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INSIDE THIS ISSUE

A TOOLKIT FOR UNDERSTANDING THE TREATMENT OF WALDENSTROM MACROGLOBULINEMIA

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Dr. Jonas Paludo is an Assistant Professor of Medicine and Oncology at Mayo Clinic in Rochester, MN. He received his medical degree from the Universidade Federal de Ciencias da Saude de Porto Alegre (UFCSPA) in Brazil. He then completed his internal medicine residency, followed by Hematology/Oncology Fellowship and Advanced Lymphoma Fellowship at Mayo Clinic in Rochester.

Dr. Paludo is a member of the Lymphoma, Cell Therapy, and Stem Cell Transplantation Disease Groups at Mayo Clinic. His research work focuses on translational and outcomes research in lymphoid malignancies, with dedicated interest and work in Waldenstrom macroglobulinemia. He is also the principal investigator in several clinical trials, ranging from early therapeutic trials to platform projects exploring the use of wearable devices and remote patient monitoring in the treatment of patients with cancer.

Receiving the diagnosis of Waldenstrom macroglobulinemia is a life-changing moment. Understandably, once the diagnosis is established, there is a sense of urgency in "doing something about it." That is when you are faced with a multitude of options and a new array of unfamiliar terms and concepts. You are left picking among apples, oranges, lemons, bananas, and pears…all options look similar, yet they are so different.

If you are not lost yet with a bad attempt at a fruit salad analogy, keep reading as we review some important concepts and terms related to the treatment of WM. The goal is to provide you with a toolkit to understand how therapies are evaluated, how other factors impact treatment (or no treatment) decisions, and how you can be empowered for a more engaged conversation with your doctor regarding YOUR treatment. The intent is not to dive deep into dozens of different drugs but to help you understand how to view and think about the current state of WM treatment.

> *Spoiler alert: When it comes to treatment for WM, there are no winners or losers; there is no single best option for everyone despite our personal preferences. The best treatment for one patient may not be the right alternative for another. The best drug for you yesterday may not be the ideal choice tomorrow. While this sounds complicated, it is a wonderful problem to have. It is the consequence of decades of hard work to generate multiple treatments to choose from, which finally allows for a personalized treatment strategy in WM.*

Let us start with the most important question: When should you be treated for WM?

When to consider treatment

You have just been diagnosed with WM, a rare form of lymphoma, and told by your doctor that no treatment will be needed, just come back in a few months. Can this be right?

Observation, or watch-and-wait, is the preferred approach for asymptomatic patients with WM (a.k.a. smoldering WM), who represent 15-25% of patients at the time of diagnosis. Since WM

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is a very slowly progressive and incurable form of lymphoma, and since early initiation of therapy has not been shown to prolong survival, there is no advantage to undergoing treatment if WM is not causing you any symptoms or putting your health at immediate risk. Initiation of therapy in this setting will not improve your quality of life. As a matter of fact, quality of life will likely worsen given the side effects from the drugs, the inconvenience of frequent appointments, and the associated financial cost. The same approach is valid when deciding on the time to resume therapy in a previously treated WM patient.

As a general principle, the impact of WM on your quality of life and overall health must outweigh the trouble of undergoing treatment. At the 2nd International Workshop on Waldenstrom Macroglobulinemia (IWWM) in 2002, a panel of experts agreed to the following guidelines on when treatment should be initiated:

- presence of constitutional symptoms (fever, drenching night sweats, unintentional weight loss, fatigue)
- symptomatic enlarged lymph nodes and/or spleen
- low blood counts (hemoglobin < 10 g/dL, platelet count <100,000/μL)
- symptomatic hyperviscosity
- symptomatic cryoglobulinemia, cold agglutinin disease
- symptomatic peripheral neuropathy
- presence of systemic AL amyloidosis
- renal insufficiency from WM

Feeling squirrely and on the fence about treatment...
Drawing by Diane Mazza

Please note that the amount of IgM protein by itself is **not** a determinant of the timing of treatment initiation. The IgM protein level is an important test which should be monitored regularly, as it correlates to the amount of lymphoma. The pace of increasing IgM levels over time could be regarded as the speed with which you are moving toward the point when treatment initiation is needed—the faster it is rising, the sooner you will need to start treatment. This is helpful in guiding how often you should be seen by your doctor during the watch-and-wait phase.

When fatigue is the sole reason to consider therapy (assuming that other causes of fatigue have been excluded), it can be challenging to decide the ideal timing of treatment initiation. I usually fall back to the general principle above: the impact of fatigue on your quality of life must outweigh the trouble of undergoing treatment. Otherwise, treatment will cause more problems than it remedies.

As the old saying goes, "If it isn't broken, don't fix it."

Understanding how treatment efficacy (effectiveness) and outcomes are measured

You have just arrived home after seeing your doctor. You have been having more symptoms over the last few months, and labs show that your hemoglobin has dropped below 10 g/dL. The time for therapy has finally arrived. Your doctor mentioned a few different treatments to choose from and how "oranges" have a higher response rate, but "apples" provide a longer remission. You are trying to learn more about your choices, but it is hard to understand them when everything you read seems to be in a foreign language.

Before we even talk about different drugs, let us review how the efficacy and outcomes of different therapies are measured. Thankfully, the same rules apply no matter what "fruit" is being evaluated.

One way to measure the treatment efficacy is by measuring how much of the cancer was eliminated and how often that happens. In medical lingo, this is called response to treatment. As mentioned earlier, the IgM protein correlates well with the amount of disease burden and serves as the cornerstone of response assessment in WM.

At the 6th IWWM (in 2010), a panel of experts defined the criteria to classify response to therapy, from the deepest response (complete remission) when no signs of WM are detected, to progressive disease when the amount of lymphoma is increasing. The table on the following page is a simplified version of the criteria defined in 2010 that is still applicable today.

When reporting the effectiveness of a treatment, studies will mention the proportion of patients achieving each response and/or the proportion of patients achieving at least a certain degree of response. For example, when treated with "oranges," let's say that 80% of patients will achieve at least a major response (PR + VGPR + CR), with 5% achieving complete remission. Please note that the 5% of CR is included in the 80% major response rate. Response rate is used to assess

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Response category	Definition
Complete response (CR)	No signs of WM detected - IgM protein within normal limits - No evidence of monoclonal protein by immunofixation - No evidence of WM in the bone marrow (by biopsy) - Any previously enlarged lymph nodes or spleen are now back to normal size
Very good partial response (VGPR)	Very good improvement - IgM protein decreased by ≥ 90% compared to pre-treatment level - Monoclonal protein can still be detected by immunofixation - Any previously enlarged lymph nodes or spleen are now back to normal size - No new signs or symptoms of active disease
Partial response (PR)	Good improvement - IgM protein decreased by ≥ 50% but < 90% compared to pre-treatment level - Monoclonal protein can still be detected by immunofixation - Any previously enlarged lymph nodes or spleen have decreased in size, but not necessarily back to normal - No new signs or symptoms of active disease
Minor response (MR)	Minor improvement - IgM protein decreased by ≥ 25% but < 50% compared to pre-treatment level - Monoclonal protein can still be detected by immunofixation - No new signs or symptoms of active disease
Stable disease (SD)	No changes - IgM protein decreased by < 25% or increased by < 25% compared to pre-treatment level - Monoclonal protein can still be detected by immunofixation - No new signs or symptoms of active disease
Progressive disease (PD)	Worsening of disease - IgM protein increased by ≥ 25% compared to lowest point - New signs or symptoms of active disease

the frequency or proportion of patients that benefit from a specific treatment.

Another way to measure efficacy of a treatment is by measuring the duration of the benefit obtained with the treatment. In medical lingo, these are described as time-to-event assessments and apply to any cancer type. It is a measure of the time from initiation of treatment until a defined event of interest. It's reported either as an average (e.g., patients treated with "apples" had an average progression-free survival of 12 months, meaning that the average time patients treated with this drug were alive and free from a rising IgM level was 12 months), or as a proportion at a time point (e.g., patients treated with "oranges" had a three-year overall survival of 90%, meaning that 90% of patients were alive at three years after initiation of therapy).

When the event of interest is the initiation of subsequent treatment, the measurement is called time-to-next-therapy (TTNT). When the progression of disease or death from any cause is the event, it is called progression-free survival (PFS). When death from any cause is the event, then overall survival (OS) is the term used. The table below lists the most common measures used when comparing cancer treatments.

Some differences here are subtle, but let us review two relevant points when considering WM:

1. PFS vs. TTNT: TTNT is a more relevant measurement than PFS in WM. Most patients with WM will meet the definition of progressive disease (an event in PFS) based on a rise in IgM protein by > 25% from nadir while still asymptomatic. As discussed previously, a rising IgM protein level does not determine when something needs to be done. Symptoms determine when a new treatment is needed. Symptoms from WM and treatment initiation are the factors that impact your quality of life. Therefore, as a general principle, measuring the time to require the next treatment is more important than measuring the time to disease progression. As in all medical discussions, there are exceptions to this.
2. OS vs. DSS: Considering that WM is an indolent disease of the elderly (average age at diagnosis of 70 years) and most patients with WM die from something else, disease-specific survival provides a more accurate impact of WM on the survival of these

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Measurement	Definition/Event of Interest
Overall survival (OS)	Time from the initiation of treatment to death from any cause
Disease-specific survival (DSS)	Time from the initiation of treatment to death from a specific disease (i.e., WM)
Progression-free survival (PFS)	Time from the initiation of treatment to disease progression (defined as a 25% increase in IgM level) or death from any cause
Duration of response (DOR)	Time from the first documentation of response to disease progression
Time-to-next-treatment (TTNT)	Time from the initiation of treatment to the next therapy

patients. On the other hand, since most WM patients die from something else, OS provides a more precise idea of the general life expectancy of WM patients.

Additional important factors to consider—the other side of the coin

We have come a long way, and I have no intention of boring you with a long list of response rates, PFS, and/or OS for dozens of different treatment regimens and drugs. With the knowledge you have gained, you can interpret these numbers for yourself. Several nicely done reviews have compiled this data and are publicly available (I have included a few in the references at the end). Your doctor should also be able to share these numbers with you when discussing different treatment options.

> *Spoiler alert: Very few studies directly comparing different treatments are available. Significant effort has been put into studies indirectly comparing different treatments, which offer the best available data to date, but these have inherent biases. With a cautious appraisal, it appears that the most-used treatment regimens currently in practice have comparable efficacy.*

Next, I would like to highlight other factors, as important as the treatment efficacy, that must also be considered when deciding on a treatment strategy.

Duration of treatment

With a great number of treatment options available, categorizing them by the duration of treatment as the first branching point makes the most sense from a patient's perspective.

Fixed-duration regimens, as the name implies, are given for a pre-specified period, often ranging from four to six months. This category includes chemotherapy-based regimens, such as BR (bendamustine + rituximab) or DRC (dexamethasone + rituximab + cyclophosphamide); it also includes BDR (bortezomib + dexamethasone + rituximab) and rituximab monotherapy. Continuous regimens, on the other hand, are given for as long as the treatment is working, or for as long as the side effects are tolerable, often going on for longer than a year. This category includes targeted therapy-based regimens, such as BTK inhibitors (ibrutinib +/- rituximab, acalabrutinib, zanubrutinib) and BCL2 inhibitors (venetoclax).

The tolerabilities of fixed-duration or continuous regimens are generally comparable, but they often differ on side effect profiles, as further discussed below. Route of administration (oral vs. intravenous) is another point to consider.

Once a decision has been made regarding the preferred duration of therapy, I would next look at the side effect profile of the different regimens or drugs within the group.

