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INSIDE THIS ISSUE

BEYOND REMISSION: UNDERSTANDING THE GOAL OF THERAPY IN WM

By Dr. Jonas Paludo
Mayo Clinic, Rochester, MN

Dr. Jonas Paludo

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.

After receiving the diagnosis of Waldenstrom macroglobulinemia (WM), the immediate next question in mind is what to do about it. It is natural to feel the urgency to fix a problem, to make it better, primarily when it is related to a serious health condition.

However, it is essential not to put the cart before the horse. Before we can delve into *what* to do and *how* to accomplish it, we need to understand the *why* behind it. The *why*, perhaps the most critical question, is often rushed amid the urgency to return to "normal life" and the anxiety associated with any cancer diagnosis. To understand *why* something is done (or not) in WM, is to understand the goals of therapy.

Over the next paragraphs, let's review the current state and understanding of the goals of therapy in WM. We will start with the assumption that you are at a point where initiation of WM-directed therapy is needed. The discussion about when to consider treatment, what our main options are, and how they are evaluated has been published in a previous article (*IWMF Torch*, October 2022, *https://iwmf.com/wp-content/uploads/2022/10/N31400-Torch-Oct-2022_web.pdf)*.

While we should always hope for the absolute best treatment outcome, the goals of therapy are still grounded in what the current therapies for WM can realistically achieve. As treatments evolve over time, so do our goals of therapy.

What can the current WM treatments achieve?

Over the last several years, we have witnessed an exponential increase in the number of new drugs and regimens being evaluated for WM that have become standard options for this disease. Anti-CD20 monoclonal antibodies have been added to several treatment regimens, and we have seen the emergence of new drug classes, such as proteasome inhibitors, BTK inhibitors, and BLC2 inhibitors. Not only have these drugs become part of our toolkit for treating WM, but also multiple generations of drugs in these categories have emerged.

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Moreover, several novel drugs and regimens are currently under investigation for WM, promising several more treatment options in the near future.

Having more treatment options is a significant accomplishment for the WM community and the scientific field, and it is a goal that we should continue to strive for. With more drugs and regimens, WM patients can live longer by having more treatments to rely on. Population-based studies have shown improvements in survival trends for WM, although the exact correlation between number of available drugs and improved survival is unknown.

The most critical point to understand about the goals of therapy is that despite the increasing number of treatment options and longer survival rates, it is important to note that the available drugs are not yet capable of achieving a cure for WM. While a larger number of treatment options can help patients live longer, they cannot yet eradicate the disease entirely.

> *A key point here is to distinguish complete remission from cure. Complete remission is the state where no evidence of cancer cells can be found, and it is achieved by a small proportion of patients after some WM-directed treatments. However, the ability to find cancer cells is limited by our current technology and diagnostic test accuracy. Despite not being detected, a small number of cancer cells are still present in the body and, given enough time, the cancer will relapse. Cure, on the other hand, is the state where all cancer cells have been eliminated and the cancer will never return.*

The second most important point to understand about the goals of therapy is that every past, current, and likely future anti-cancer drug will cause side effects in the process of treating the malignancy. Side effects may vary from one drug class to another and from patient-to-patient. It is difficult to predict the specific side effects and severity that each patient will encounter with different drugs, but we can be confident that side effects will be part of any treatment used in WM.

The third most important point to understand about the goals of therapy is that when studies exploring the natural history of WM are considered, no evidence suggests that treating patients with smoldering (asymptomatic) WM improves survival compared to initiating treatment once symptoms occur. Furthermore, with rare exceptions, delaying therapy until the onset of symptoms does not adversely affect the response to treatment. Patients with smoldering WM may have a life expectancy that is similar to that of the general population.

If a cure is not (yet) a possibility, then what is the goal of therapy?

Since we are not yet capable of eradicating this disease or making smoldering WM patients live longer with the available treatments, the overarching goal of WM-directed therapy is to *improve quality of life*. This is the *why*, the reason to start, continue, and stop/change treatments.

