyloidosis (build-up of abnormal proteins in the body's organs);
  - bleeding problems;
  - auto-immune conditions like Schnitzler's syndrome, which affects the skin.
- **B-symptoms** include fever, night sweats, and loss of more than 10% body weight over six months.
- **Lymphoma-related features** include B-symptoms, as well as fatigue, reduced numbers of different cells in the blood (due to infiltration of lymphoma cells in the bone marrow), and enlarged spleen and lymph nodes.

B symptoms are derived from the Ann Arbor staging system for lymphomas which includes both a number (stages I–IV) and a letter (A or B). "A" indicates the absence of systemic symptoms, while "B" indicates their presence. B symptoms may occur in WM due to its biological behaviour as a lymphoma. However, the Ann Arbor system is not itself appropriate as all patients with WM have bone marrow involvement (which would be Stage IV). The way the Registry is set up means that B-symptoms can be reported separately, even when falling blood counts and enlarged spleen or lymph nodes are not apparent.

Table 7 overleaf shows the most common indications for first-line treatment recorded in the Registry. 122 of the 548 patients have no indication recorded in the Registry. But among the 426 patients who do have an indication recorded, paraprotein-related features are recorded in about half of patients (211), and lymphoma-related features are also recorded in about half of patients (220).

Note that people can have more than one type of symptom recorded as an indication. In fact, the combination of lymphoma- and paraprotein-related features is a hallmark of WM that distinguishes it from other forms of lymphoma. As such, 58 patients have both paraprotein- and lymphoma-related features recorded as indications to treat – representing just over a quarter of patients in either group, and 14% of patients overall.

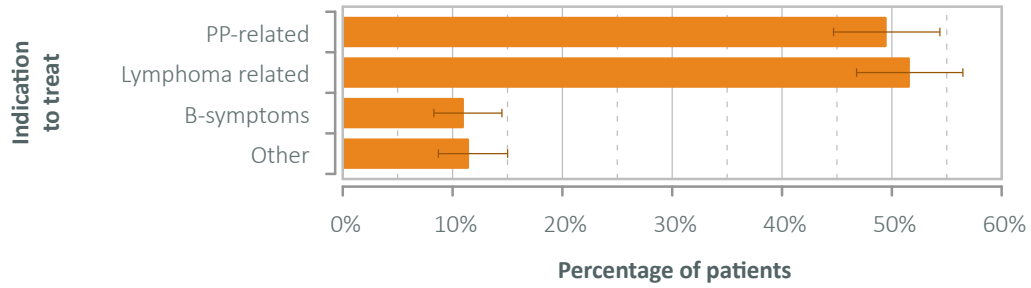
159 patients (37% of all patients) had *only* paraprotein-related features (not lymphoma features) as an indication to treat. This illustrates the distinction between WM and other types of lymphoma.

In only a small proportion of patients – around 11% – are B-symptoms (or other symptoms) recorded as the indication for first treatment.

Table 7: Indication to treat at the time of first-line therapy

		Incidence			
		No	**Yes**	**Unspecified**	**Rate**
Indication to treat	PP-related	215	211	122	49.5%
	Lymphoma-related	206	220	122	51.6%
	B-symptoms	379	47	122	11.0%
	Other	377	49	122	11.5%

Figure 4: Indication to treat at the time of first-line therapy (n=426)



Further details about the paraprotein- and lymphoma-related features recorded as indications are shown below. Note again that each patient can have more than one symptom recorded as an indication for treatment.

Table 8 below and Figure 4 overleaf show details of paraprotein-related features recorded as indications for first treatment. The most common paraprotein-related feature recorded is hyperviscosity, present in 56.5% of patients, followed by peripheral neuropathy, present in 28.0%.

Table 8: Details of paraprotein (PP)-related features

		Count	**Rate**
Details of PP-related features	Peripheral neuropathy	52	28.0%
	Hyperviscosity	105	56.5%
	Amyloid	11	5.9%
	Bleeding problems	16	8.6%
	Skin-Schnitzler syndrome	3	1.6%
	Auto-immune	23	12.4%
	Unspecified	25	
	Patient count	**211**	

Figure 5: Details of paraprotein (PP)-related features (n=186)

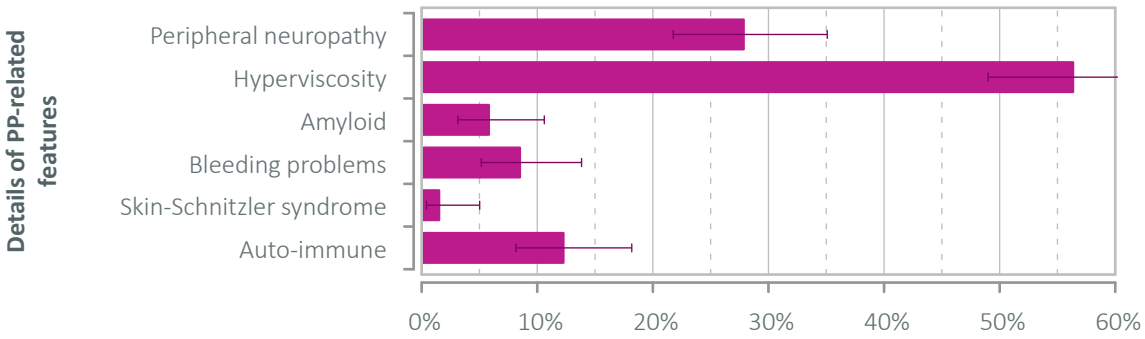


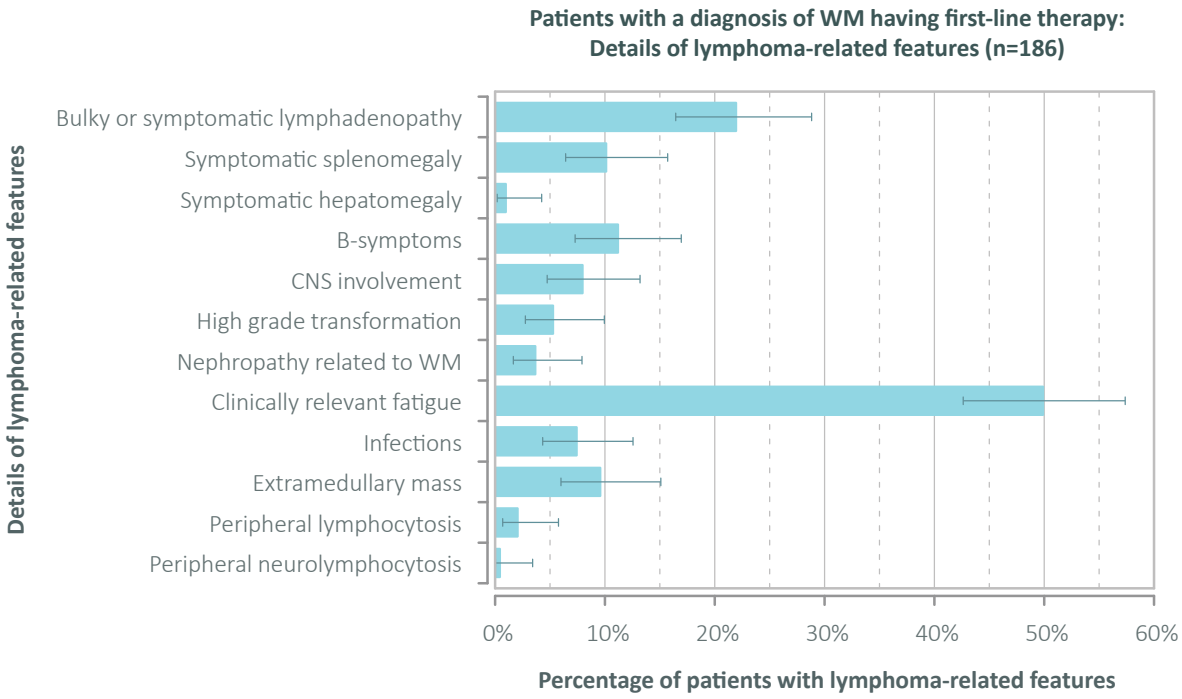
Table 9 below and figure 6 overleaf show detailed lymphoma-related features recorded as indications to start first treatment.

Clinically relevant fatigue (that is, related to the underlying WM rather than any other cause) is the most common indication recorded, present in 50% of patients. Following that, bulky or symptomatic lymphadenopathy (enlarged lymph nodes), B-symptoms, and symptomatic splenomegaly (enlarged spleen) are the next most common indications, present in 22.0%, 11.3% and 10.2% of patients, respectively.

Table 9: Details of lymphoma-related features

		Count	Rate
Details of lymphoma-related features	Bulky or symptomatic lymphadenopathy	41	22.0%
	Symptomatic splenomegaly	19	10.2%
	Symptomatic hepatomegaly	2	1.1%
	B-symptoms	21	11.3%
	CNS involvement	15	8.1%
	High grade transformation	10	5.4%
	Nephropathy related to WM	7	3.8%
	Clinically relevant fatigue	93	50.0%
	Infections	14	7.5%
	Extramedullary mass	18	9.7%
	Peripheral lymphocytosis	4	2.2%
	Peripheral neurolymphocytosis	1	0.5%
	Unspecified	34	
	Patient count	**220**	

Figure 6: Details of lymphoma-related features (n=186)



47 patients had B-symptoms recorded as the top-level indication for first-line treatment (as seen on Table 7 on page 30). Of these, night sweats and weight loss were the most common, reported in 27 patients each (data not shown)

Patient perspective

It's interesting to see that there is such a range of reasons for starting treatment. It's not surprising as patients with WM present with different symptoms – we're all different even if we have the same underlying disease. Although there is a huge variety, the data demonstrates that fatigue is a significant feature for many of us. It may not be something that can always be measured, but it can be debilitating.