Side effect profile

Side effect profile is the medical lingo that refers to the side effects of a treatment. Each drug has a unique side effect profile, but some side effects are the same across different drugs, and similar drugs can have different side effects. For example, different chemotherapy drugs share the same side effect of causing low blood counts and increased risk of infections. The risk of developing atrial fibrillation (abnormal heart rhythm) is different between ibrutinib and zanubrutinib even though these drugs are both BTK inhibitors.

When fine-tuning the selection of a treatment, your doctor will review the side effect profile with you. Your preferences and other medical problems, which could be aggravated by specific side effects, should be taken into consideration when selecting the therapy. For example, if you have a history of peripheral neuropathy from diabetes, a treatment regimen containing bortezomib is less desirable, given that peripheral neuropathy is a common side effect of this drug. Uncommon, but serious, side effects or complications, such as heart toxicity or risk of second cancer, should also be discussed.

While the incidence and severity of individual side effects can be measured and reported as a proportion of patients experiencing it for different drugs, the comparison of side effect profiles within drug classes is a difficult exercise and not easily quantifiable.

Clinical trials

Clinical trials should always be considered when deciding on the best treatment strategy. They provide a treatment

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option that would otherwise not be available, while reserving standard treatments for later use. Keeping in line with the discussion above, the experimental treatment characteristics (preliminary efficacy, side effect profile if known, and duration of administration) should be factored in while selecting the best next treatment.

Bringing it together

I hope this article helped you understand how treatment options are appraised, gave you a framework on how to weigh treatment options, and provided you a glimpse of the most important considerations that need to be made before choosing a treatment. This was not meant to be a comprehensive review, but rather just an introduction to this topic. Many other important aspects surrounding treatment, such as financial burden, disruptions to work/family, impact on caregivers, and mental health, are not covered here. Most larger institutions and cancer centers have counseling staff who can help with some of these considerations. Take advantage of these resources if available.

Another topic not covered in this article and integral to treatment selection are the goals of therapy. While every therapy should aim to improve symptoms and quality of life in this indolent and incurable disease, how to achieve that goal by balancing symptom control, depth of response, and toxicity remains a major topic of debate in WM.

As you have realized by now, there is no simple answer to "What's the best treatment for WM?" or "What's the new go-to treatment?" Be wary of generic or dogmatic answers. The choice of therapy must be individualized, at least taking in consideration efficacy, duration of therapy, side effect profile, and patient's preference.

Partnering with a doctor knowledgeable about this disease is key to formulating YOUR treatment strategy, but there is also no true personalized treatment without the patient's input. I hope you are feeling more empowered to have a productive conversation with your doctor when the time for treatment arrives.

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THE IWMF WM GLOBAL PATIENT INITIATIVE: REVOLUTIONIZING WM EDUCATION AND SUPPORT

By Carl Harrington, IWMF President Emeritus and Chair, Global Patient Initiative

Do you remember how devastated you were when you were diagnosed with an incurable cancer that you couldn't pronounce? Do you remember your search for information and support to help you deal with this unwelcome intrusion?

While the IWMF has done a pretty good job so far, the IWMF WM Global Patient Initiative is intended to revolutionize WM patient education and support, just like the IWMF-LLS Strategic Research Roadmap revolutionized WM research efforts.

As Chair of the Global Patient Initiative, let me give you an inside peek into how this Initiative is coming together to help both newly diagnosed and veteran WM patients and caregivers as they deal with the ups and downs of a life with WM.

Who are our partners?

The IWMF has partnered with an all-star crew of patient advocacy organizations: Our Working Partners are the Leukemia & Lymphoma Society (LLS), Cancer*Care* (CC), Lymphoma Coalition (LC), Lymphoma Research Foundation (LRF), Cancer Support Community (CSC), and National Comprehensive Cancer Network (NCCN), while our Advocacy Partners are the American Cancer Society (ACS) and Stand Up to Cancer (SU2C). To keep the initial steps manageable, we are starting in the US and then expanding globally.

What are the goals?

The four goals of the initiative are to:

- Ensure easy access to accurate, current, and reliable information about WM to enhance the overall quality of life for WM patients – Right now, a WM patient or caregiver who googles WM can find a wide variety of conflicting information, even about how long one might expect to live. You will see 3-5 years and 16-20 years. As a WM patient, I certainly prefer the 16-20 year estimate (which is the accurate one). I bet you agree!
- Bring about more effective and efficient delivery of programs and reduce unnecessary duplication of effort – Currently, we and our partners provide programs that conflict with one another and draw upon the same speakers, such as Drs. Steven Treon, Stephen Ansell, and Jorge Castillo. We plan to coordinate our activities and reduce the strain on our generous speakers and the duplication of topics, so that more topics of use to patients can be covered.
- Provide skills ("literacies") to enable WMers to best utilize the information produced – To make sure patients and caregivers can best use what we create, we will focus on four skills that I'll describe in a minute.
- Build awareness of WM and WM resources among WM health care professionals and patients

From left to right: Carl Harrington, IWMF; Carl Lisman, IWMF; Paul Kitchen, IWMF; Cristin Barnett, Leukemia & Lymphoma Society; Lorna Warwick, Lymphoma Coalition; Karen Costello, Cancer Support Community; Karen DeMairo, Leukemia & Lymphoma Society; Newton Guerin, IWMF; Christine Verini, CancerCare

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worldwide – Since patients usually first hear about WM when they are diagnosed, it is critical that doctors, nurses, and other health care professionals know about the IWMF and refer patients to us as soon as they are diagnosed.

What are those "literacies" or skills?
We're going to focus on four areas:

- Health literacy - This is the degree to which individuals have the capacity to obtain, process, and understand basic health information needed to make appropriate health decisions. This does not necessarily correlate with how well-educated you are. Under the leadership of Debra Entin, a new hire at the IWMF, we will make sure that all our booklets, communications, and website are easily understood by "jus' folks," i.e., a person who didn't go to med school—someone like you or me. Debra is a master of simple language and a genius at organizing material so that it's easy to understand.
- Financial literacy - Let's face it, WM treatments, especially the oral drugs, are expensive. We will continue to promote access to co-pay assistance via the LLS, Patient Access Network (PAN) Foundation, and National Organization for Rare Disorders (NORD), but we'll expand our resources by partnering with Cancer Support Community, which has financial counselors available. (Don't rush to call them now, as we'll have that in place near the end of the year.) If you do want some help now, go to *https://iwmf.com/financial-assistance/*.
- Communication with your medical team – As part of this project, Dr. Morie Gertz of the Mayo Clinic has updated two of his articles. They are also now part of the InfoPak that every newly diagnosed patient can receive from the IWMF:

  Getting the most from my provider visit.
  https://iwmf.wpengine.com/wp-content/uploads/2020/10/Gertz7Provider.pdf

  Should I get a second opinion?
  https://iwmf.com/wp-content/uploads/2021/02/GertzSecond-1.pdf

  On a related note, we will also be expanding the number of doctors listed in the IWMF Physician Directory. Stay tuned for that!
- Digital literacy - All the material on our website is available 24/7. And most of our publications are available in at least seven languages. But that doesn't do much good if you don't have the computer skills or computer access to get to the information. Sara McKinnie, IWMF Manager of Meetings and Partner Engagement, is leading a project with a new partner, Patient Empowerment Network (PEN), to enhance the digital skills of WMers. Since many WM patients are diagnosed at 70 years or older, lots of us can use the help. You'll hear more about this, but PEN uses "digital sherpas"—live guides who can shepherd you through the technical aspects. If the sherpas in Nepal can get people to the top of Mt. Everest, our sherpas will be able to give you more confidence in using the internet.

OK, that sounds good, but remind me what the IWMF-LLS Strategic Research Roadmap did?
Our old process "worked" like this. Research proposals:

- Arrived randomly throughout the year
- Were evaluated by lay IWMF members
- Requested random amounts
- Were written in individual styles, making comparisons difficult
- Focused on random topics with no overall strategic goals

Our Board was always a little afraid to approve a project, because something better might come along. Now, the IWMF Strategic Research Roadmap process works like this:

- An RFP (Request for Proposals) is issued yearly based upon five strategic pillars developed by the best WM research minds in the world
- The research proposals are evaluated by leading WM experts, led by Dr. Stephen Ansell of the Mayo Clinic, using a National Institutes of Health (NIH) process
- The proposals are written in a standard style, for standard amounts of funding and time
- There are three separate grant types: Roadmap funding ($480,000 for two years); Robert A. Kyle Career Development Awards ($157,500 for two years); and IWMF Research Seed Grant Initiative ($90,000 for one year)

And how has the Roadmap worked?
"Really well" is the short answer. Here are a few highlights:

- WM patients are leading longer, higher quality lives with fewer side effects and longer, deeper remissions. Our projected lifespan after diagnosis of 3-5 years has become 16-20 years, and four drug treatment options have become 45+.
- There are about 7,000 rare diseases in the US affecting 30 million people, or about 9% of the population. Fewer than 10% of these rare diseases have US Food and Drug Administration-approved treatments, but WM has two (ibrutinib and zanubrutinib)!
- Of the 25 research projects approved under the Roadmap, 17 are from researchers we never funded before, 16 are from institutions we never funded before, and 10 are international (Canada, Germany, France, Italy, the Netherlands, and Spain). Put another way, we are now getting the best minds in WM globally to work on better treatments and a cure for our disease.

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- Research funding is also global, as donors include the IWMF, LLS, WMFC, WMUK, WM France, an individual in China, and the Leukaemia Foundation of Australia.

Well, I'm glad the Roadmap is working, but what else is happening on the WM Global Patient Initiative?
So far, the benefits of the WM Global Patient Initiative include:

- Strengthened relationships in the WM community – We've had four Zoom calls with our partners and an all-day meeting in New York City on August 11. As you well know when you build trust with people, good things happen! We've agreed to set up a sub-group with LLS, CC, and LRF, headed by Sara McKinnie, to coordinate activities and prevent duplication of effort. And we've developed new partnerships with Patient Empowerment Network (PEN), American Community Cancer Centers (ACCC), and Scientific Education Support (SES). The IWMF page at SES is here: *https://scientificeducationsupport.com/updates/the-international-waldenstrom-s-macroglobulinemia-foundation-and-scientific-education-support-announce-new-strategic-collaboration-in-waldenstrom-s-macroglobulinemia*
- Creation of a WM Communication Principles document – Each of our partners sent a complete list of their WM materials to me. Our partners asked me if I could summarize the differences—I looked at the huge amount of material and thought I could do that by 2029 or so! Instead, I created a two-page WM Communication Principles document with Dr. Stephen Ansell of the Mayo Clinic and Dr. Steven Treon of the Dana-Farber Cancer Institute to guide all future WM publications by any partner. This makes sure that questions such as "How long I will live?" "Will my kids get WM?" and "What is IgM flare caused by rituximab?" get covered consistently.
- Creation of a Physician's Guide – Our partners said "Hey, this is great. How about turning it into something for community oncologists who don't see many WM patients?" Fortunately, Drs. Jorge Castillo and Shayna Sarosiek of Dana-Farber Cancer Institute agreed to create a physician's guide to answer common questions about Waldenstrom's macroglobulinemia.

Is anything else coming?