I recognize that this goal is not an objective or easily measurable target; quality of life cannot be monitored with routine labs every few months, rather it is an individualized and fundamental concept. The next natural question that comes to mind is, what is quality of life? The World Health Organization (WHO) defines it as one's perception of their reality relative to their goals, as observed through the lens of their culture and value system. It is an individualized sense of well-being, balancing positive and negative elements, which may change from time-to-time as our reality and goals in life evolve.

I cannot tell you what quality of life means to you, but I'm sure you can feel it.

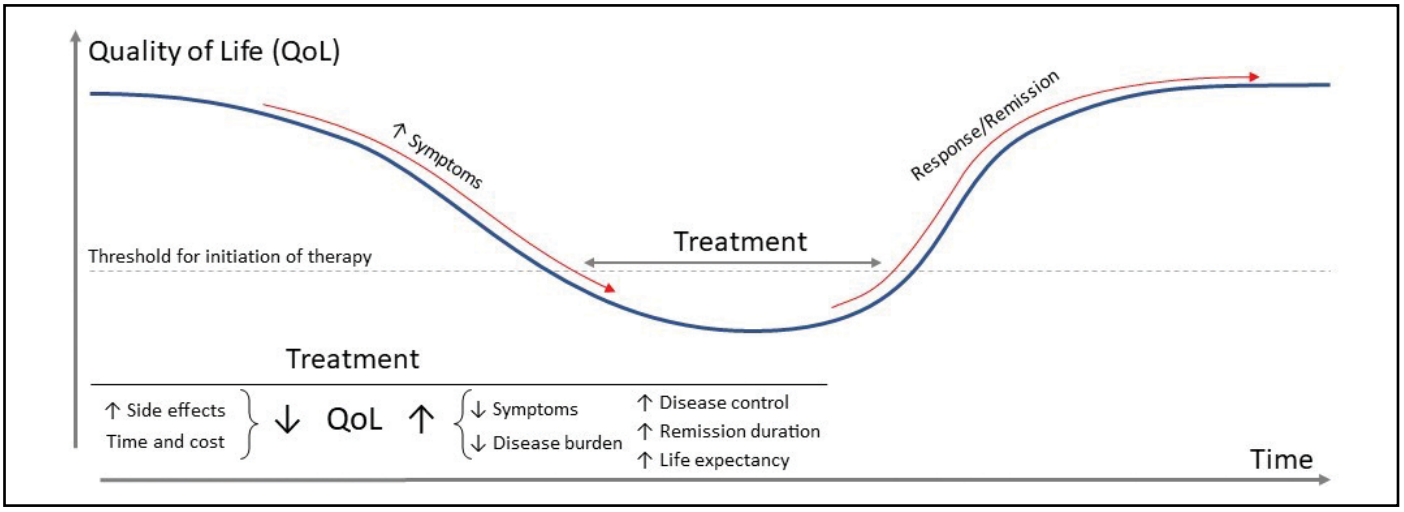
The primary mechanism by which WM affects quality of life is through symptoms. For example, fatigue interferes with your daily life, or peripheral neuropathy causes discomfort or affects your balance. This is the rationale for our general recommendation of reserving initiation of treatment to patients who are symptomatic. Once the interference of WM with your quality of life is enough to counterbalance the potential side effects of therapy, it is time to consider initiation of treatment.

An especially critical point to make here is that routine visits with your doctor for clinical assessment and labs are essential even though you may not currently have any symptoms from WM. These assessments are intended to detect early complications that may require treatment before they become overtly symptomatic. For example, WM may cause kidney failure, which can become symptomatic at a point only when it is irreversible and hemodialysis is needed. The need for hemodialysis, fortunately an exceedingly rare scenario, would significantly compromise quality of life, so preemptive initiation of treatment would be indicated. This is just one example of an extreme situation. Several other clinical changes might prompt proactive initiation of therapy before symptoms arise, so that quality of life is not significantly affected.