Harriet Scorer

Clinical perspective

The high prevalence of paraprotein-related symptoms underscores important distinctions between WM and other lymphomas, as demonstrated by approximately half of patients presenting with such symptoms, and just over a third presenting with only paraprotein-related symptoms.

The frequency of hyperviscosity as an indication to treat may reflect the bias in the Registry towards specialist centres, where hyperviscosity is more frequently sought out and testing is more available.

The prevalence of fatigue is striking and matches my observations in the clinic. Fatigue has a multitude of contributors, including bone marrow insufficiency (leading to anaemia and less oxygen delivery to the tissues) as well as chronic inflammation that goes hand-in-glove with a condition such as WM. Fatigue levels do not always correlate well with measurable parameters, but if present to a debilitating degree, such that it interferes with daily life, it should be considered as an indication for treatment. Low iron levels (another notable feature of WM) should be corrected if present – this can help to alleviate fatigue.

Shirley D'Sa

First-line treatments

There is no standard first-line treatment for WM, though DRC ± rituximab and bendamustine-based therapies are popular choices. Treatment for WM has become more streamlined in the last five years.

In this section we discuss different first-line treatments for WM; that is, the first medicines that people with WM will receive. Many of these treatments are combinations of several drugs. Table 10 below gives a list of common first-line treatment regimens.

(Note the symbol ± means 'plus or minus', indicating that the drug after the symbol is sometimes included in the regimen and sometimes not).

Table 10: Regimen names commonly abbreviated

	Full name for the regimen	Abbreviation
Regimen	Cyclophosphamide, doxorubicin, vincristine, prednisolone ± rixtuximab	**CHOP ± R**
	Cyclophosphamide, vincristine, prednisolone ± rituximab	**CVP ± R**
	Dexamethasone, rituximab, cyclophosphamide	**DRC**
	Etoposide, methylprednisolone, cytarabine, cisplatin ± rituximab	**ESHAP ± R**
	Idarubicin, dexamethasone, cytarabine, methotrexate ± rituximab	**IDARAM ± R**
	Methotrexate, cytarabine, thiotepa, rituximab	**MATRIX**

Table 11 overleaf shows the first-line treatments given to patients in the Registry between 2015 and 2020, representing treatments patients are most likely to receive today.

The data show that there is a wide variety of first-line treatments given to patients in the Registry, with no standard treatment regimen. The most common treatment regimen is DRC (sometimes given with two additional doses of rituximab), given to 71 of the 216 patients (37.2%) whose first treatment was recorded during 2015 to 2020.

The next most common treatment is any regimen containing the chemotherapy drug bendamustine, given to 63 patients (33.0%) during 2015-20. This is followed by rituximab alone, given to 17 patients (8.9%) during 2015-20.

The patients in the Registry are mostly being treated at a small number of hospitals which represent specialist centres (see Table 1 from page 13). This means that the first-line treatments recorded might be skewed towards treatment protocols at these centres, which are often large hospitals with more specialist experience of treating WM compared to smaller local hospitals. Smaller centres may deliver local treatment at the recommendation of the specialist centres.

Regimens such as IDARAM and MATRIX are used in patients with WM affecting the central nervous system (Bing-Neel syndrome), a setting where there is no consensus as to the optimum approach.

Table 11: First-line treatment regimens started between 2015 and 2020

Regimen	Count	Percentage
Dexamethasone, rituximab, cyclophosphamide ± rituximab	71	37.2%
Bendamustine based	63	33.0%
Rituximab	17	8.9%
Chlorambucil	7	3.7%
Methotrexate, cytarabine, thiotepa, rituximab	7	3.7%
Bortezomib combination	6	3.1%
Cyclophosphamide, vincristine, prednisolone ± rituximab	6	3.1%
BTK inhibitors	5	2.6%
Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone	5	2.6%
Purine analogue	4	2.1%
Unspecified	25	
All	**216**	

To illustrate how WM has been treated in the past, Table 12 below shows the first-line regimens recorded for all WM patients in the Registry across all time periods. The earliest first treatment retrospectively recorded into the Registry was in 1984.

DRC and bendamustine-based regimens are the most common first-line treatments across patients in the Registry. CHOP ± rituximab has been a popular treatment for WM historically, but does not feature highly in Table 11 of treatments during 2015-20. The same applies to chlorambucil and purine analogues, which have become less popular for various reasons. These changes follow the development of evidence-based consensus guidelines which have helped to refine treatments for WM.[10]

Treatment has also been streamlined over time, with fewer options being used during 2015-20, compared to treatments used across all time periods.

Table 12: All recorded first-line treatment regimens

Regimen	Count	Percentage
Dexamethasone, rituximab, cyclophosphamide ± rituximab	128	26.4%
Bendamustine based	76	15.7%
Purine analogue	65	13.4%
Chlorambucil	61	12.6%
Cyclophosphamide, doxorubicin, vincristine, prednisolone ± rituximab	50	10.3%
Rituximab	44	9.1%
Cyclophosphamide, vincristine, prednisolone ± rituximab	36	7.4%
Bortezomib combination	9	1.9%
Methotrexate, cytarabine, thiotepa, rituximab	7	1.4%
BTK inhibitors	5	1.0%
Allograft stem cell transplant	2	0.4%
Etoposide, methylprednisolone, cytarabine, cisplatin ± rituximab	1	0.2%
Idarubicin, dexamethasone, cytarabine, methotrexate ± rituximab	1	0.2%
Unspecified	63	
All	**548**	

To further illustrate how treatment for WM has changed over time, Figure 7 below shows how the prescription of individual treatments has changed year-by-year. The treatments represent six of the most common first-line therapies for WM patients in the Registry: chlorambucil, purine analogue chemotherapy drugs, rituximab, DRC, bendamustine-based regimens, and CHOP ± rituximab.

DRC and bendamustine-based regimens have become increasingly popular choices for treating WM patients in the Registry. From 2011, DRC ± rituximab has made up 30-40% of all first-line treatments prescribed to WM patients in the Registry; prior to this, it was less than 8%. Bendamustine-based regimens have increased in usage, making up 28-38% of first-line treatments from 2014 onwards, having been prescribed only rarely before then.

Conversely, the use of chlorambucil, purine analogues, and CHOP ± rituximab have all declined over time. The usage of rituximab alone as a first-line treatment has been fairly consistent since 2006.

Figure 7: Changes in first-line regimens over time

Patient perspective

"When faced with having to make a decision about starting treatment, it can be confusing to understand the different treatment options and why there seem to be so many. It is interesting to see that these options appear to be becoming more streamlined. It would be good if the evidence-based guidelines which exist for treating WM were followed everywhere."

Harriet Scorer

Clinical perspective

"Over recent years, as we learnt more about the additions to the treatment arsenal (DRC and bendamustine), there have been concurrent concerns about toxicity of existing agents in widespread use (chlorambucil and fludarabine). So the increase in use of the former with the decline of the latter is no surprise – more appropriate treatments have taken the place of the older agents. The fall in the use of CHOP ± R reflects consensus guidelines that recommended the restriction of this treatment for 'transformed' disease (see page 56)*."*

Shirley D'Sa

Response to first treatment

Most WM patients respond well to their first-line treatment, with 70% of patients in the Registry having a partial response or better.

Table 13 and Figure 8 below show, for the 548 patients in the Registry who have completed a first-line treatment, how their disease responded to that treatment. 466 patients have information recorded in the Registry about this response.

Only 14 patients (3.0%) had progressive disease after first-line treatment – that is, their disease continued to grow despite treatment. 326 patients (70.0%) had a partial response or better to their first treatment (also known as a 'major response') which is at least 50% reduction in IgM levels.

'No response' was originally intended as an option where information about treatment response had not been recorded in the Registry. However, it appears that some entries which use 'No response' also have end dates for treatment, which suggests that some people entering data have instead used this option to indicate where the patient's disease did not respond to the treatment (i.e. similar to 'stable disease' or 'progressive disease'). There are also instances where response to treatment is 'Unspecified', which means no data about treatment response was entered at all. The lack of clarity around the 'No response' option will be addressed in future versions of the Registry.