- We'll be doing a major mailing in the fall to about 18,000 community oncologists and nurses who work in blood cancer. This mailing will be endorsed by six organizations: IWMF, LLS, LRF, LC, CC, and CSC. It will include a cover letter, the Castillo/Sarosiek document, and the "About the IWMF" brochure. If you want to share this mailing with your doctor, check the *iwmf.com* website for the link, as it was not yet available at *Torch* press time.
- A joint IWMF-LLS podcast to doctors and nurses in September will support this mailing. This podcast will feature Dr. Sarosiek.
- Scientific Education Support from the United Kingdom will create a WM section of the Lymphoma Hub, which is a global website targeted to medical professionals. It reaches thousands of oncologists, hematologists, and medical professionals.
- The IWMF and LLS will jointly offer Continuing Medical Education (CME) on WM in 2023. This will be our first large-scale education effort targeted to the medical profession.
- Also in 2023, we will be expanding our efforts to our affiliates and to the rest of the world, with our initial focus to be on Europe, Australia, Canada, South Africa, India, New Zealand, and China.

What will the WM Global Initiative accomplish?
We didn't know all the benefits that would occur when we started the IWMF-LLS Strategic Research Roadmap in 2015. And we don't know all the benefits that will accrue from the WM Global Patient Initiative. We just know that the world will be a better, safer place for the WM community worldwide.

We also know that it's a great fit with these Compelling Intentions from the IWMF Strategic Plan:

- Become the global thought leader and authoritative source of information and resources in WM
- Ensure every doctor and nurse worldwide who works in blood cancer knows about the IWMF and the resources we offer
- Ensure every person diagnosed worldwide with WM knows about the IWMF and the resources we offer
- Expand worldwide awareness of WM and the IWMF

The WM Global Patient Initiative is designed to close the book on duplication of effort, to slam the door on misinformation, to enhance the cooperation among patient advocacy groups globally, and to create better tomorrows for the WM community. Please join us. Ask your friends and family and medical team to join you in supporting the IWMF.

If you have any comments or questions, contact the IWMF office at *info@iwmf.com* or post something on IWMF Connect at *https://groups.io/g/iwmfconnect/post* or on the Facebook WM Support Group at *https://facebook.com/groups/wmsupportgroup.*

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MARCIA KLEPAC, WINNER OF THE JUDITH MAY VOLUNTEER AWARD FOR 2022

By Peter DeNardis, IWMF Trustee and Chair of the Board

It is with great pleasure that we announce Marcia Klepac as the 2022 recipient of the IWMF's Judith May Volunteer Award, which was presented to her in August at the IWMF Educational Forum.

The annual award recognizes the spirit of volunteerism that Judith May so aptly demonstrated throughout her 20+ year career with the IWMF, including leadership in member services, research, advocacy, and as president of the IWMF from 2005 to 2012.

Marcia was diagnosed in January 2001 and began treatment in August 2002. Since then, she's had 12 different treatments, including eight clinical trials—all in the quest to get her WM symptoms under control. In fact, her current health status is better than at any time since diagnosis, due to the combination therapy of ibrutinib (140 mg) and venetoclax (400 mg), with her IgM at its lowest point in 21 years.

She began volunteering for the IWMF in 2007 as a support group co-leader with Shari Hall for Eastern Ohio, WV, and Western PA. Marcia also served on the IWMF Board of Trustees for six years between 2012 and 2018 and worked hard to set up a strong US support group network and develop education and training opportunities for support group leaders in the US and internationally.

You might find it interesting to know that Marcia had talked to the founder of the IWMF, Arnie Smokler, in 2000 when her father was diagnosed with WM just six months before she was. While she never got to meet Arnie in person, she did meet the subsequent IWMF President, Ben Rude, at her first Ed Forum in 2002.

In her professional career, Marcia worked in various nursing positions and as a nursing instructor. She took a long hiatus (12 years) when her children were little and then worked as a diabetes educator, coordinating at the graduate school level in health education for the next ten years. However, because of WM complications, she had to retire from that role in 2001. She fully planned to return to the health field but had to contend with just too many relapses. Managing WM became her "part-time job" with extensive travel to clinical trials.

Marcia Klepac and the Judith May Volunteer Award

Marcia continues to serve as co-leader of her IWMF support group and does her best to encourage fellow WMers to be strong advocates for their own health. She lives with her husband Glenn in Pittsburgh, has two children, Jason and Lauren, and one new grandson, Otto. She loves gardening and travel (although, like for many of us, travel is on temporary hold due to COVID) and is passionate about patient empowerment and social justice issues.

Thank you, Marcia, for doing such an amazing job of supporting all of us over the years. It is through your efforts that the IWMF support group network is as strong as it is today and that the meetings are as effective as they are in providing comfort, support, and education to WM patients and caregivers.

Like other Judith May Volunteer Award recipients, Marcia is the perfect example of the many, many unsung heroes in the IWMF community who play critical roles in ensuring that the IWMF continues to excel in its efforts to support everyone around the world affected by WM, while advancing the search for a cure.

Everyone is encouraged to do their part to help their fellow WM patients and caregivers on their journey with the disease—working together, we can find comfort and support, and someday achieve a world without WM. If you're interested in volunteering your talents, drop the IWMF a note at: *https://iwmf.com/volunteerism/*.

IWMF ANNOUNCES 2022 RESEARCH GRANT RECIPIENTS

By Glenn Cantor
IWMF Trustee and Science Editor

The IWMF is pleased to announce seven new research grant awards, totaling $1,154,000, in 2022.

The cornerstone of the IWMF research portfolio has been the IWMF-LLS Strategic Research Roadmap grants. These are major awards (up to $480,000) in targeted research areas that have been identified through strategic discussions with WM experts, the IWMF, and the Leukemia & Lymphoma Society (LLS). Grant proposals are rigorously evaluated by the IWMF Scientific Advisory Committee, composed of about 20 worldwide WM researchers.

This year's Roadmap grant was awarded to Dr. Gareth Morgan at the Grossman School of Medicine at New York University for a proposal entitled "Using mutographs to define the molecular landscape and cell of origin of WM." An article describing his research is published in this issue of the *Torch*. See page 12.

Also this year, the IWMF awarded the following four grants for the IWMF Research Seed Money Initiative. One of the criteria in the selection of a Roadmap grant is preliminary data. Is there enough evidence to convince the scientific reviewers that the proposed ideas are worthwhile investigating? The IWMF introduced Seed Money grant awards to enable researchers to generate these preliminary data, and they are intended to encourage innovative, novel ideas and bring new scientists to the WM field. These are one-year awards for up to $90,000, with which investigators can test intriguing new ideas and potentially generate the preliminary data that are necessary to write successful Roadmap grants in the future.

> Leslie Crews, University of California San Diego, San Diego, CA, USA, "Targeting an IRF4/CXCR4 axis to reverse drug resistance in WM"
>
> Damien Roos-Weil, APHP Pitié-Salpêtrière Hospital, Paris, France, "Analysis of molecular and microenvironmental landscape and its role in drug resistance in WM"
>
> David Moreno, Fundació Clinic per a la Recerca Biomèdica, Barcelona, Spain, "Analysis of the chromatin accessibility landscape and regulatory networks of IgM monoclonal gammopathies: Towards a better understanding of progression mechanisms"
>
> Bruno Paiva, Clinica Universidad de Navarra, Pamplona, Spain, "Single-cell multiomics for minimally invasive assessment of treatment efficacy in WM"

The IWMF is also continuing the Robert A. Kyle Career Development Awards, which were initiated in 2021. These are two-year awards for up to $157,500 to young investigators in the WM field. The young investigators are junior faculty members or postdoctoral fellows who are in a mentoring environment. The strategic intent is to foster a new generation of talented WM researchers. This year, the IWMF selected two new awardees:

> Signy Chow, University of Toronto, Sunnybrook, Ontario, Canada, "Characterization of genomic alterations in treatment naive patients with WM through a course of targeted treatment and disease progression"
>
> Simone Ferrero, Fondazione Italiana Linfomi (FIL), Alessandria, Italy, "A multi-omics approach for deciphering the mechanisms of progression in premalignant IgM gammopathies: New insights from the FIL BIO-WM trial"

Articles describing the Seed Money and Kyle Career Development research projects awarded this year will appear in future issues of the *Torch*.

IWMF-FUNDED RESEARCH: NEW 2022 GRANT UNDER THE IWMF-LLS STRATEGIC RESEARCH ROADMAP

By Glenn Cantor, IWMF Trustee and Science Editor

Dr. Gareth Morgan, New York University Grossman School of Medicine, New York, NY, USA

Using mutographs to define the molecular landscape and cell of origin of WM

Dr. Gareth Morgan

There are many ways that a person's normal cells can turn into cancerous WM cells. And since it is well known that "no two WM patients are alike"—there are probably different kinds of WM cells.

Understanding how normal cells can turn into cancerous WM cells is like studying a map of my town, Bend, Oregon. Starting in Portland, there are many ways to get to Bend. You can drive on Route 26 over the slopes of Mt. Hood or you can take Route 20 over Santiam Pass. If there's a lot of snow in the mountains, you can drive through the Columbia River Gorge to Hood River and then take Highway 35. You can even take the long way by driving through The Dalles or Biggs Junction, or, if you really like road trips, come from the south, through Klamath Falls.

But it's even more complicated since there are different neighborhoods in Bend. There's the west side, the downtown area, and the east side. No two neighborhoods are the same.

Let's say there's a natural disaster such as a volcanic eruption (a big concern in this part of the country), and the police want to keep non-essential traffic out of Bend. Setting up a road block on one highway such as Route 26 would decrease some of the traffic, but they would really need to look at a good, accurate map and shut off all the roads coming into town, including all the neighborhoods.

It's the same with WM. Not only are there different kinds of WM, but there are different routes by which normal cells can become WM cells.

If scientists could work out all the ways that normal cells develop into WM, it might be possible to use existing drugs or develop new drugs to stop the development of WM. That is the focus of the recently awarded IWMF-LLS Strategic Research Roadmap grant to Dr. Gareth Morgan of New York University.

In Dr. Morgan's project, he will use DNA clues to trace the routes of development of WM cells. Most cells in the

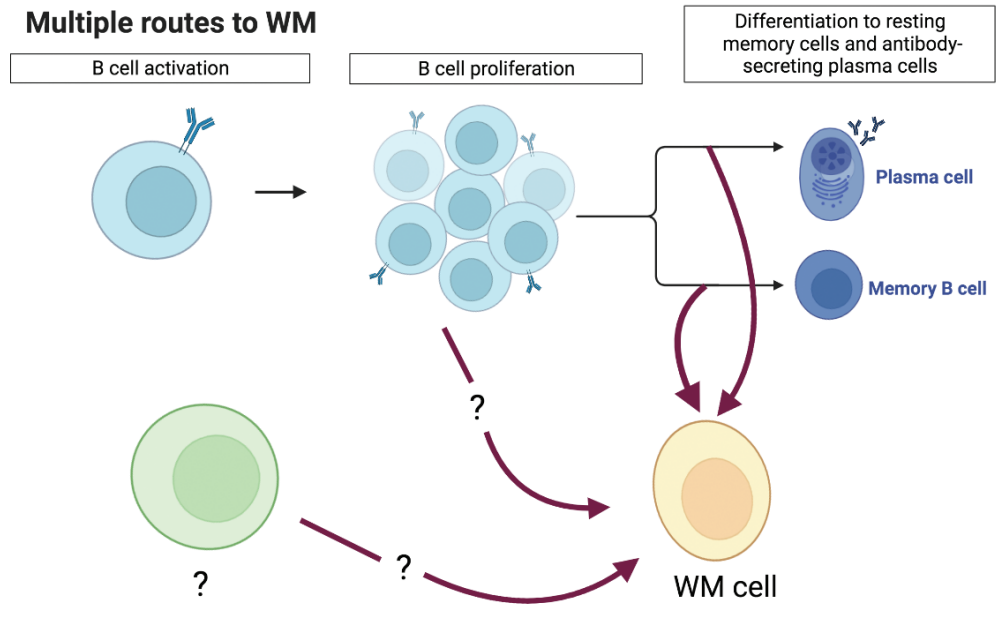

Figure 1. B cell differentiation – Normally, B cells are activated, then they proliferate and differentiate to resting memory cells or plasma cells (black arrows). There are many ways in which these pathways can go awry, leading to the development of WM cells. (Adapted from "Steps in B-cell differentiation," by BioRender.com (2022). Retrieved from *https://app.biorender.com/biorender-templates.*