Reflecting on quality of life

Please take a moment to reflect on what quality of life means to you and how it has changed over the years (positively and negatively), particularly since your diagnosis with WM. Consider how WM symptoms interfere with your daily life, including activities with your family, friends, and work. Peace of mind is also an important consideration, which has a variable and individualized impact on quality of life. Finally, with the help of your doctor, reflect on how side effects (ongoing if already on treatment, or potential if considering a new therapy) could interfere with your quality of life. Remember that side effects are part of

Beyond Remission, cont. on page 4



any treatment, but there could be specific ones that you consider incompatible with your quality of life goals.

This exercise helps identify your priorities for living a better life with WM and is fundamental for your doctor to know how to best guide your treatment strategy. Treatment strategy is not only limited to the choice of drugs, but also factors in the sequence of treatments and the right timing to start, stop, or hold therapy. Furthermore, characteristics of different treatments are weighted when developing a treatment strategy, including duration of therapy (fixed-duration vs. continuous therapy), depth of response (aiming for more profound responses for longer periods of remission vs. control of disease), and how potential side effects may interfere with other co-existing medical issues.

Closing the loop

I hope this article helps you understand the current view on the goals of therapy in WM. While we strive to develop better treatments—and considerable progress has been made with your help over the last several years—and we hope for a potential cure for this disease, our therapy goals are constrained by what current treatments can achieve.

Improvement of quality of life remains the overarching goal of therapy in WM. Remember to consider the *why* before jumping into *how* and *what* treatment to start. You may feel the need to decide quickly, but it is important to take some time to reflect and discuss with your doctor.

If possible, seeking a second opinion before making any treatment decisions is often a good idea. This is particularly important with a rare disease such as WM and considering the variety of different treatments available. Timing for initiation (or discontinuation) of therapy and treatment strategy should always be guided by your view of quality of life, your disease status, and your priorities in life.

WM-NET: A NEW SOLUTION TO THE CLINICAL TRIAL CHALLENGES IN WM

By Dr. Jorge Castillo, Dana-Farber Cancer Institute

Dr. Jorge Castillo

Becoming a participant in a clinical trial is a decision of utmost importance. After signing the consent form, the patient becomes a "participant," and the treating doctor becomes an "investigator." The relationship, therefore, changes to some degree. The investigator still acts and reacts, having the participant's best interest at hand, as is usually done between a physician and a patient. However, the actions and reactions in a clinical trial are delineated and guided by a protocol, or plan, guaranteeing that all participants be treated alike in a way that can be reproduced and shared with the rest of the world once the clinical trial results are published.

One of the purposes of a clinical trial is to evaluate a new agent or combination of agents that might (or might not) be safe and effective in treating a disease. Most of the time, previous laboratory or clinical studies using these investigational agents provide a preliminary, reasonable signal of efficacy that prompts our interest. However, there are still multiple unknowns. We do not know how effective the treatment is going to be. We do not know if an unknown side effect will be observed. Despite these unknowns, clinical trials are the most important way to advance the medical field. Without clinical trial participation, developing now-standard agents such as rituximab, bendamustine, proteasome inhibitors, BTK inhibitors, or BCL2 antagonists would have been impossible.

Clinical trial participants are usually "poked and probed" more often, as complete data are required to understand how the study treatment is benefiting (or not) the participant. Given these requirements and unknowns, some patients are not interested in participating in clinical trials, which is understandable. It is essential to note that the decision to participate in a clinical trial should be made after careful consideration of the pros and cons of standard approaches and with the understanding that participation is purely voluntary and can be stopped at any time.

Waldenström macroglobulinemia (WM) poses several challenges for developing clinical trials. As all of you know, WM is a rare disease, with a prevalence of less than 50,000 individuals yearly in the United States. Additionally, most WM patients are still treated in community health care settings with little or no knowledge of clinical trials. On the other hand, multiple clinical trials may be running concurrently and competing for the already rare patient who is a candidate for a clinical trial. An additional obstacle is that clinical trials are typically offered at single institutions, representing a high degree of travel, time, and financial commitment from participants.