Table 13: Response to first-line therapy

		Count	Percentage
Response	No response	33	7.1%
	Complete response	47	10.1%
	Very good partial response	83	17.8%
	Partial response	196	42.1%
	Minor response	50	10.7%
	Stable disease	43	9.2%
	Progressive disease	14	3.0%
	Unspecified	82	
	All	**548**	

Figure 8: Response to first-line therapy (n=446)

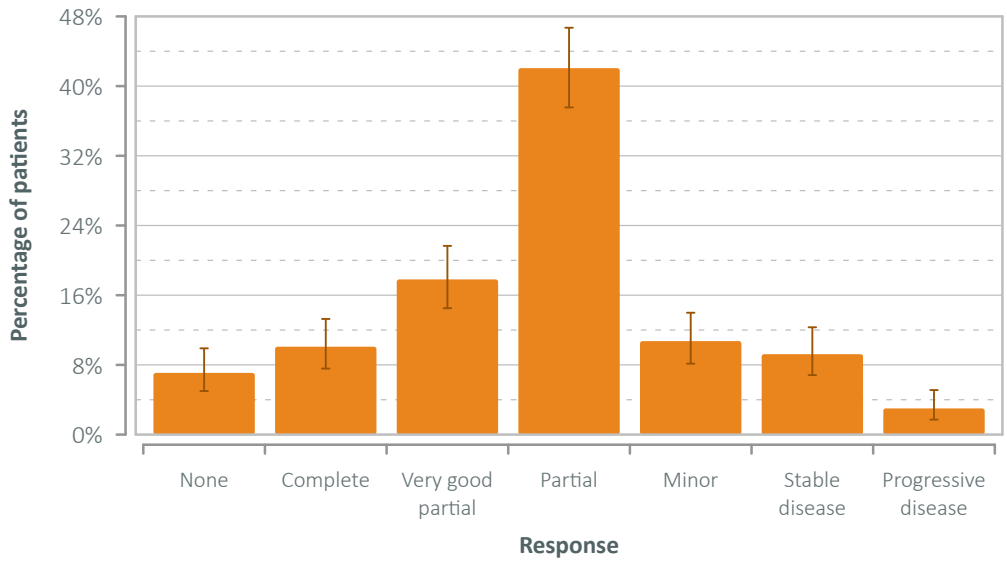


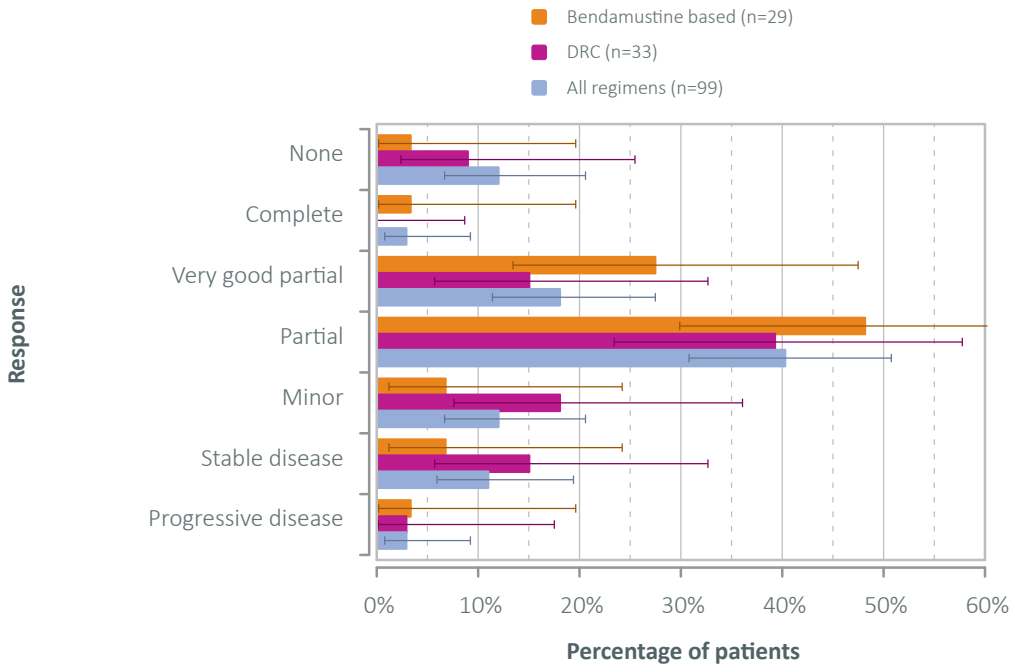
Table 14 and Figure 9 below show in more detail the response to two most common first-line treatment regimens: bendamustine-based regimens and DRC (dexamethasone-rituximab-cyclophosphamide). Only one patient each on either DRC or bendamustine-based regimens had progressive disease following treatment.

Though the numbers of patients involved are too small to draw any firm conclusions, bendamustine-based regimens as a first-line treatment appear to have better results compared to other treatment regimens. Of the 29 patients who received bendamustine-based regimens with a response recorded in the Registry, 23 patients (79.3%) had a partial response or better, compared to 61.6% of patients (61 of 99) who had received any first-line treatment.

Table 14: Response to specific first-line regimes

Response	Bendamustine based	DRC	All
No response	1	3	**12**
Complete response	1	0	**3**
Very good partial response	8	5	**18**
Partial response	14	13	**40**
Minor response	2	6	**12**
Stable disease	2	5	**11**
Progressive disease	1	1	**3**
Unspecified	8	9	**29**
All	**37**	**42**	**128**

Figure 9: Response to specific first-line regimes



Patient perspective

"Although WM is an incurable disease, it is treatable. The data shows that we shouldn't be too despondent as most patients have a reasonable response to treatment."

Harriet Scorer

Clinical perspective

"WM is by-and-large a predictable and 'obedient' disease. Of course, it can produce clinical challenges but it is highly unusual for a lack of response to first-line therapy. If this happens, it is important to monitor the patient more frequently over time. If the patient is well despite the apparent 'lack of response', a period of observation spanning a few weeks or months is advisable before moving to another line of therapy.

It is also crucial to be on the lookout for a possible 'IgM flare', following rituximab-containing therapy, which is more common when the pre-treatment IgM is >40 g/L. This flare may give a false impression of disease progression, so care should be exercised before switching therapy."

Shirley D'Sa

Time to second-line treatment

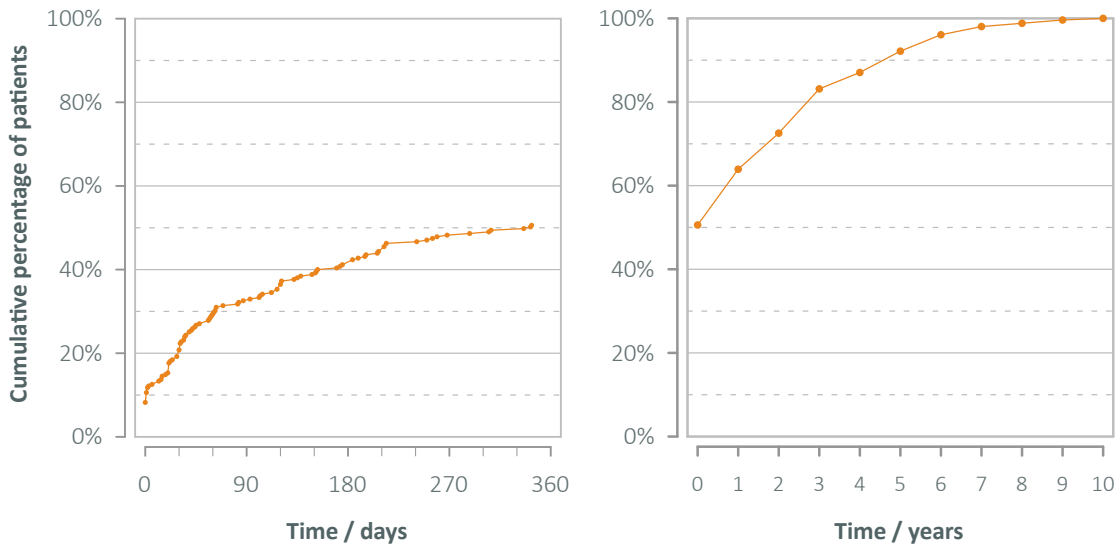
Half of WM patients in the Registry who have started their second-line therapy began treatment within one year of completing their first-line therapy.

There are 321 WM patients in the Registry who have started a second-line therapy (the second treatment after their diagnosis).

Figure 10 below shows the cumulative total percentage of people who have started their second-line therapy. It presents a 'running total' of all the patients who have started a second-line therapy by a specific point in time. The graph on the left shows when patients started second-line therapy within the first year after completing their first-line treatment, and the graph on the right shows when patients started second-line therapy within 10 years.

More than 40% of patients started their second treatment within 180 days (around six months) of completing their first treatment. Just over half (50.6%) started their second-line therapy less than one year after completing their first-line therapy. 87.0% of patients began their second treatment within five years.

Figure 10: time from the end of first-line therapy to the start of second-line therapy (n=255)



It is surprising to see that so many of this group of patients start second-line therapies so soon after first-line therapy. There are many explanations for why WM patients start their second-line treatment. For example, symptoms may return which trigger treatment, the first-line treatment fails to control the disease, or side-effects of the treatment may become intolerable. The decision to start the next line of therapy is often based on the treating physician's judgement.

Patient perspective

"I am surprised to see so many patients recorded as starting second line treatment so soon after their first treatment and it doesn't seem to reflect the experience of many WM patients. This is something which we need to look into further and ensure that the Registry is recording the true picture of what is happening."

Harriet Scorer

Clinical perspective

"It's startling to see so many patients in the Registry starting a second-line therapy within one year of completing their first. While this could be a reflection of the practice at participating centres (such as a concentration of more complex cases at specialist centres), it might include a number of patients who are prematurely commenced on next line therapy by their treating physician.

Clinicians should remember that a careful assessment of the kinetics of response to therapy in WM is important. For example, therapies such as BR and DRC often lead to significant B□cell depletion in the marrow but suboptimal IgM responses, due to their selective targeting of B cells. There is also a recognised lag in paraprotein response in many patients due to the longer time it takes for the plasmacytic fraction of the disease to shrink.[11]

It is most important that the patient should be assessed from the clinical point of view and not on numbers alone – do they feel better? Are their blood counts better? Satisfactory IgM responses are subsequently documented in the majority of patients, with maximum responses documented at a median of 6 months. Thus, a period of observation spanning 3 to 6 months is recommended before making the decision to switch therapy, as long as the patient has preserved well-being. Seeking advice from a WM specialist is encouraged."