IWMF-Funded Research, cont. on page 13

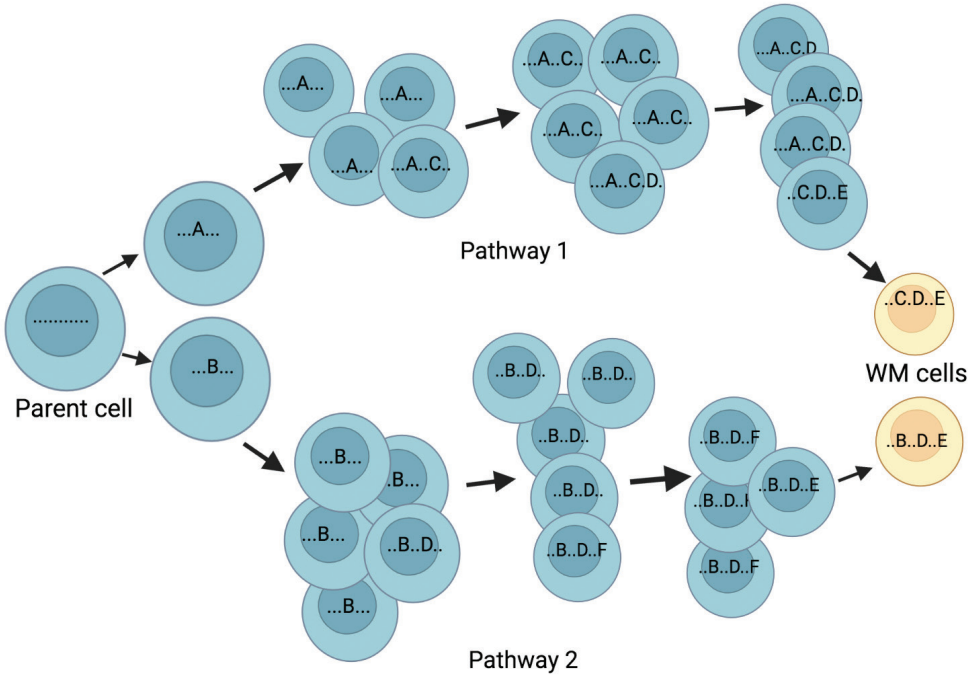

Figure 2. Mutation analysis to see pathways – *In this simplified diagram, two pathways of mutations lead to the development of WM. Sequencing the DNA in multiple individual cells reveals the mutations (the "mutograph"), which can show the pathways of how the WM cell developed. Here, a parent cell divides. One daughter cell has mutation A, while another has mutation B. Cells with mutation A proliferate, but one of them develops an additional mutation, C. In turn, the cells with mutations A and C proliferate, and one of them develops a third mutation, D. Cells with mutations A, C, and D proliferate. One of them loses mutation A, but develops mutation E. The new cell, with mutations C, D, and E is a WM cell. A similar process of incremental gain of mutations occurs in Pathway 2.*

body contain DNA, which encodes our genes. Normally, when a cell divides and produces more cells, its DNA is copied so that each "daughter" cell contains an identical copy of the original "parent cell's" DNA. But sometimes, small accidents happen, and the DNA isn't copied perfectly. These small accidents are called "mutations."

Some mutations have serious impacts on cells—many WMers know about mutations that cause MYD88 or CXCR4 to become overly active in WM cells. However, the majority of DNA mutations have no impact at all. They are just there, like small stains on a pair of blue jeans. Even normal cells can carry many mutations, which are only revealed if a scientist sequences large pieces of DNA from within the cell.

Let's say that one day, a healthy 35-year-old person develops a small mutation in the DNA of one of her cells. It is a harmless mutation, just a small difference between that particular cell and the rest of her cells. A few weeks later, that particular cell divides and forms two "daughter cells." Each daughter cell contains the mutation. A month or so later, the daughter cells divide. Now the person has four cells with the mutation. And so on…until the person has, let's say, a hundred cells with the mutation. Then, one of those hundred cells develops another mutation, again, just a small difference that doesn't affect the person's health at all. Over the years, inside our subject's body, cells copy their DNA and divide, sometimes perfectly, sometimes imperfectly, and the descendants of that cell accumulate more and more harmless mutations. But then, when our subject is 68-years-old, one of those cells just happens to make an imperfect DNA copy that triggers the development of WM. Those cells divide more rapidly, and our subject goes to her doctor and is diagnosed with WM.

Dr. Morgan proposes to use the pattern of mutations, called a "mutograph," to trace the route of development of WM cells. WM cells don't just have one mutation in a critical gene. By sequencing large amounts of DNA (called whole genome sequencing, which includes non-coding regions), Dr. Morgan's laboratory can identify numerous mutations, including patterns of harmless mutations that cells have accumulated over the years. Using computer systems that he developed for the study of related cancers such as multiple myeloma, Dr. Morgan can analyze these patterns of mutations to trace the route by which WM cells arise in individual patients.

One problem facing most WM researchers is how to get enough samples. Because WM is a rare disease, most doctors see only a limited number of patients, and not all patients are willing to donate their bone marrow or blood samples for research purposes. One of the strengths of Dr. Morgan's project is that he has set up collaborations with a number of other WM researchers so that he can combine their data with data from his own hospital. In that way, he can analyze enough WM patients to reach meaningful conclusions. It's a bit complicated, since each laboratory used somewhat different methods, but he has developed computer methods to adjust for the differences among labs to make the data comparable.

MEDICAL NEWS ROUNDUP

By Sue Herms, IWMF Research Committee Member

NCCN Revises Clinical Practice Guidelines for WM/LPL – The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for WM/LPL (lymphoplasmacytic lymphoma) document has been revised as of July 6, 2022. Notable updates from the previous Guidelines include the following: 1) adding new pages that address the management of asymptomatic or minimally symptomatic disease and the management of Bing Neel syndrome; 2) moving rituximab + cyclophosphamide + dexamethasone as primary (first-line) therapy from the "preferred regimens" category to "other recommended regimens" category; 3) removing some alternative bortezomib-based regimens from the list of primary therapy; 4) removing fludarabine- and cladribine-based regimens from the list of primary therapy; 5) adding ixazomib + rituximab + dexamethasone for previously treated patients to the "other recommended regimens" category; 6) removing some alternative bortezomib-based regimens from the list for previously treated patients; and 7) moving fludarabine- and cladribine-based regimens for previously treated patients from the "other recommended regimens" category to the "useful in certain circumstances" category.

ASPEN Study Updates Comparisons of Zanubrutinib to Ibrutinib with Long-Term Follow-Up Data – Researchers who conducted the Phase 3 ASPEN study comparing zanubrutinib (Brukinsa) to ibrutinib (Imbruvica) in WM patients reported long-term follow-up data at 43 months to the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting. In the group of patients with the MYD88 mutation, zanubrutinib continued to demonstrate a higher combined complete response and very good partial response (CR + VGPR) rate of 36%, as compared to ibrutinib with a CR + VGPR rate of 22%. When broken down between subgroups of patients with and without CXCR4 mutations, a statistically significant advantage in the CR + VGPR rate was restricted to the subgroup with wild-type (unmutated) CXCR4, at 45% for zanubrutinib and 28% for ibrutinib, while the subgroup with mutated CXCR4 showed a non-statistically significant but clinically relevant CR + VGPR rate of 21% for zanubrutinib and 5% for ibrutinib.

Final Results at Five Years of Follow-Up Reported for Phase 2 Trial of Acalabrutinib in WM – Final results at five years of follow-up were reported for the Phase 2 trial of acalabrutinib (Calquence) in 106 WM patients, of whom 14 were treatment naïve at the start (TN) and 92 were relapsed or refractory (R/R). The overall response rate was 93% in the TN group and 95% in the R/R group; major response rates were 79% and 82%, respectively. The median progression-free survival was not estimable in the TN group and 68 months in the R/R group, while overall survival was not estimable in both the TN and R/R patients. The most common adverse events of any grade were headache, diarrhea, fatigue, joint pain, nausea, and dizziness. Atrial fibrillation/flutter occurred in 7% of the TN group and 12% of the R/R group; hypertension (high blood pressure) occurred in 0% and 8%, respectively; and hemorrhage occurred in 71% and 61%, respectively. The trial results were presented as an abstract at the European Hematology Association (EHA) 2022 Congress and published in the journal *HemaSphere*.

The US Food and Drug Administration has granted ***Orphan Drug Designation*** *to* ***MB-106*** *for the treatment of WM.*

US FDA Grants Orphan Drug Designation to CAR T Cell Therapy for WM – The US Food and Drug Administration has granted Orphan Drug Designation to MB-106 for the treatment of WM. MB-106 is a CAR T cell therapy that targets the surface molecule CD20 on B cells. Orphan Drug Designation would entitle the therapy to seven years of market exclusivity for WM. A Phase 1/2 trial of MB-106 to include WM patients will be enrolling soon in multiple centers, and its identifier on *www.clinicaltrials.gov* is NCT05360238.

Mayo Clinic Reports Phase 2 Trial Results for the Combination of Ixazomib, Cyclophosphamide, and Dexamethasone in Patients with Light Chain Amyloidosis – The Mayo Clinic conducted a Phase 2 study of ixazomib, cyclophosphamide, and dexamethasone for patients with previously untreated light chain amyloidosis, which can be a rare and serious complication in WM patients occurring when an abnormal protein, called amyloid, deposits in the organs and interferes with their normal function. Initial treatment of all three drugs was followed by ixazomib-only maintenance until disease progression. Thirty-five patients were included, with the most common major organ involvement from amyloidosis occurring in the heart and kidneys. The overall hematologic response to initial treatment was 63% and included complete responses in 11.4% and very good partial responses in 37.1% of patients. With a median follow-up of 29.7 months, the two-year progression-free and overall survival were 74% and 78%, respectively. Ixazomib (Ninlaro) is an oral proteasome inhibitor in the same drug class as bortezomib (Velcade). The study results appeared in the journal *Blood Advances*.

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Treatment of Bing Neel Syndrome Described in Abstract Presented During EHA 2022 Congress – An abstract presented during the European Hematology Association (EHA) 2022 Congress by the University College London Hospital and the Centre for Neuromuscular Disease, National Hospital for Neurology and Neurosurgery in London described their treatment experience with Bing Neel syndrome (BNS), a rare complication that can occur in WM when the characteristic lymphoplasmacytic lymphoma (LPL) cells infiltrate the central nervous system (brain and spinal cord). Data from 35 BNS patients were collected between 2011-2021. All patients were symptomatic, and in 12 patients, BNS was the first presentation of lymphoma. Approximately half had previously received therapy for LPL, and the median time to diagnosis of BNS in these patients was 49 months. The majority of the LPL cells were of the kappa light chain type. Most patients were treated with intensive regimens (the combination of rituximab, methotrexate, and cytarabine ± thiotepa/idarubicin) and less commonly, with ibrutinib (Imbruvica) or bendamustine + rituximab. Three proceeded to autologous stem cell transplant, and ten proceeded to indefinite ibrutinib treatment. The two-year overall survival was 91%.

Retrospective Study Analyzes the WM Population in Latin America – A retrospective study published in the journal *JCO Global Oncology* analyzed WM patients in Latin America diagnosed between 1991 and 2019 in order to investigate their clinical characteristics, therapies, and outcomes. Researchers identified 159 cases from 24 centers in seven countries. At diagnosis, the median age was 67, and patients were predominantly male; most patients (95%) were symptomatic at diagnosis with lymph node enlargement (28%), spleen enlargement (25%), and hyperviscosity symptoms (20%) as the most common manifestations. Of 23 patients tested for the presence of MYD88 L265P, 89% had the mutation. The median time-to-therapy after diagnosis was 35 days, with the researchers suggesting that delayed access to specialized cancer care in many health care systems may have been a contributing factor to the short time between diagnosis and treatment. Chemoimmunotherapy was the most common first-line (66%) and second-line (45%) treatment approach, consisting primarily of dexamethasone + rituximab + cyclophosphamide or bendamustine + rituximab. Less than ten percent of patients received bortezomib or ibrutinib therapy (ibrutinib is not available in most Latin American countries). With a median follow-up of 69 months, the five-year overall survival rate was 81%. In treated patients, the five-year overall survival and progression-free survival rates were 78% and 59%, respectively.

US FDA Approves New Tablet Formulation of Acalabrutinib That Can Be Taken with Gastric Acid-Reducing Agents – AstraZeneca announced that the US Food and Drug Administration (FDA) has approved a new tablet formulation of acalabrutinib (Calquence) that will allow patients on the drug to take it with gastric acid-reducing agents, including proton pump inhibitors, antacids, and H2-receptor antagonists. In the ELEVATE-PLUS clinical trial, the new tablet formulation was equivalent to the capsule formulation in safety and effectiveness, indicating that the same dosing strength and schedule can be used for the tablet as for the capsule.

Emergency Use Authorization for Evusheld Updated by US FDA – The US Food and Drug Administration (FDA) issued an update to its emergency use authorization of Evusheld for the pre-exposure prevention of COVID-19 disease in moderately or severely immunocompromised individuals. The FDA's previous Fact Sheet for Healthcare Providers did not provide a specific recommendation on the dosing interval between Evusheld treatments because of possible concerns about the effectiveness of Evusheld against newly-emerging omicron variants. Testing is still showing acceptable effectiveness, so the updated information now recommends a repeat after six months with a 300 mg injection of each drug in the Evusheld formulation for patients still requiring protection.

The US Food and Drug Administration (FDA) has issued ***emergency use*** *authorization for the* ***Novavax COVID-19 vaccine*** *in adults.*

New COVID-19 Bivalent Booster Shots Authorized in US – The US Food and Drug Administration (FDA) recently authorized Pfizer's and Moderna's new bivalent COVID-19 booster shots, which target both the original strain that started the pandemic and the omicron subvariants BA.4 and BA.5 that are currently dominant. Pfizer's booster is authorized for those 12 years and older, while Moderna's is for adults; both will be used only for booster shots, as the original vaccines will remain in use for primary (initial) vaccination. The bivalent boosters can be given at least two months after the last primary shot or after a previous booster. Meanwhile, a Moderna bivalent vaccine with an omicron variant BA.1 component was recently authorized in the United Kingdom. Moderna has completed regulatory submissions for its bivalent booster in Australia, Canada, and the European Union; Pfizer has also completed a submission to the European Union for authorization of its bivalent COVID booster.

Novavax for COVID-19 Vaccination Receives Emergency Use Authorization for Adults in the US – The US Food and Drug Administration (FDA) has issued emergency use authorization for the Novavax COVID-19

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vaccine in adults. Novavax is administered in two primary doses, three to eight weeks apart (three weeks for the immunocompromised). The vaccine contains the coronavirus spike protein and an adjuvant that enhances the immune response of the vaccinated individual, using a more traditional technology than that of the mRNA vaccines made by Pfizer and Moderna. In a clinical trial, the vaccine was 90.4% effective in preventing mild, moderate, or severe COVID-19 infection; however, the vaccine was 78.6% effective in the subset of participants 65 years of age and older. The trial was conducted prior to the emergence of delta and omicron variants. The most commonly reported side effects included pain/tenderness, redness, and swelling at the injection site; fatigue; muscle pain; headache; joint pain; nausea/vomiting; and fever. Clinical trial data provided evidence for increased risks of myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of tissue surrounding the heart). According to Centers for Disease Control and Prevention (CDC) vaccination guidelines, Novavax is not currently authorized as a booster for those who have already received Pfizer, Moderna, or J&J as their primary vaccine.

CDC Posts Latest COVID-19 Vaccination Guidance for Immunocompromised Adults – The US Centers for Disease Control and Prevention (CDC) has posted the latest COVID-19 vaccination guidance for moderately and severely immunocompromised adults. **Recent guidance has added Novavax as a primary vaccine and authorized a booster shot of updated bivalent Pfizer or Moderna vaccine (see news items above).** To view the complete guidelines, go to *https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-vax*, scroll down to the section "COVID-19 Vaccines, Recommendations, and Schedule," and click on the heading "People who are immunocompromised." To briefly summarize the guidelines:

- Novavax is now authorized as a primary vaccine in a two-shot regimen. In the immunocompromised, the second shot should be given three weeks after the first. An updated bivalent booster shot of Pfizer or Moderna should be given at least two months after the second primary shot. Currently, Novavax is not authorized as a booster shot.
- For those who receive the initial two original Pfizer or Moderna vaccines, a third primary shot of original Pfizer or Moderna vaccine should be given at least four weeks afterward. An updated bivalent booster shot of Pfizer or Moderna should be given at least two months after the third primary shot or after a previous booster to those who have already received original booster shots of Pfizer or Moderna.
- For those who receive the initial J&J vaccine, a second primary shot of original Pfizer or Moderna vaccine should be given at least four weeks afterward. An updated bivalent booster shot of Pfizer or Moderna should be given at least two months after the second primary shot or after a previous booster to those who have already received original booster shots of Pfizer or Moderna. The US Food and Drug Administration has strictly limited the use of the J&J vaccine because of a rare but serious risk of blood clots. The J&J vaccine is available only to adults who specifically request it and will not otherwise accept vaccination or who are unable to receive other COVID-19 vaccines because of allergic reactions or other conditions.
- Note that primary vaccination shots for Pfizer, Moderna, or J&J vaccines still use the original vaccine formulation. All booster shots, however, will now be given with the updated bivalent Pfizer or Moderna vaccines. This guidance replaces all previous booster recommendations.

*All **booster shots,** however, will now be given with the updated bivalent **Pfizer** or **Moderna vaccines.***

Australian Study Looks at Vaccination Responses in WM and Follicular Lymphoma Following Third Vaccine Dose – An ongoing study from researchers in Australia is looking at the effectiveness of the third COVID-19 vaccine dose in individuals with WM and follicular lymphoma, including a subset of WM patients vaccinated during a pause in their BTK inhibitor treatment. Immune responses are being initially assessed by measuring anti-spike antibody titers 21-28 days after a third mRNA vaccine. The study also seeks to determine if a better immune response can be gained by pausing BTK inhibitor therapy prior to, and up to four weeks after, the third vaccine dose; patients in this part of the study are closely monitored during the pause with weekly clinical, blood count, and IgM assessments. At the time of publication, 56 of 125 patients, including 28 with WM, had completed their third vaccine and antibody response assessment. Most patients who had responded to a second COVID vaccine showed a decline in their antibody titers over time but saw increased titers following the third dose. However, only 20% of patients without detectable antibody titers prior to the third dose showed improvement after the third dose. Although the initial data are small, patients who paused BTK inhibitor therapy showed a greater increase in their antibody titers when compared to a control group who did not pause therapy. Additional testing will include T cell responses to the third vaccine dose. The study was published in the journal *HemaSphere*.

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Retrospective Study Discusses Management of Hypertension in Patients on BTK Inhibitors – A multicenter retrospective study presented as an abstract at the European Hematology Association (EHA) 2022 Congress and published in the journal *HemaSphere* looked at hypertension (high blood pressure) associated with the use of BTK inhibitors in patients with lymphoid malignancies. Hypertension is considered an adverse event of the BTK inhibitor ibrutinib (Imbruvica) and, to a lesser extent, second generation BTK inhibitors such as acalabrutinib (Calquence). The study aimed to identify from a variety of anti-hypertension drugs the ones that may be most effective in these patients and included 196 patients from 12 centers. Eligible patients were divided into two groups: 1) those with pre-existing hypertension before BTK inhibitor treatment (118 patients) and 2) those who developed hypertension after starting a BTK inhibitor (78 patients). The majority of patients had chronic lymphocytic leukemia and were on ibrutinib. In the group with pre-existing hypertension, a trend toward significant blood pressure reduction was only achieved with the combination of hydrochlorothiazide (a diuretic) and a beta-blocker. In the group who developed hypertension after starting a BTK inhibitor, the combination of hydrochlorothiazide and an ACE inhibitor/angiotensin II receptor antagonist was associated with a significant blood pressure reduction. Gender or race did not modify these results. The study's authors suggest that these findings need to be further assessed in patients taking newer generation BTK inhibitors and confirmed in large prospective clinical trials.

Recent Article Reports Mechanisms of Acquired Resistance to BTK Inhibitor Pirtobrutinib in CLL Patients – *The New England Journal of Medicine* included a recent article discussing mechanisms of resistance to noncovalent (reversible) BTK inhibitors in patients with chronic lymphocytic leukemia (CLL). While researchers have studied resistance to covalent BTK inhibitors such as ibrutinib, not much is known about resistance to noncovalent BTK inhibitors such as pirtobrutinib. In this article, researchers performed genomic analyses of pre-treatment specimens as well as specimens obtained at the time of disease progression from nine of 55 patients with CLL who were treated with pirtobrutinib and relapsed. They identified several new mutations in BTK itself (V416L, A428D, M437R, T474I, and L528W), as well as in a downstream signaling molecule called PLCγ2.

Results Presented at EHA 2022 Congress for Phase 1 Trial of Antibody-Drug Conjugate to Treat Relapsed/Refractory Blood Cancers – Researchers at the European Hematology Association (EHA) 2022 Congress discussed the results of a multicenter Phase 1 dose escalation trial of the intravenous antibody-drug conjugate called MK-2140 (zilovertamab vedotin) for the treatment of relapsed/refractory blood cancers. WM patients are eligible to participate in the trial, which is ongoing. Of the 51 patients enrolled in the first dosing group of the trial, treatment-related adverse events occurred in 72.5%, most commonly peripheral neuropathy, fatigue, neutrophil count decrease, nausea, and diarrhea. Patients in the trial diagnosed with non-Hodgkin's lymphoma achieved an overall response rate of 36.6%. MK-2140 targets the ROR1 signaling pathway that regulates cell survival. The trial identifier on *www.clinicaltrials.gov* is NCT03833180.

New Phase 1 Study Will Evaluate Noncovalent BTK Inhibitor HMPL-760 in Patients with CLL, SLL, and NHL – A presentation at the European Hematology Association (EHA) 2022 Congress discussed a new Phase 1 study that will evaluate the safety and tolerability of the noncovalent BTK inhibitor HMPL-760 in patients with previously treated chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) or other non-Hodgkin's lymphomas (NHL). HMPL-760 was developed to inhibit malignant growth of B cells with either wild-type BTK or with mutated BTK C481S that results in acquired resistance to ibrutinib and other covalent BTK inhibitors. The study plans to enroll a subgroup of WM patients who have failed prior BTK inhibitor therapy. On *www.clinicaltrials.gov*, the study identifier is NCT05176691, and it is being offered at several locations in the US.