Shirley D'Sa

Indications for second-line therapy

Similar to indications for first-line therapy, the most common symptoms which trigger second-line treatment in WM are paraprotein- and lymphoma-related features, each present in just under half of WM patients.

Data can be submitted to the Registry on any symptoms which acted as a trigger for second-line therapy (indications to treat), as is the case for first-line therapy.

Table 15 and Figure 11 below outline the indications for second-line therapy for WM patients in the Registry. Note that more than one indication can be recorded for each patient.

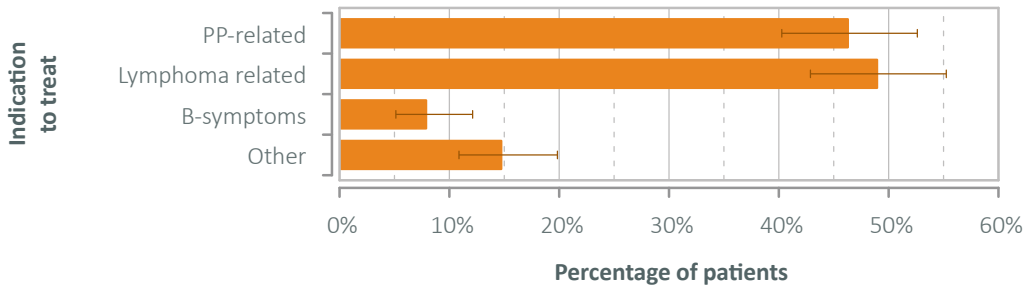
These indications for second-line therapy follow a similar pattern to those for first-line therapy (see page 29). Paraprotein (PP)-related features and lymphoma-related features are the leading indications for second-line therapy, present in 46.4% and 49.0% of patients, respectively.

B-symptoms (including weight loss, fever, and night sweats) are recorded in 8.0% of patients as indications for second-line therapy.

Table 15: Indication to treat at the time of second-line therapy

		Incidence			
		No	Yes	Unspecified	Rate
Indication to treat	PP-related	141	122	84	46.4%
	Lymphoma-related	134	129	84	49.0%
	B-symptoms	242	21	84	8.0%
	Other	224	39	84	14.8%

Figure 11: Indication to treat at the time of second-line therapy (n=263)



Patient perspective

"For those of us who require additional treatment, it seems that the symptoms that required treatment in the first place are those that are likely to return."

Harriet Scorer

Clinical perspective

"In most patients, the clinical pattern remains true throughout the course of the illness – initial symptoms or features tend to become apparent once again if WM relapses. The degree to which this occurs depends on the speed of relapse and the frequency of follow-up."

Shirley D'Sa

Second-line treatment regimens

Ibrutinib has become the leading choice for second-line therapy, since it became available to WM patients on the NHS through the Cancer Drugs Fund in 2017.

Table 16 below shows the range of second-line treatment regimens received by patients in the Registry, split into treatments recorded during two time periods: 2015-2016, and 2017-2020.

In the years 2015-16, there was a wider range of treatment used in second-line therapy. Bendamustine-based regimens accounted for 30% of second-line therapies. This is followed by acalabrutinib (a next-generation inhibitor of BTK) representing 22% of second-line therapies. The use of acalabrutinib probably reflects that many of the hospitals involved in the Registry were also recruiting patients for a clinical trial of acalabrutinib[12] which ran from 2014 to 2015.

However, during 2017-20, ibrutinib became the leading choice, making up 65.5% of second-line therapies. Ibrutinib was recommended for use in the Cancer Drugs Fund for treating WM in 2017, which explains this large increase in usage.

As ibrutinib has become the favoured choice for second-line therapy, there has been a corresponding decline in the use of other regimens. These include bendamustine-based regimens, dexamethasone-rituximab-cyclophosphamide, and rituximab alone.

Table 16: Recorded second-line regimens, by year of treatment

Regimen	Year of treatment			
	Counts		Percentages	
	2015-2016	2017-2020	2015-2016	2017-2020
Ibrutinib	0	57	0.0%	65.5%
Bendamustine based	15	7	30.0%	8.0%
Etoposide, methylprednisolone, cytarabine, cisplatin +/- rituximab	7	5	14.0%	5.7%
Zanubrutinib	0	4	0.0%	4.6%
Dexamethasone, rituximab, cyclophosphamide	7	3	14.0%	3.4%
Methotrexate, cytarabine, thiotepa, rituximab	1	3	2.0%	3.4%
Rituximab	5	2	10.0%	2.3%
Cyclophosphamide, doxorubicin, vincristine, prednisolone +/- rituximab	1	2	2.0%	2.3%
Cyclophosphamide, vincristine, prednisolone +/- rituximab	0	2	0.0%	2.3%
Bortezomib combination	0	1	0.0%	1.1%
Chlorambucil	0	1	0.0%	1.1%
Acalabrutinib	11	0	22.0%	0.0%
Purine analogue	2	0	4.0%	0.0%
Idarubicin, dexamethasone, cytarabine, methotrexate +/- rituximab	1	0	2.0%	0.0%
Unspecified	1	7		
All	**51**	**94**		

Clinical perspective

"The rapid rise in the use of ibrutinib is not a surprise since it became available on the Cancer Drugs Fund in 2017. It offered a non-chemotherapy alternative that physicians and patients had become aware of following publication of trial results in 2015.[13] The use of the BTK inhibitor zanubrutinib reflects the globally-run ASPEN clinical trial (zanubrutinib compared to ibrutinib in relapsed or refractory patients, also known as the BGB-3111-302 trial[14]) that opened in the UK in 2017, which continues in follow-up.

The challenge remains the role and place of BTK inhibitors in the treatment algorithm. Further follow-up and new trials are needed to establish this."

Shirley D'Sa

Response to second treatment (non-BTKi)

For most WM patients in Registry, their disease responds well to second-line therapy, with 68.6% of patients having a partial response or better.

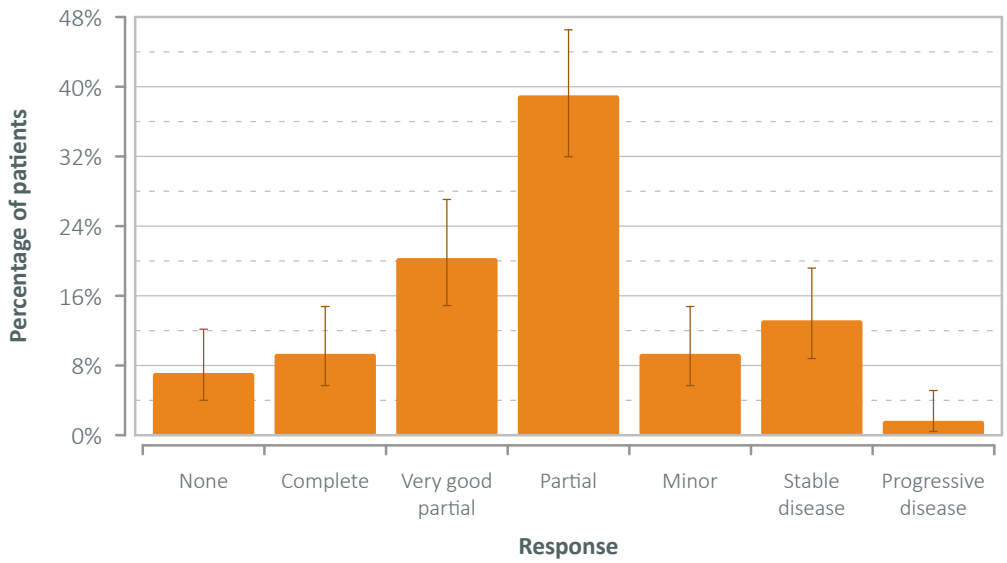
Table 17 and Figure 12 below show, for 221 WM patients in the Registry, how their disease responded to any second-line therapy not including BTK inhibitors (BTKi). Data regarding response to the BTKi ibrutinib as a second-line therapy is outlined separately on page 49.

The response to second-line therapy follows a similar pattern to the response to first-line therapies, as seen on Figure 8 on page 37. 68.6% of WM patients have a partial response or better to their second-line therapy (known as a 'major' response). Only three patients (1.6%) experienced progressive disease during second-line therapy.

Table 17: Treatment response to non-BTKi treatments

Response	Count	Percentage
No response	13	7.1%
Complete response	17	9.3%
Very good partial response	37	20.3%
Partial response	71	39.0%
Minor response	17	9.3%
Stable disease	24	13.2%
Progressive disease	3	1.6%
Unspecified	39	
All	**221**	

Table 12: Treatment response to non-BTKi treatments



Patient perspective

"It is reassuring to see that most patients respond well to a second-line therapy, if they require one."

Harriet Scorer

Clinical perspective

"WM is typically a gradual disease that generally shrinks in response to chemotherapy. The aim is to maximise the duration of response at each point of treatment so that the total time adds up to decades, whilst keeping adverse effects at bay, such as suppression of the bone marrow and immune system. These data show that chemotherapy remains effective beyond first-line use. ."

Shirley D'Sa

Subsequent treatments

As WM is often a slow-growing disease, patients may receive multiple lines of therapy – with some patients in the Registry receiving five or more different treatments.

Table 18 and Figure 13 below show the most recent line of therapy recorded for 802 WM patients in the Registry.