Hypertension** is considered an adverse event of the BTK inhibitor **ibrutinib (Imbruvica)...

Researchers Discuss New Phase 1 Clinical Trial to Open for Novel Drug NX-2127 to Treat Relapsed/Refractory B Cell Malignancies – Researchers at the 2022 American Society of Clinical Oncology (ASCO) Annual Meeting described a new Phase 1a/b clinical trial to evaluate the safety, tolerability, and preliminary effectiveness of oral NX-2127 in patients with relapsed/refractory B cell malignancies. The novel approach of NX-2127 combines the activity of a protein called cereblon that breaks down both wild-type BTK and the C481-mutated BTK protein, along with activity that increases T cell activation of patients' own immune systems. Relapsed/refractory WM patients are eligible to participate, and enrollment has begun in the US for the Phase 1a part of the trial. The trial identifier on *www.clinicaltrials.gov* is NCT04830137.

New BCL-2 Inhibitor to Be Tested in Phase 1 Study of Patients with Relapsed or Refractory Blood Cancers – Another new Phase 1 study discussed at the 2022 American

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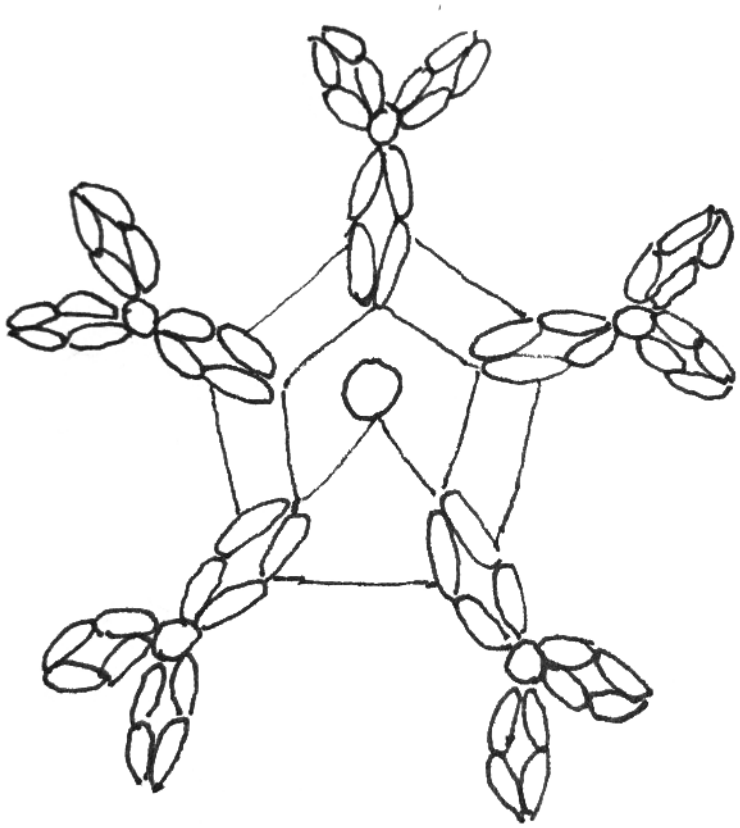
Society of Clinical (ASCO) Annual Meeting was LOXO-338, an oral BCL-2 inhibitor, in the same drug class as venetoclax (Venclexta). Part 1 of the study for patients with relapsed or refractory blood cancers will evaluate LOXO-338 as single agent therapy with different dosing strategies, and Part 2 will evaluate the drug in combination with pirtobrutinib, a BTK inhibitor. Eligible patients include those with WM, and the study is currently enrolling patients in the US and overseas. On *www.clinicaltrials.gov*, the study identifier is NCT05024045.

Phase 1 Trial to Assess BTK Protein Degrader BGB-16673 in Relapsed or Refractory B Cell Malignancies – Australian and US researchers are recruiting participants for a Phase 1 trial to assess the safety and tolerability of BGB-16673 in relapsed or refractory B cell malignancies, including WM. BGB-16673 is an oral agent that degrades both the wild-type and mutated forms of the BTK protein and may have activity in patients who have progressed on BTK inhibitor therapy. The trial identifier on *www.clinicaltrials.gov* is NCT05006716.

The author gratefully acknowledges the efforts of Glenn Cantor, Grete Cooper, Steven De Cenzo, Peter DeNardis, Julianne Flora-Tostado, Tom Hoffmann, Pavel Illner, Meg Mangin, Colin Perrott, Howard Prestwich, Richard Savoy, Charles Schafer, Ron Ternoway, and others in disseminating research news of interest to the WM community. The author can be contacted at suenchas@bellsouth.net *for questions or additional information.*



IgM pentamer by Diane Mazza

FROM THE FACEBOOK WM SUPPORT GROUP: FALL 2022

By Betty Ann Morton

Friends are so important to the quality of my life. I am fortunate to have a loving husband who is certainly a friend, two sisters who communicate with me most days by text, next-door neighbors who water our plants when we're away, my Tuesday walking group, and two Spanish conversation groups. Over time I have learned whom I can count on to encourage me or to listen to my concerns—and with whom it's better to avoid serious topics.

I am seeing more and more that the Facebook WM Support Group members are a reliable group of people who count as friends.

As **GG** explained in a recent post, "Thank you for sharing your heart thoughts. I have never been excited to join a group, but I figured this would be a good place to get information about WM. I was instantly and utterly amazed at not only the information, but most importantly the love and support here. It is a place to enjoy every day. I feel as if I am with friends. I love that everyone understands even though we all experience WM differently. I am so grateful to have this safe place to be a person with cancer. No pity, just caring! Thank you to everyone!"

AC managed to express the feelings of many of us when we were first diagnosed: "It just hit me; I have got cancer! I was diagnosed last December and a bit like grief, my thoughts and the realization came in waves as my brain processed the news. With the days and weeks that passed, the waves grew further apart, but every now and then, it hits me, out of the blue, I've got cancer! I want the world to stop spinning, sit up, and take notice! I've spent so long smoothing it over for people, friends, family, neighbors—downplaying it so as to avoid awkwardness. Glad I can come on here and share my thoughts.

DR responded, "Yes, although indolent it is STILL cancer!!!! Sometimes I feel it is "downplayed" a lot! I know we have to be positive and grateful as it could be FAR worse but I think we need to give ourselves permission to feel sorry for ourselves even just for a bit! Then try to deal with this 'new' (or old) normal! Always feel blessed that we have this forum!"

ES shared some wisdom: "In my first six months I always guided my thoughts to be positive. A psychologist I was seeing to have my cognitive processes measured (I have a WM brain tumor) gently informed me that only allowing positive thoughts was a form of denial. Instead, I needed to allow all feelings/thoughts…so I could undergo a grief process and finally come to true acceptance."

A member's post about fatigue, soreness, and weakness elicited this response, "If you are like me, it isn't so much tiredness, it is feeling weary. A tiredness that rest and sleep don't fix. I try to rest and feed myself hope, joy, acceptance, possibilities, happy thoughts and find ways to gain energy from creating and exploring. Add some surprise to your life. Send a card to someone you haven't connected with for a long time! You will hear back that you cheered them up, and you will feel better! Just small things that add smiles and joy. I have reconnected with several cousins and friends from long ago. Even people without WM are feeling low right now. We all need one another. You have us."

Naturally, group members have many questions about treatment: When is treatment needed? What treatment is best? What about side effects? How can I pay for expensive drugs? Any ideas about managing side effects?

Although each WMer has a unique history and experience with the disease, **SAG**'s request is typical. "My name is S… and I am 33 years old. I was diagnosed with WM in 2017, being very young…Since then I did not receive treatment until 2019 (carfilzomib + rituximab + dexamethasone). After chemo, I had three years of peace since. I will soon start my second round; it is a new drug called zanubrutinib. I am a little scared about the drug because of the side effects, since some of them seem quite serious. I would like, please, if anyone has had the experience of taking this medication, could you tell me how it went? Thank you very much."

Various people responded, describing their own experiences. **SSK**, for example, said, "My husband has been on it for a year. Results are great. Everyone has different side effects. He is a little tired and gets some spots on his arms, but he is 71. Has had WM for 19 years." **JP** added, "Zanubrutinib/Brukinsa is my life saver! Side effects…sore joint pain. But with yoga stretching, pain is minimal. Good luck!" **MD** also has had a positive response, "Hi. I've been on zanubrutinib since June. It's been amazing. Little or no side effects, and my blood numbers have done a 180. Good luck!"

JMH shared a different experience, "I also have done the carfilzomib, Rituxan, and dexamethasone. First time was 2015-16. It bought me four years, five months and 12 days. I chose to do it again when I relapsed in April 2021. I finish in November. It's a lot of medication over a long time, but I haven't had a hard time with side effects or long-lasting effects from it."

SAP wrote, "So far zanubrutinib has been so much easier than Imbruvica and rituximab. No A-fib or anything major. Some itching, but I take Claritin and it helps with stopping

From the Facebook WM Support Group, cont. on page 20

the itching. More importantly it has calmed my WM symptoms down. I was faced with doing bendamustine (a chemo drug) with rituximab, but the thought of sitting in that chair for days and weeks didn't seem like something I wanted to do again. With rituximab, I had to have it administered over two days. For me, having control over taking a pill which was on my time versus going in for those infusions, it just made sense."

Canadian **CS** asked for input about clinical trials, "Hello good people...My husband and I are wondering if anyone is on or has completed the BRAWM study? It's headquartered at the Sunnybrook Health Services Centre (Toronto). He had an initial consult with his oncologist this morning. As newly diagnosed with WM, he is a candidate for the BRAWM study, but the decision rests with him as to whether or not to participate. If not, other options are standard of care (bendamustine + rituximab) or ibrutinib on its own. By the way, we got through four pages of questions at this morning's appointment that included many of those suggested by this group, so thank you!" **MCM** added "Those who participate in this clinical trial will be helping to determine if adding acalabrutinib to bendamustine and rituximab for one year will result in better outcomes than B + R alone."

MCM summarized another discussion about treatment decisions: "There's no 'best' treatment for any age. Both B + R and a BTK inhibitor are very good treatments. Your choice depends on what your doctor recommends and how you feel about a time-limited treatment versus pills that you take continuously until they stop working. Potential adverse effects are there regardless of what course you decide. You've gotten opinions from others, now the decision will be between you and your physician."

Note: WMers and their family members and support people are welcome to join this group. We all need friends. To join the Facebook WM Support Group, go to *https://facebook.com/groups/wmsupportgroup*. In order to join, people must answer two membership questions. Since the group is private, only group members are able to see the posts. If you need additional help with the process, please contact the IWMF office 941-927-4963 or email to *office@iwmf.com*.

EDITOR'S NOTE:

As the support group section continues to evolve away from individual reports, we begin to spotlight certain groups, activities, or people. As always, for particular information about when and where meetings are being held, go to the Events Calendar for listings: ***https://iwmf.com/events-calendar/***

BY SHARON RIVET

As a yoga teacher and practitioner for 30+ years, as well as coming from the corporate world, I understand the Buddhist concept of impermanence—meaning all that exists is impermanent; nothing lasts: change, change, change!

In August 2018, I was one year into retirement, enjoying travel with my husband and devoting more time to teaching yoga classes and workshops. I joked how I was more tired as a retiree than when I was working. It was during my routine physical that my doctor found abnormalities in my blood work, leading to my Waldenstrom's macroglobulinemia (WM) diagnosis. Like many people who hear the words, "You have cancer," you quickly learn what the Buddha was expressing with his final words—"impermanence is inescapable." And now I was faced with the challenge: Can I practice what I preach and teach? Can I let go of what I planned for my golden retirement years? Do I truly appreciate this simple but profound concept? Will I find peace and understanding if I am calm and mindful?

Sharon Rivet in sukhasana (easy pose)

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I knew I could not control what course WM had planned, but I also knew that projecting myself into the future was not going to be helpful. I believe in the adage that knowledge is power, so learning about this rare disease, from symptoms to treatment options, would be a huge benefit.

Volunteering *for IWMF has been a truly* **amazing benefit** *to me.*

I contacted my local American Cancer Society, and they pointed me to the IWMF and all its resources, from information packets to our Facebook group—a truly supportive, caring, and informative group. I began to build a knowledge base (even though I still stumble over pronouncing macroglobulinemia) by reading the IWMF educational resources and learning about the Foundation and everything its website has to offer. During this time, we entered the COVID shutdown, and my usual volunteer activities were also shut down. Now what?

I found my answer one day while perusing the IWMF website under "How to Help – Volunteerism for IWMF." Completing one form led me to opportunities I never expected!

My first volunteer opportunity came after a call with Sara McKinnie and Shelly Postek at the IWMF office in Sarasota. In my previous life before retirement, I was in corporate training and quality. Sara and Shelly thought I would be a good fit on the IWMF Educational Forum Committee. Through this experience of plotting and planning agendas and speakers for the 2021 and 2022 forums, I started to learn more about the medical professionals who treat us, where they are located, and their specialties. I have been able to meet and work with the wonderful IWMF staff, seeing first-hand their dedication and the lengths to which they extend themselves to ensure we are educated and have resources. I also met other WM volunteers who have helped provide support and insight on my questions, from what I need to know or ask about IVIG to a hotel recommendation for my visit to Dr. Jorge Castillo at Dana-Farber Cancer Institute in Boston.

A relatively new volunteer activity I am involved with is the Lymphoma Research Foundation (LRF) Ambassador Program (AP), an IWMF partner. The AP objectives are to raise awareness of lymphoma and the specific needs of those affected by this type of blood cancer among the general population.

LRF is in the process of rebranding communication materials, website, and marketing. We have been providing feedback as they build their new platforms and messaging. I am excited to become more involved as LRF relaunches in the near future!

I also participate on the BeiGene Patient Advocacy Counsel. BeiGene seeks to integrate empowered and informed patients, caregivers, and their community advocates into their business to focus holistically on the drivers of health and well-being that impact rare lymphoma and CLL communities. There are representatives from The Leukemia & Lymphoma Society, American Cancer Society, Cancer*Care*, and the Lymphoma Research Foundation, as well as oncologists, nurses, and other blood cancer patients. The Council gathers insights and real-world expertise in the patient/caregiver experience to identify the unmet psychosocial needs of patients and families and to explore solutions to improve the patient/caregiver experience. I am one of four blood cancer patients who share our experiences: diagnosis, treatment, financial concerns, and mental health support. We also provide feedback, as BeiGene is in the process of redesigning its website to make it more accessible for patients and providers. This volunteer opportunity has also provided a chance to learn and interact with organizations and patients beyond WM.

Volunteering for IWMF has been a truly amazing benefit to me. I have met a wide network of people and learned much more about WM than I think I ever would have on my own, while hopefully giving something back to our WM community.

All by clicking on "How to Help – Volunteerism for IWMF" at *www.iwmf.com!*

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Spotlight on Support Groups, cont. from page 21

AN INTERVIEW WITH IWMF SUPPORT GROUP MEMBER JASON EUZUKONIS

By Eileen Sullivan, Eastern Massachusetts Support Group

Jacob Euzukonis and family

Eileen Sullivan, leader of the Eastern Massachusetts Support Group, recently interviewed Jason Euzukonis, a member of her support group and the Young WM Support Group, to bring his story to Torch *readers. Jason was diagnosed in 2018 at the age of 43.*

Eileen:
Jason, I remember when you first came to our support group with your very interesting story. Can you give us a little bit of background? How did you find out you had WM at such a young age?

Jason:
The whole journey started for me in the winter of 2018. I've been a lifelong runner so I'm very tuned in to how my body feels. I've had times over the years when I would feel tired on a run but could still put one foot in front of the other. I started noticing that there were points in my run when I had to stop. My body just didn't want to keep going. My wife Lisa and I were on a Caribbean cruise, and I was doing laps on the top deck. It was a lot warmer, and I had to stop less than a mile in, but I just kind of shrugged it off.

It was in May of 2018 when things started to really escalate. I got four minutes into a run, and it felt like my body was shutting down, as if oxygen just wasn't getting to the rest of my body. I wondered if there might be something going on with my heart, so I finally reached out to my primary care and said "Something is not right!" I went in for blood tests, and she wanted me back right away for more because the counts were very low. My hemoglobin was 7.8! She sent me to a nearby hematologist for more testing. That doctor called me back quickly to say that it could be some type of leukemia.

In that moment, my life changed forever. Going in, you're thinking something is not right, but until you actually get a name for it you don't really think it's that big a deal. I was in tears instantly. My wife was right there. My first thought was "Am I going to see my kids grow up?" My children were seven and three at the time.

The bone marrow biopsy results pointed toward WM. The doctor said that all these types of lymphomas are treated the same way—with chemotherapy. That didn't sound right to me, so I got a second opinion. I saw a great doctor at Beth Israel who took her own sample, and when the results came in, she wanted me to start treatment right away. That's when the reality of things started to set in. I'd seen other people go through a cancer diagnosis and treatment, so I expected that I would have a couple months of chemotherapy, feel like crap, go into remission, and I'd be good to go for a while. I didn't know much about this WM world! That was when she got some results back which showed that, based on genetic markers, the new targeted therapies called BTK inhibitors could work well. She prescribed ibrutinib for me, along with eight infusions of rituximab early on. The idea that I was just going to be on this drug indefinitely was a very different feeling from anticipating chemo for a while, and then off I'd go. Now

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I'm on this drug for who knows how long. I just thought, "I'm turning 44 with two young children—this can't be happening." It was all a whirlwind.

When I learned about the Bing Center for WM [at Dana-Farber Cancer Institute], I was working with the team at Beth Israel. My insurance wasn't taken at Dana-Farber. During that year, my wife and I decided to change our health insurance, knowing that it will cost a bit more, but I needed to try and stay alive for another 30-40 years! I met with Dr. Jorge Castillo in June of 2019. I was scared, but this first meeting was a turning point for me because, although I know there are still going to be some bumps in the road ahead, I had this sense that the team there had a really good understanding of the biology of this disease. Dr. Castillo seemed confident that I'd get to see my kids grow up.

At that point, I came to a WM support group meeting.

Eileen:
I do remember very well that first support group meeting. I was so glad that you had found us and were brave enough to share your story.

Jason:
I understand that at the end of the day there are no guarantees with this disease, but it just was a good feeling to think "this is doable." Since that time, my perspective has definitely changed, and I feel a lot better about everything. Physically I feel great. At one point my hemoglobin got down to about 7.1 [g/dL], but now it's about 15. My IgM was never over 1,000 [mg/dL] but a little over four years later, it's down to 150. So yes, that's quite a story.

Eileen:
How did you find out about the IWMF? How did you find the support group?

Jason:
I'm a research geek! These days, with easy access to the internet, I was constantly online researching WM. Once you start going down that path of searching for WM, it's pretty much impossible not to find the IWMF and then the support groups. But I'm sure there are a lot of people out there with WM who don't know about the resources that they have.

Eileen:
I've heard a bit about the work you did with Dr. Shayna Sarosiek and the pharmaceutical company. Could talk a little about that?

Jason:
Yes, this was at a BeiGene sales conference in April in Boston, mostly for their sales reps. They wanted to have a session dedicated to the patient perspective and were looking for someone doing well on zanubrutinib, which I had switched to from ibrutinib. I'm sure they wanted to put a human face on the treatment and to understand what it's like to live with a disease like this while on a targeted therapy. I worked with Dr. Sarosiek from Dana-Farber, and it was an interview in which she asked me questions about my journey with WM. After the interview, the sales reps had a chance to ask me questions. It was a good experience, and I enjoyed it.

Eileen:
Could you share a bit about how your family is doing these days, now that you're feeling so good and looking like yourself again?

Jason:
In the beginning, it was hard not being able to tell my kids what was going on. They were too young to understand. I can't say enough about how fantastic my wife has been. She's a mental health clinician with a specialty in wellness. I've worked hard to regain my strength. Certainly, the treatment was the most important factor, but I also made a lot of changes to my lifestyle and decided to change the way I eat. I'm running better than I have since my mid-20s. I've brought other things like prayer and meditation into my daily routine to get myself centered. Lisa has really helped me with the meditation piece, especially early on when I was really scared. I didn't like the idea of people looking at me as someone who was sick. It's a fine line between not ignoring the fact that I have this disease but at the same time wanting to show everyone that you can get a disease like this and still thrive.

Fast forward to now—I honestly go through much of my day without thinking about WM, except for twice a day when I pop my pills. My kids are doing really well. I think Lisa was pretty scared early on, but she's got confidence now that, between the team at Dana-Farber and my lifestyle changes, things are going very well. My kids are getting older, so I've started having conversations with them about it. I think their seeing me fit and healthy is helpful, and I've tried to explain that there are lots of different types of cancers, and that I'm doing really well. We're excited to get back to taking vacations again.

There are so many WM patients who aren't aware of all the options they have at their fingertips and all the progress that's being made with treatments. I remember thinking early on that something like this is a death sentence. That's not really the case. I just needed time to get used to living with this. As my kids get older and, hopefully, time starts to free up a little bit, I can become more involved with various IWMF support groups and use my experience to help others.

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WM POC MEETING HOSTS DR. LISA MERRITT

By Pat Greenleaf James

The WM People of Color (POC) group graciously received Dr. Lisa Merritt's presentation on managing WM and the factors that may increase its risk during their August Zoom meeting.

Dr. Merritt is a board-certified physiatrist and is a leader in her field. She is a longstanding member of several professional organizations, and serves as Executive Director in her practice, Multicultural Health Institute (MHI). Some of her initiatives include "Know No Bounds," the "Positive Aging Senior Wellness" series, The Sarasota Community Health Guide, The Multicultural Action Team (MAT), and Gatekeepers and Safekeepers of Community Health.

During her visit with our group, Dr. Merritt focused on the following factors that may increase the risk to develop Waldenstrom's:

- Being older – WM may occur at any age, but generally at 65 and older
- Being male
- Being white
- Family history of lymphoma
- Environmental impact

Dr. Merritt further noted that causes of WM are unclear. It is a rare form of blood cancer that results in too many abnormal lymphocytes (a type of white blood cell) in the bone marrow. These cells produce an excessive amount of IgM protein that circulates in the blood. Though there is no cure for WM, there are treatments that help manage symptoms. She suggested the following to help patients manage their WM:

- Try to achieve total wellness—what you eat, do, think, and where and how you spend time—this can have negative or positive impact
- Maintain a nutrient-dense, balanced diet
- Acknowledge fatigue
- Limit smoking
- Increase physical activity—engage in "joyful movement"
- Pursue medical and emotional support
- Self-advocacy is key

The POC group valued the information shared by Dr. Merritt and committed to following her suggested practices. The more knowledgeable we are about our disease, the better advocates we can become.