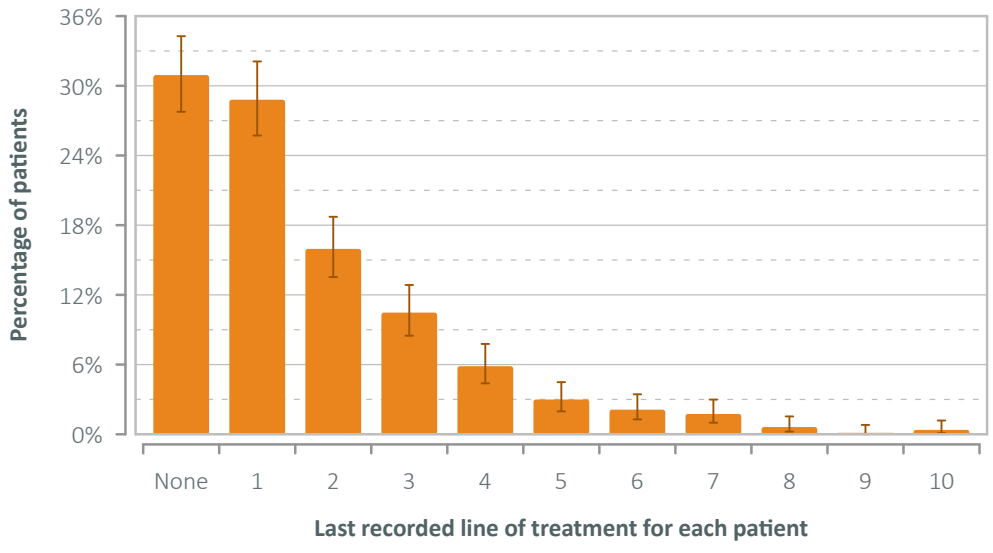
The 248 patients who have no lines of treatments recorded are those that are currently on 'watch and wait' before their first treatment (on the data cut-off on 1st September 2020). See page 25 for more information about 'watch and wait'.

231 patients (28.8%) in the Registry have only one line of treatment recorded, and 128 patients (16.0%) have only had two lines of treatment recorded. Consistent with the idea that WM is a disease that people can live with for a long time, the data shows that a small number of patients (7.9%) have had five or more lines of treatment recorded in the Registry.

Table 18: Last line of treatment recorded for each patient

		Count	Percentage
Last recorded line of treatment	None	248	30.9%
	First	231	28.8%
	Second	128	16.0%
	Third	84	10.5%
	Fourth	47	5.9%
	Fifth	24	3.0%
	Sixth	17	2.1%
	Seventh	14	1.7%
	Eighth	5	0.6%
	Nine	1	0.1%
	Tenth	3	0.4%
	All patients	**802**	

Figure 13: Last line of treatment recorded for each patient (n=802)



Ibrutinib

Ibrutinib is a popular choice for WM patients in the Registry since it was made available through the Cancer Drugs Fund in 2017. For most patients, their disease responds well to ibrutinib, and they can continue to take the drug for years.

Ibrutinib is a drug which inhibits a protein called Bruton's tyrosine kinase (BTK), which is crucial to the growth and development of WM cells. Blocking this protein helps to stop lymphoma cells from replicating, and eventually kills these cells. Since 2017 it has been available to patients in the UK on the NHS through the Cancer Drugs Fund. In this section we present a range of information about the use of ibrutinib among patients in the Registry.

There are fundamental differences between BTK inhibitors and conventional chemotherapy. Firstly, BTK inhibitors are taken orally (as pills that are swallowed) and for as long as needed, whereas chemotherapy is given in distinct cycles for a fixed duration, often via intravenous 'drips' at a hospital. As such, chemotherapy (which is typically given with rituximab) has more prominent side effects during the time of administration. However, over time, the longer duration of treatment with BTK inhibitors means that side-effects may have more of an impact on quality of life for patients. In addition, ibrutinib may not result in a 'deep' response like some chemotherapy regimens, but that does not necessarily mean it is not effective. These are the subjects of ongoing trials of these agents.

Numbers taking ibrutinib by year

Table 19 below shows how the use of ibrutinib has changed over time among patients in the Registry. Since 2013, a total of 113 patients in the Registry have received ibrutinib as part of their treatment (in any line of therapy).

Ibrutinib was recommended for use on the NHS in the Cancer Drugs Fund from September 2017, which has led to a large increase in its use. Of the 113 patients in the Registry who have received ibrutinib as part of their treatment for WM, all except two have started ibrutinib treatment from 2017 onwards.

The peak year in the Registry for use of ibrutinib was 2018, when 52 patients in the Registry started ibrutinib treatment. Ibrutinib is recommended for any patient who has had at least one previous line of therapy, so the peak in 2018 may represent a large 'push' for prescribing ibrutinib for WM patients after it was included on the Cancer Drugs Fund.

It's important to bear in mind that this data from the Registry may not reflect the wider picture of how WM is treated with ibrutinib. We know from data obtained from NHS England that 616 WM patients have received ibrutinib on the CDF since September 2017.[15] The proportion that we have captured in the Registry reflects the numbers receiving ibrutinib that are at Registry centres.

Table 19: ibrutinib as a line of treatment

		Ibrutinib treatments	
		Count	**Percentage**
Year of treatment start	2013	1	0.9%
	2014	0	0.0%
	2015	1	0.9%
	2017	27	23.9%
	2018	52	46.0%
	2019	25	22.1%
	2020	7	6.2%
Treatment regimens		113	
Patients		**113**	

Lines of therapy prior to ibrutinib

Table 20 and Figure 14 below show, for the 113 people in the Registry who have been treated with ibrutinib, how many lines of therapy they had previously received.

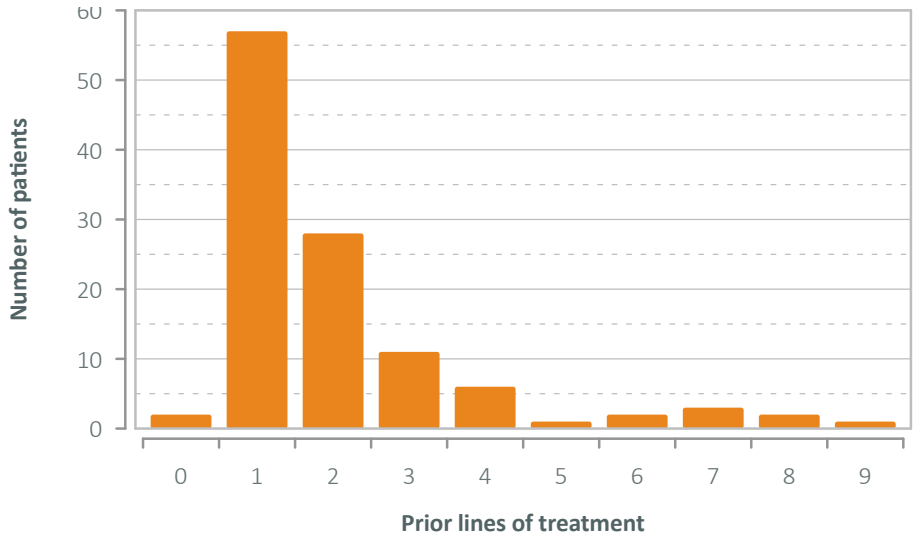
Just over half of patients who have been treated with ibrutinib (50.4%) had only one previous line of therapy, indicating it was used as a second-line therapy. Indeed, since its inclusion in the Cancer Drugs Fund in 2017, it is now the most popular choice for second-line therapy for patients in the Registry (see Figure 16 on page 44).

Nine patients who have received ibrutinib (8.1%) have had five or more previous lines of therapy. Only two patients (1.8%) had no prior lines of therapy before ibrutinib – most likely prior to its inclusion in the Cancer Drugs Fund in 2017.

Table 20: Lines of treatment prior to treatment with ibrutinib

Previous line of treatment	Patients treated with Iburtinib	
	Count	Percentage
0	2	1.8%
1	57	50.4%
2	28	24.8%
3	11	9.7%
4	6	5.3%
5	1	0.9%
6	2	1.8%
7	3	2.7%
8	2	1.8%
9	1	0.9%
All	**113**	

Figure 14: Lines of treatment prior to treatment with ibrutinib (n=113)



Response to ibrutinib

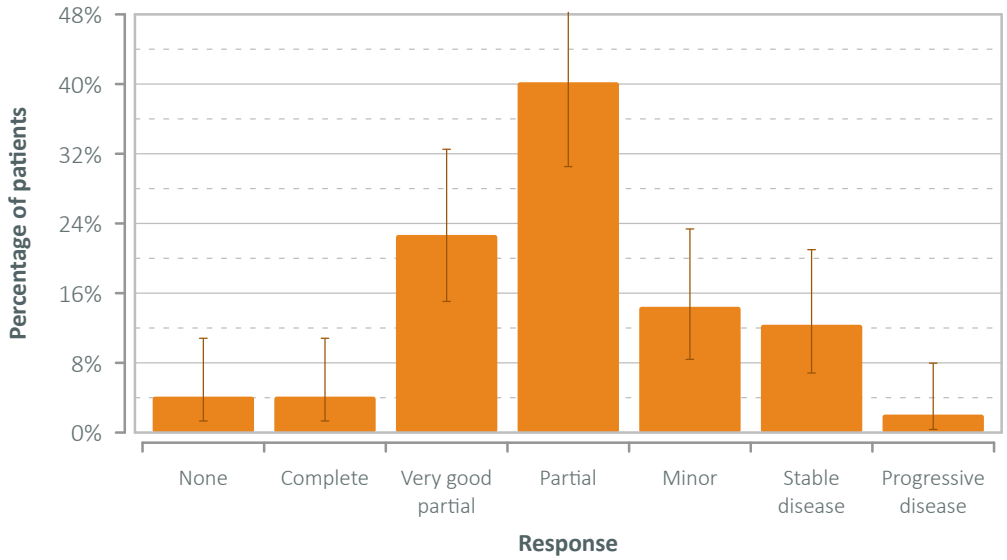
Table 21 and Figure 15 (overleaf) show response to ibrutinib recorded for the 113 patients who've received it as part of their treatment for WM. Note that because ibrutinib is taken indefinitely, these responses represent the 'best response' during that time.

Of the 97 patients who have a response recorded, 65 patients (67.0%) have had a partial response or better to ibrutinib (known as a 'major' response). Only two patients (2.1%) had 'progressive disease' recorded as their 'best' response during ibrutinib treatment.

Table 21: Response to ibrutinib treatment

		Count	Percentage
Response to ibrutinib	No response	4	4.1%
	Complete response	4	4.1%
	Very good partial response	22	22.7%
	Partial Response	39	40.2%
	Minor response	14	14.4%
	Stable disease	12	12.4%
	Progressive disease	2	2.1%
	Unspecified	16	
	All	**113**	

Figure 15: Response to ibrutinib treatment (n=97)



Duration of ibrutinib therapy

Table 21 below outlines for how long WM patients in the Registry have been on ibrutinib therapy.

The table shows that patients who went on to receive further treatments after ibrutinib had a shorter duration of ibrutinib therapy, compared to those who have had no further treatments following ibrutinib. The median average duration of ibrutinib therapy was 145 days for patients who had further lines of therapy, compared to 344 days for those with no further lines of therapy.

Table 22: Duration of BTKi therapy

		Duration of therapy / days	
	Count	**Median** (inter-quartile range)	**Average** (95% CI)
Ibrutinib			
No further therapy - no end date for BTKi therapy	85	762 (537-965)	756 (678-833)
No further therapy - end date for BTKi therapy recorded	13	344 (40-551)	319 (188-451)
Further line of treatment recorded	15	145 (98-279)	212 (125-299)

It's possible that this is connected to how the disease responded to ibrutinib. Patients whose disease had a 'poor' response to ibrutinib may have switched to a different therapy sooner, whereas those who have a 'good' response to ibrutinib may have continued taking it for longer and may have not needed any further treatment since. However, this is only speculation as we're not able to make a direct comparison between the response to ibrutinib and duration of therapy.

Where there is no end-date for ibrutinib therapy, and there is no further line of treatment recorded, the duration is defined from when ibrutinib treatment started up to the data cut-off date for this report of 1st September 2020. It therefore represents a 'snapshot' of the people who are currently still taking ibrutinib (on 1st September 2020). Of the 85 patients who are currently on ibrutinib, the median duration of their therapy so far is 762 days, just over two years.

Again, we might speculate that, because these patients have not yet stopped ibrutinib treatment, it indicates that ibrutinib is successfully controlling their disease and that they are tolerating the side-effects well. However, more analysis of the data in the Registry would be needed to confirm this. To enable this to be studied in more detail, new data entry fields have been added to the Registry to collect information about BTK inhibitor treatment duration, side effects, and reasons for discontinuation.

Patient perspective

The availability of ibrutinib for patients who require subsequent treatments has been a breakthrough, in many cases reducing the need for chemotherapy. It is good to see that so many patients have been taking it for a reasonable length of time and are able to control their disease, which is important when considering quality of life.

Harriet Scorer

Clinical perspective

BTK inhibitors are a game-changer for WM. We await further clinical follow-up of currently treated patients (in and out of trials), as well as new trials in which BTK inhibitors are combined with other agents and the development of the next generation BTK inhibitors. Their place in the treatment of WM is a work-in-progress.

Shirley D'Sa

Outlook for patients

WMUK

The UK charity for **Waldenstrom's macroglobulinaemia**

Overall survival

Survival rates for WM patients in the Registry are good. The five-year survival rates for patients diagnosed with or without symptoms are 86.6% and 94.5%, respectively. Younger age at diagnosis appears to be associated with improved survival in the short-term, compared to those diagnosed at an older age. It is important to remember that overall survival is not the same as WM-specific survival.

WM is a slow-growing cancer that people can live with for many years. This section provides information about survival of the patients in the Registry. It's not possible for an individual WM patient to tell from this data what will happen in their situation, as survival from WM (as with any cancer) depends on a range of factors.

Limitations

We should be cautious when interpreting this survival data from the Registry for a variety of reasons. Firstly, the patients in the Registry are mostly being treated at specialist centres, which could affect the survival rate in either one of two ways. On the one hand, it's possible that the patients are being treated at specialist centres because they have more complex and therefore 'higher-risk' disease. However, because these patients are being treated at specialist centres, they may in fact have a higher chance of survival compared to others, since they are benefiting from expert knowledge. Either way, it's unclear how representative the patients in the Registry are of WM patients more generally.

A second reason to interpret the data carefully is because treatments for WM have changed over the years that the Registry has been operating. As new treatments become available and routinely used in treating WM, survival and life expectancy should increase. Therefore, data collected so far on the survival of patients in the Registry should not be taken as the expected survival for people diagnosed today or in the years to come.

Another important thing to note is that the survival data represents overall survival, which is related to death from any cause – not just WM or its complications. It is normal for people diagnosed with WM to die from other causes, particularly as they reach older age.

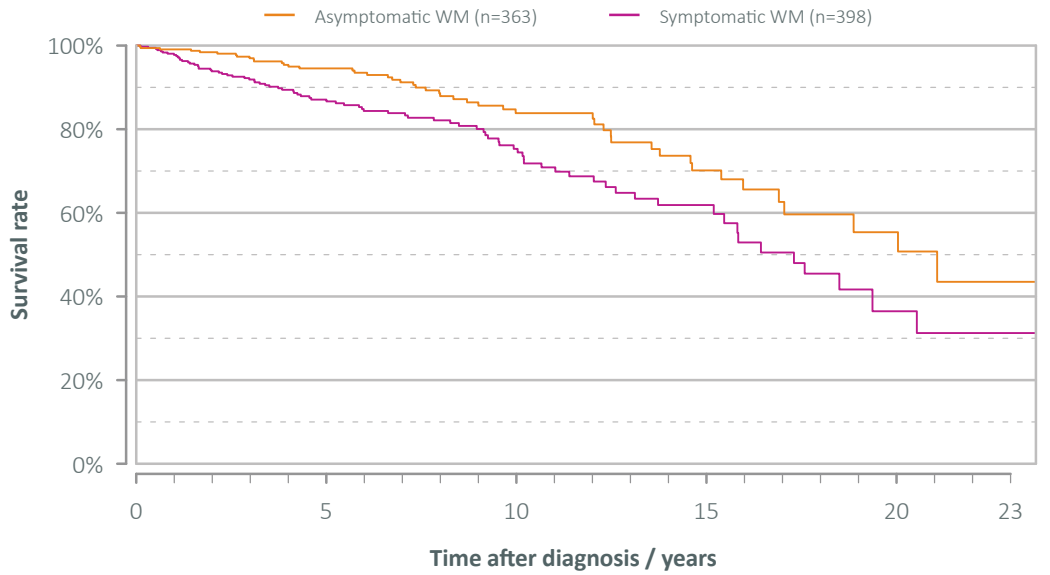
Overall survival by symptoms at diagnosis

Figure 16 overleaf shows overall survival over time for people diagnosed with WM in the Registry. Overall survival is the length of time for which patients live after diagnosis. The data is grouped by whether they were diagnosed with symptoms or without (asymptomatic).

Five- and ten-year survival rates

A common way to interpret survival data like this is by five-year and ten-year survival rate, which is the percentage of people who are alive at five or ten years after diagnosis. For WM patients in the Registry diagnosed with symptoms, the five-year overall survival rate is 86.6%, and for those diagnosed without symptoms (asymptomatic), it is around 94.5%. In other words, 86.6% of patients in the Registry diagnosed with symptoms, and 94.5% diagnosed without symptoms, lived for at least five years after their diagnosis.

Figure 16: Overall survival post-diagnosis, by symptomatic/asymptomatic



The ten-year overall survival rate for WM patients in the Registry diagnosed with symptoms is 75.3%, and for those diagnosed without symptoms is 83.8%.

How does this compare to other cancers? According to Cancer Research UK, the five-year net survival rate for people diagnosed with non-Hodgkin's lymphoma in England is 65.6% (10-year is 54.7%; ref 3), and for people diagnosed with any cancer is 54.3% (10-year is 49.8%[16]).

Note that these figures from Cancer Research UK are net survival (disease-specific survival), as opposed to the overall survival rates from the Registry data. Overall survival rates for people living with cancer are almost always lower than net survival rates. This is because overall survival rates include deaths from any cause, whereas net survival rates are adjusted so that they relate only to death from one specific cause, i.e. the cancer.

Therefore, it is reassuring that the overall survival rates for WM patients in the Registry are noticeably higher than the net survival rates for other forms of lymphoma.

Median survival

Another way of interpreting the survival data is by looking at 'median survival', which gives an idea of the average length of time WM patients in the Registry live for after diagnosis. Median overall survival is the length of time from diagnosis that half of the patients are still alive. Again, it is important to remember that overall survival relates to death from any cause, not just WM.