Thank you, Dr. Merritt!

Have Your Say

The *Torch* welcomes letters, articles, or suggestions for articles. If you have something you'd like to share with your fellow WMers, please contact *IWMF Torch* editor Shirley Ganse at *shirleyganse@hotmail.com*

GERMANY
The Waldi Meeting in Ulm, Germany
May 19-21, 2022

Waldenstrong group in front of Ulm Cathedral, Ulm, Germany

It was one of those days in our Waldenstrom WhatsApp support group, founded by Uwe Joseph Kercher a year ago, when one piece of bad news followed another. It was a Friday, and a member of our group, let's call him George, thought it wouldn't be good to start the weekend in such a desperate mood.

George brought up a completely different item, proposing that we should think about a personal meeting to celebrate the first anniversary of our group's existence. The reaction was overwhelmingly positive: maps of Germany were immediately produced, marking where different group members lived to identify the best place for a reunion. George prepared a draft of the meeting schedule and concluded that an additional highlight was required. He contacted Professor Christian Buske, the specialist for Waldenstrom's macroglobulinemia (WM) at the University of Ulm, a city in South Germany on the banks of the river Danube. Dr. Buske agreed to give the group a special presentation on WM that would include a question-and-answer session. George informed the group the meeting would take place in Ulm.

It turned out to be a very special event. Dr. Buske took us through the basics of our disease, explained in clear words complex medical and biological interrelationships, talked about the gene defects causing WM, and described what's going on in our bodies. We learned about the different potential treatments and how they are linked to the specific types of gene defect, which requires analysis before treatment commences. Afterward we felt well-informed about the latest status of WM research. The complete session is available as a video stream on our website *www.waldenstroem.de*. The session was livestreamed, and people participated online.

The meeting in Ulm was also a social event. We had openly exchanged thoughts and unrestricted information for over a year and were curious to meet each other in person. From the very beginning, it was almost a kind of family reunion. No barriers existed—which does not automatically happen when people from Austria, Germany, and Switzerland come together for the first time. A guided tour through the city of Ulm, led with much humor by a charming lady, rounded up the program of this very first meeting of ours.

We all agreed that it had been an efficient and valuable meeting, despite the fact that we left with a lot of additional questions concerning WM. We will keep in touch and are grateful that Dr. Buske promised to continue to support us.

Reported by Jürgen R. Goetz, Waldenstrong Germany

A Walk for Waldenstrom's group of clinicians from University College London Hospitals (UCLH). In the picture are four doctors, including WM global superstar Shirley D'Sa, two clinical nurse specialists, and three patients—including Bob Perry, who provided the photo.

27th Annual IWMF Virtual Educational Forum videos and presentations are now available online at:

https://iwmf.com/iwmf-2022-virtual-educational-forum-videos-presentations/

IWMF EVENTS
2022 IWMF EDUCATIONAL FORUM
Living, Learning, and Thriving with WM

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FUNDRAISING CAN BE A CHALLENGE

By Alix Redmonde, Director of Development and Communications

Fundraising can be a challenge even in the best of times.

The question is, how do you raise awareness, support, and funds for a rare, little known medical condition with a name that's hard to pronounce even for those with top elocution skills?

Now, throw in a global pandemic!

You get the idea. Unless you are a person living with Waldenstrom's macroglobulinemia (WM) or know someone living with it, you have probably never heard of it.

WM community members are incredibly generous and supportive. But WM is rare, affecting about 200,000 people in the US and approximately the same number in the rest of the world. We need to reach out beyond our community, educate everyone about WM, and gain their support.

As the IWMF's Director of Development and Communications, I make it my mission to tell everyone I meet about the IWMF and what I've learned from people living with WM who are brave enough to share their story in an effort to help others. I also love a good challenge. Getting the word out about WM is the first step in fundraising. No one will donate to something they know nothing about! So, we are ramping up efforts to raise awareness through social media, TV shows, news, and print.

The IWMF is creating campaigns and partnering with companies that offer unique opportunities. Most recently we partnered with FreeWill, a company that makes estate planning warm, intuitive, and totally FREE!

You may not know this, but 70% of US adults do not have a will. I find this a little odd, as so many of us have worked hard and want to make sure the fruits of our labor and things we treasure in life are left to people, pets, and causes we truly care about. August was Make a Will Month, and several of our community members took advantage of using this free online tool to include the IWMF in their future gift giving. Between August and the first week of September, $100,000 in bequests were made to our organization.

When you make a provision for a future gift to the IWMF, you are honorably recognized by the **Ben Rude Heritage Society (BRHS)**, which is named in recognition of the second president of the International Waldenstrom's Macroglobulinemia Foundation. The whole process takes only about 15 minutes, and, when finished, you will most likely exhale a sigh of relief because you can put it away and know you took care of business.

Another underutilized way to raise awareness and funds is through social media.

I received a wonderful call from a 92-year-old woman whose granddaughter asked people to donate to the IWMF in lieu of a gift on her online wedding registry. This incredible lady stayed on the phone while I talked her through the steps of gift giving; she was overjoyed her loving granddaughter considered donating to an organization so near and dear to her heart.

You can also post a birthday fundraiser on your Facebook page. Think creatively—a graduation, accomplishments, honoring someone, and finishing a project are all worthy of consideration.

Many of us are technophobic and hesitant to push buttons, but for popular online sites it's easy: just follow the directions step by step, or you can always call the IWMF office at 941-927-4963. One of us will be more than happy to help you!

BEN RUDE HERITAGE SOCIETY

The Ben Rude Heritage Society recognizes those who have made provisions for a future gift to the IWMF, such as a bequest, listing the IWMF as a beneficiary for a life insurance policy or qualified planned asset (such as 401k or IRA), or a life income agreement, such as a Charitable Remainder Trust. Legacy gifts represent an important component of the IWMF's financial future. There are many ways to support the IWMF through a planned gift, but a bequest is perhaps the easiest and most tangible way to leave a lasting impact. The following supporters are members of the Ben Rude Heritage Society:

ANONYMOUS (7)
JEAN-MARC AUDIBERT*
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* Deceased
◊ Founding Member

RESEARCH PARTNERS

For a commitment of $50,000 per year for a minimum of two years, or a lump sum of $100,000 or more, you can become a research partner supporting a specific IWMF research project approved by the IWMF's Scientific Advisory and Research Committees. Research Partners will have an opportunity to be kept informed of the progress of the research project and will be formally acknowledged by the investigators in their report of the project as well as in any resulting publications. Generally 10 to 12 research projects are underway with new projects under consideration each year. The following funds support current IWMF research:

The David and Janet Bingham Research Fund of the IWMF has supported the following research projects:

- Brad H Nelson PhD & Julie S Nielsen PhD, Deeley Research Centre - *Mutant MYD88: A target for adoptive T cell therapy of WM*
- Aldo M Roccaro MD, PhD, Dana-Farber Cancer Institute - *Further genomic characterization of Waldenstrom's macroglobulinemia: unveiling the role of the CXCR4 somatic mutation, a crucial regulator of pathogenesis and important target for therapy*

The Elting Family Research Fund of the IWMF has supported the following research projects:

- Shahrzad Jalali, PhD, Mayo Clinic - *Modulation of T-cell function by metabolomic signature of the bone marrow microenvironment in Waldenstrom's Macroglobulinemia*
- Larry W Kwak, MD, PhD, Beckman Research Institute of the City of Hope - *Anti-tumor and immune microenvironment responses following a first-in-human DNA fusion vaccine for asymptomatic WM*
- Sherie L. Morrison, PhD, The Regents of the University of California - *Novel antibody-targeted interferons in combinatorial therapies for Waldenstrom's macroglobulinemia*
- Dr. Bruno Paiva & Dr. Jose Angel Martinez Climent, Clinica University of Navarra - *Single-cell next-generation flow and sequencing to unravel the pathogenesis of Waldenström's Macroglobulinemia and to design genetically driven human-like experimental models*
- Dr. Marzia Varettoni, Fondazione Italiana Linfomi Onlus - *Non-invasive diagnostics and monitoring of MRD and clonal evolution in Waldenström's Macroglobulinemia*

The Lynn M. Fischer Research Fund of the IWMF

The Robert Douglas Hawkins Research Fund of the IWMF

The K. Edward Jacobi Research Fund of the IWMF has supported the following research project:

- Dr. Morie Gertz, Mayo Clinic - *Biology to Treatment: Prognostic factors, Bone Marrow Microenvironment, Genomic and Proteomic Profile of Light Chain Amyloidosis in Waldenström's Macroglobulinemia*

The Michael and Rosealie Larsen Research Fund of the IWMF

The Leukaemia Foundation of Australia has supported the following research project:

- Zachary Hunter, PhD, Dana-Farber Cancer Institute - *Multiomic analysis of DNA, RNA and epigenomic networks for prognostication and novel target identification in Waldenstrom's Macroglobulinemia*
- Gareth J. Morgan, PhD, New York University Grossman School of Medicine - *Using mutographs to define the molecular landscape and cell of origin of Waldenstrom's Macroglobulinemia*

The Ed and Toni Saboe Research Fund of the IWMF has supported the following research project:

- Larry W Kwak, MD, PhD, Beckman Research Institute of the City of Hope - *Anti-tumor and immune microenvironment responses following a first-in-human DNA fusion vaccine for asymptomatic WM*

The Paul and Ronnie Siegel Family Research Fund of the IWMF

The Carolyn Morris Research Fund of the IWMF

The Yang Family Research Fund of the IWMF has supported the following research projects:

- Steven Treon, MD, PhD, Dana-Farber Cancer Institute - *Targeting MYD88 in Waldenstrom's Macroglobulinemia*
- Zachary Hunter, PhD, Dana-Farber Cancer Institute - *Multiomic analysis of DNA, RNA and epigenomic networks for prognostication and novel target identification in Waldenstrom's Macroglobulinemia*

The Robert and Nadeline White Family has supported the following research project:

- Steven Treon, MD, PhD, Dana-Farber Cancer Institute - *Targeting MYD88 in Waldenstrom's Macroglobulinemia*

The Marica Wierda Research Fund of the IWMF

The WMFC has supported the following research projects:

- Zachary Hunter, PhD, Dana-Farber Cancer Institute - *Multiomic analysis of DNA, RNA and epigenomic networks for prognostication and novel target identification in Waldenstrom's Macroglobulinemia*
- Dr. Signy Chow, Sunnybrook Research Institute - *Characterization of Genomic Alterations in Treatment Naive Patients with Waldenstrom's Macroglobulinemia Through a Course of Targeted Treatment and Disease Progression*

NAMED GIFT FUNDS

For a commitment of $10,000 per year for five years, or a lump sum of $50,000 or more, you can establish a named fund at the IWMF in your own name or in the name of someone you wish to honor. The following funds support information, education, mission programs, research, or a combination of each:

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If you have discretionary giving power and would like to help move our research program forward in a special way, we invite you to join those listed above. For more information about Research Partners and Named Gift Fund opportunities and potential gifting options that might make that possible, please contact Director of Development and Communications Alix Redmonde at *aredmonde@iwmf.com*.

BETWEEN JUNE 1, 2022, AND AUGUST 31, 2022, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN MEMORY OF:

William A.S. Akana
Margaret Akana

John T. Baronowski
Gail Swensen

Jacob Block
Harriet Block

Lynda Bradley
John Anagnostopulos
William and Ellen Mnich

Philip Brody
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2023 IWMF EDUCATIONAL FORUM

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The 28th Annual IWMF Educational Forum will be a unique experience to learn from medical experts and WM community members from around the world.

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