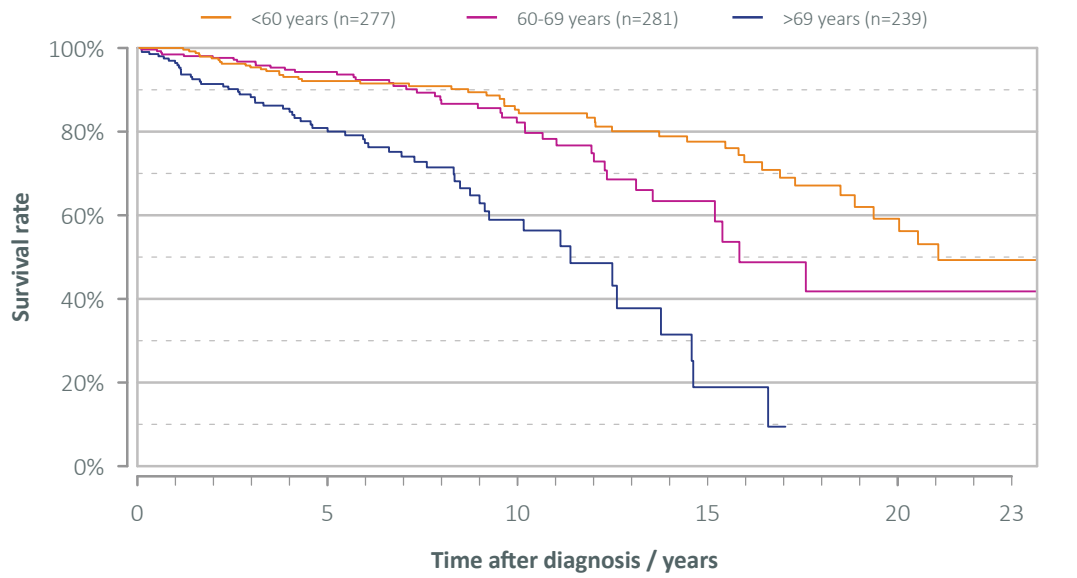
According to Figure 16 (looking at the time at which the bold lines cross the '50% survival' line on the graph), median survival for patients in the Registry diagnosed with symptoms is around 16 years, and for patients diagnosed without symptoms (asymptomatic) is around 21 years.

The International WM Foundation (IWMF) estimate that median survival for WM is around 14-16 years,[4] so the survival of patients in the Registry is in line with this, and maybe slightly better.

Overall survival by age at diagnosis

Figure 17 below shows the survival rates by age at diagnosis. The five-year overall survival rate for those diagnosed at 60 years or younger is 92.1%, for those diagnosed aged 60-69 is 94.3%, and for those diagnosed over the age of 69 it is 80.0%.

Figure 17: Overall survival post diagnosis, by age



Though it appears that those diagnosed younger have a more favourable outlook, we should be careful with interpreting this data. An important question for those diagnosed with WM is how the disease affects life expectancy, the age that someone can expect to live to after a diagnosis. Further analysis of the Registry data is needed before a conclusion can be reached on the impact of WM on life expectancy.

Overall survival by age and symptoms at diagnosis

People diagnosed with symptoms tend to be diagnosed at a slightly younger age than those who are diagnosed without symptoms: the average age of diagnosis with symptoms is 62.5 years, whereas the average age of diagnosis without symptoms is 64.1 years (data not shown). Despite overall survival declining as age at diagnosis increases, people diagnosed with WM without symptoms still have a slight advantage in terms of overall survival compared to those diagnosed with symptoms. The reason for this is not known.

High-grade transformation

WM can sometimes progress and develop into a more aggressive form of non-Hodgkin's lymphoma called diffuse large B-cell lymphoma. This is known as 'high-grade transformation'. If this occurs, well-being can change more quickly, and B symptoms are more likely to appear due to the faster growth of these cells.

In the Registry there are 24 patients with high-grade transformation recorded in their clinical record. 14 patients had their high-grade transformation recorded at diagnosis, in other words at the same time that they first presented with WM. For 23 patients they had high-grade transformation recorded as an indication for treatment. Five patients have high-grade transformation recorded in a follow-up record after treatment for WM.

The treatment for high-grade transformation includes different chemotherapy drugs to those used in WM. Notably, BTK inhibitors are not effective in transformed disease.

Patient perspective

"Survival estimates for people with WM appear to be significantly better than estimates for a number of other cancers.

This report has outlined the effectiveness of treatments for WM, with some very significant treatment options coming to the fore in the last few years. We know that options which could lead to further progress are being vigorously investigated, and the Registry can play an important part in this process.

We need to get a better idea of life expectancy factors for the many people diagnosed at an earlier age. Getting more data into the Registry is an important first step in relation to this aim."

John Mordue

Clinical perspective

"These data highlight that a diagnosis of WM is not a "death sentence". We have numerous good treatments available, so we need to ensure that our treatment is optimised for maximal response but importantly with as little toxicity that will allow WM patients to maintain a good quality of life."

Dima El-Sharkawi

Quality of life

Quality of life is important for WM patients, and is therefore essential data to collect in the Registry. Most patients report good quality of life overall, but for some, WM is having a significant effect on their lives. A significant proportion of patients report symptoms of anxiety and depression and poor overall health.

As WM is a slow-growing illness which patients can live with for a long time, maintaining a good quality of life is important. To reflect this, the Registry invites WM patients to submit information about their quality of life, sometimes known as Patient-Reported Outcome Measures, or PROMS. For the Registry there are four different questionnaires that WM patients can complete:

- **BIP (Brief Illness Perception questionnaire)**[17]
  The aim of this tool is to understand people's perception of their own illness: how WM patients feel about their illness, their relationship with their condition, and what they believe caused it. Its frequently used in medical research across lots of different illnesses.
- **EQ-5D (Euro-QoL five-dimensional questionnaire)**[18]
  This is a widely-used tool to measure quality of life across five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. As an additional part of the tool, people are asked to rate their health today on a scale from 0 to 100.
- **EORTC QLQ C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire)**[19]
  This is a widely-used questionnaire designed for cancer patients to assess their quality of life. It involves 30 questions on a range of topics.
- **HADS (Hospital Anxiety and Depression Scale)**
  This is a tool designed to measure symptoms of anxiety and depression among hospital patients. Scores for anxiety and depression are reported separately below.

These four questionnaires were selected to capture the range of people's experiences of WM across physical, psychological, and emotional dimensions. As they are existing questionnaires which have been previously tried and tested in similar groups of patients, the results can be considered reliable.

Patients who have data in the Registry are sent questionnaires four times a year via email, to track how quality of life changes over time and during their disease. WMUK has also run several campaigns to encourage WM patients outside the Registry to complete the questionnaires, to gather a broad picture of what it is like to live with the condition. Such data are of great importance to commissioning and regulatory bodies when they assess new treatments, as they provide a voice for patients to complement clinical data.

The Quality of Life data in the Registry is at an early stage of development, and much more work needs to be done with expert input to make sense of this data. However, we hope that this section of the report shows that it is feasible to acquire quality of life data from patients through the Registry, and that patients are clearly motivated to supply this data.

Number of forms completed

Table 23 below shows how many people have filled out these forms, and how many times they have done so (patients can fill out a questionnaire more than once). Taking the BIP questionnaire as an example, 88 patients have completed the BIP questionnaire once, 4 have completed it twice, 10 have completed it three times, and so on. 198 patients have completed it at least once, and in total the BIP questionnaire has been completed 780 times.

There is a significant number of people in the Registry who have not completed any quality of life questionnaires (top row of the table). This is partly because of a delay to fully implementing the quality of life module in the Registry after the clinical part of the Registry was rolled out.

Each questionnaire has been completed by between 198 and 255 patients. This shows a high level of commitment to the process of collecting quality of life data. Since patients can complete a questionnaire multiple times, each questionnaire has been completed more than 800 times in total (apart from the BIP questionnaire which has been completed 780 times).

Table 23: Quality of life questionnaires completed

		BIP	EQ5D	EORTC	HAD anxiety	HAD depression
Number of forms completed per patient	0	842	817	785	818	820
	1	88	108	135	112	110
	2	4	11	13	5	5
	3	10	10	11	9	9
	4	12	12	11	11	10
	5	14	12	13	15	16
	6	18	18	17	16	16
	7	10	14	11	14	13
	8	24	19	22	22	23
	9	14	15	16	14	14
	10	4	3	4	3	3
	11	0	1	2	1	1
	>=1	**198**	**223**	**255**	**222**	**220**
	Forms completed	**780**	**802**	**864**	**805**	**805**

Anxiety

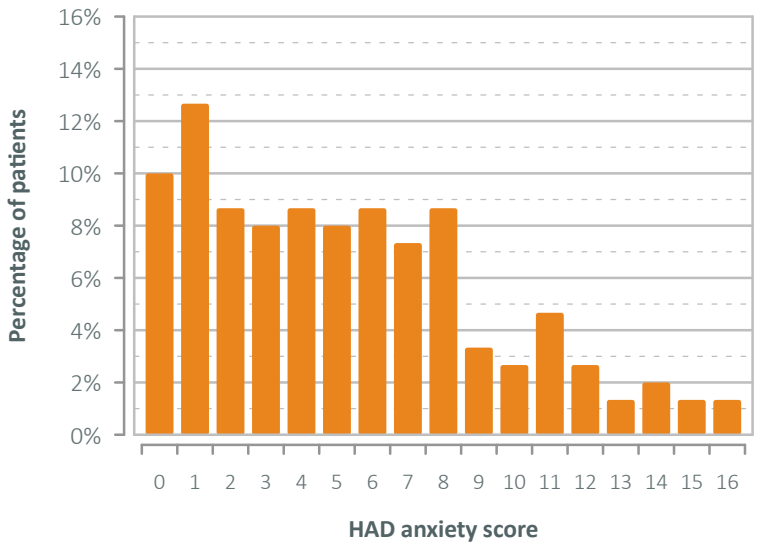
Figure 18 overleaf shows the range of Anxiety scores collected through the HADS questionnaire during August 2020. A total score of 8 or more points out of a possible 21 means considerable symptoms of anxiety, with 8-10 indicating mild anxiety, 11-14 moderate anxiety, and 15 and above indicating severe anxiety.

The figure shows that 72% of WM patients have scores lower than 8, indicating no anxiety. However, a significant number of patients (28%) have scores of 8 and above, indicating symptoms of anxiety.

According to the World Health Organisation (WHO), 4.2% of people living in the UK have an anxiety disorder.[20] Therefore, it appears that the number of WM patients living with anxiety could be significantly higher than the general population, although it is important to note that these are two different ways of measuring anxiety which may not be directly comparable. It's also important to note this data was collected during the COVID-19 pandemic, which may have contributed to higher levels of anxiety.

Further research is underway to correlate these scores with treatment status (on treatment, following treatment, or never treated) as well as other parameters, with the aim of devising helpful strategies to mitigate these anxiety levels.

Figure 18: HAD Anxiety score (n=150)



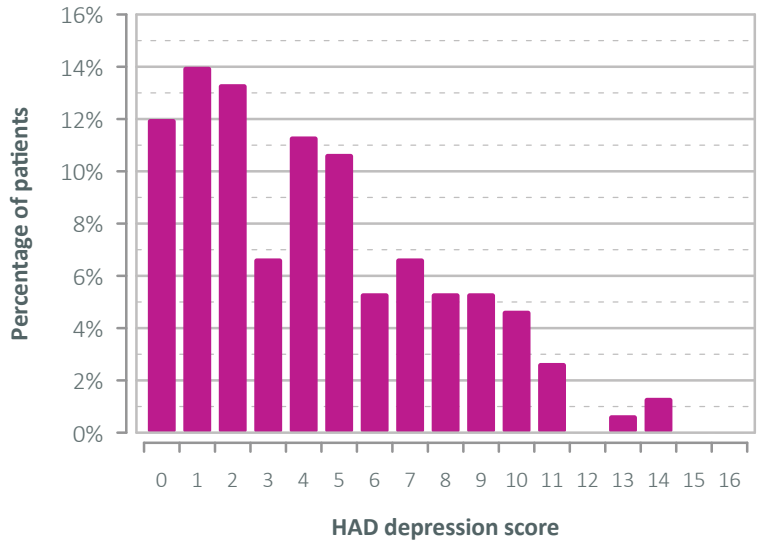
Depression

Figure 19 below shows the range of Depression scores collected through the HADS questionnaire returned during August 2020. Scores of 8 or more out of a possible 21 indicate that the person has considerable symptoms of depression, with 8-10 indicating mild depression, 11-14 moderate depression, and 15 and above indicating severe depression.

The figure shows 80% of patients have scores less than 8, meaning no depression. However, 20% of patients have scores of 8 and above, indicating elevated symptoms of depression.

According to WHO estimates, 4.5% of people in the UK have a depressive disorder.[20] Like the anxiety data above, this suggests that more WM patients are living with depression than the UK general population overall, though again, these are two different ways of measuring depression which may not be directly comparable. It's also important to note this data was also collected during the COVID-19 pandemic, which could have increased symptoms of depression in this group.

Figure 19: HAD Depression score (n=150)

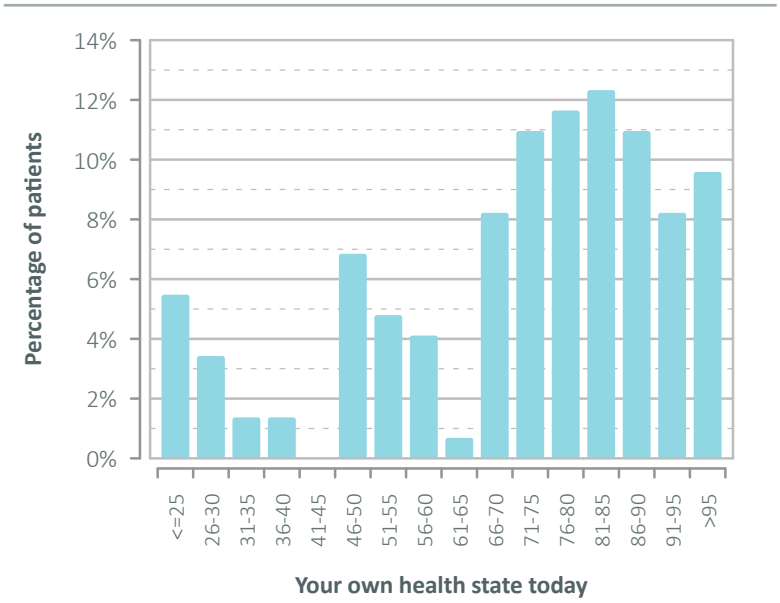


Quality of health today

Figure 20 below shows the EQ-5D 'health status' scores returned to the Registry during August 2020. This relates to part of the EQ-5D questionnaire which asks people to rate their health today on a visual scale from 0 to 100, with 100 being the best health and 0 being the worst health they can imagine.

The figure shows that most patients are reporting good health, with 71.9% reporting scores of 66 or above. However, a significant proportion (11.7%) report poor health, with scores of 40 or less.

Figure 20: EQ5D health status today (n=146)



Overlap of clinical and quality of life data

The data collected in the quality of life questionnaires, which are submitted by patients directly, is separate to that of the clinical Registry data submitted by hospitals. However, there is significant overlap between the patients included in both datasets.

As an example, of the 150 patients who returned HADS anxiety and depression questionnaires in August 2020, 63 patients (41%) are also included in the clinical Registry with a WM diagnosis. 62 of the 148 patients (42%) who completed an EQ-5D questionnaire in August 2020 are also a WM patient in the Registry.

This overlap between the two datasets raises the possibility in the future of combining the analysis of the two: for example, looking at the impact of different treatments on quality of life of patients in the Registry.

Patient perspective

"*It is encouraging that such a high proportion of patients are living well with WM. But it is of concern that a significant proportion of patients report anxiety, depression and poor health. It is clearly important that these conditions are also managed appropriately and proportionately.*

The quality of life data is a very important part of the Registry, and we need to encourage many more people to contribute, repeatedly and consistently. We may need to review what is being asked of people and to make this less burdensome if possible. And finally, there is a need to review how best to utilise the quality of life data to better promote understanding of WM, and so improve outcomes for patients."

John Mordue

Clinical perspective

"This is a really good size dataset on quality of life, which has often been overlooked in clinical trials in the past. Whilst the data we have now is a good snapshot at the present time, I think the power of this data will be seen in the future as patients send in repeated questionnaires, enabling us to start to see trends over time. It will be particularly useful to be able to link the quality of life data to that in the clinical registry."

Dima El-Sharkawi

Conclusions

In recent years, a greater consensus has been developed on how WM should be managed. New treatment options have emerged and are proving very effective, and as such, treatment for WM has a good record of success. Also, more experience has emerged as to how best to use existing treatments.

The insights obtained from the data in the Registry challenge some of the preconceptions of the disease, notably showing that WM is prevalent among people under 60, women and people from ethnic minority groups.

WM is a rare and unique condition, and this report illustrates how data can help us understand it better. We hope the report provides insights to help healthcare professionals improve the lives of people living with the disease. Further analysis of the Registry data will glean new insights into the experiences of different groups of WM, for example younger patients. In that regard, we plan to continue to publish reports from the Registry, and invite researchers to use the data to publish their own academic papers and analyses.

We hope too that our commercial partners will find this report helpful as they seek to gain approval for their therapies within the UK NHS. Real Word Evidence (RWE) is key to filling the gaps left by a dearth of clinical trials and lack of long-term follow up.

It is also important to contribute to the pool of RWE so that commissioning bodies such as NICE are better equipped in their decision-making processes as they appraise promising novel therapies that have significant financial implications for the NHS. Although not easy to demonstrate, enabling people affected by WM to remain healthy and active members of society through judicious use of such therapies, means more productivity by those individuals and probably less healthcare resource use.

However, we have to acknowledge that the data in the Registry are skewed towards people linked to specialist hospitals, which have more experience in managing more aggressive or complex disease. We are constantly looking at ways to improve how we collect Registry data, and how we can reduce the burden of data collection and incentivise engagement. We hope this will boost input from people linked to non-specialist services, to understand the wider picture of WM.

Patients themselves can also make a valuable contribution to our understanding of the disease. We would encourage everyone with WM to speak to their doctors to make sure that their hospital is signed up to contribute data to the Registry, either directly or via connection with specialist centres. Patients can also make a difference by submitting Quality of Life questionnaires – email registry@wmuk.org.uk to sign up to receive questionnaires every three months.

WMUK has recently been conducting a strategic review of the Registry, to identify how best to build upon the successes and lessons learnt so far to improve the lives of people living with WM. Key aims for the future include increasing our understanding of the effects of the disease and treatment on patients, and using the data we already have to support the licensing of new treatments for patients on the NHS. To help do this, we will continue to focus on collecting comprehensive in-depth patient data to complete our data sets. We will also secure the long-term future of the Registry through good governance and financial planning.

We hope this will ensure that the Registry plays a significant part in helping people with WM to live well with the condition for as long as possible.

Finally, we wish to give our thanks once more to the people living with WM and the healthcare professionals who look after them for taking the time to submit data to the Registry.

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