Recently, a patient with WM came to see me in clinic. The patient was diagnosed 20 years ago and had received multiple lines of therapy. The disease had been well controlled on a BTK inhibitor for several years, but now the patient presented with evidence of disease progression causing fatigue and other symptoms. Given the extensive history of previous therapies, we discussed the limited treatment options available. We focused the discussion

Dr. Steven Treon, Newton Guerin, Dr. Tom Hoffmann, Dr. Jorge Castillo at the Cambridge, MA, meeting of the WM-NET.

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on clinical trials; this patient would have been an ideal candidate. Unfortunately, the patient felt a clinical trial in Boston would be too demanding. The patient lived alone and depended on friends for transportation. The trial required lab checks two days in a row for a few weeks, meaning the patient had to stay overnight in a hotel in Boston. The study was out of the question. If only a clinical trial were available closer to home.

At Dana-Farber Cancer Institute (DFCI), we have devised a way to address, at least in part, the issues mentioned above: the creation of WM-NET, a United States-based think tank aimed at designing and executing scientifically driven clinical trials and research projects to improve the lives of WM patients. We would start by convening a collaborative group of practicing clinician-researchers who can identify critical clinical questions and design studies to answer them. This network of clinical investigators would facilitate a more rapid translation of study results into practice. Additionally, a committed group of like-minded clinical investigators with a sustainable infrastructure to share information would allow for faster patient accrual into trials, facilitate bringing innovative trials closer to patients, encourage the participation of underrepresented populations, and provide leverage to negotiate with funding sources (such as pharmaceutical companies) to design clinically meaningful trials.

With the help of several strategic partners, such as the IWMF, and donors, such as the Brettschneider Family Fund, the Kaplan Family Fund, the Kissam Family Fund, the Siegel Family Fund, and the WMR Fund, we were able to secure funding to run WM-NET for five years. Over the following years, it is expected that WM-NET will activate clinical trials concurrently in multiple centers, accelerating

WM-NET current participating facilities

the access to novel agents. WM-NET will also be advised by the patient community and represented by members of the IWMF and by WM specialists outside of the United States.

In October 2023, clinician-researchers from 17 institutions gathered for the first WM-NET meeting in Cambridge, Massachusetts. During this three-day event, we discussed unmet needs in clinical trials, and different network members presented several innovative clinical trial concepts. The excitement for this initiative was evident. The highest interest was in developing limited-duration clinical trials using agents with novel mechanisms of action. The clinical trials should include cutting-edge genomic testing, biobanking, and quality-of-life assessments.

At the conclusion of the event, it was evident that much work is still needed, but the first WM-NET meeting was a decisive step in the right direction.

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*

THE TORCHBEARER REPORT: OUTLOOK FOR 2024

By Newton Guerin, IWMF President and CEO

Newton Guerin

As a mission driven, not-for-profit organization, we recognize that innovation plays a key role in addressing challenges and creating positive change. To continue to better meet the needs of the global WM community, it is critical that the International Waldenstrom's Macroglobulinemia Foundation (IWMF) creates a culture to promote continuous improvement and fully embrace fostering growth and innovation in all our information, education, support, and research programs. We do this by listening to our stakeholders: people living with WM, caregivers, donors, health care providers, and the WM research community.

Our Board of Trustees has set a very compelling vision for the organization: "A world without WM." To achieve this vision, we must grow and keep growing. We can't just settle for the status quo. Our mission statement to "Support and educate everyone affected by WM to improve patient outcomes while advancing the search for a cure" guided our Board of Trustees in identifying and agreeing on our Global Imperatives (strategic priorities) going forward. These include expanding research; increasing patient awareness, education, and support; increasing health care professionals' awareness of WM; partnering with like-minded organizations; and increasing and diversifying fundraising (see *https://iwmf.com/vision-and-mission/*).

Each of you, as an IWMF stakeholder, is the ultimate judge of the quality and value of our programs and the impact they make. That motivates us to continually look at our programs and ways of accessing these programs from the "customer" perspective.

To help guide us in "doing the right things" and not just "doing things right," we established an Education Committee (EC) to serve as the primary strategic and advisory group responsible for developing an organization-wide plan to ensure that IWMF educational offerings meet the needs of people affected by WM. This committee is composed of staff and Board representatives from each of the IWMF's information, education, and support programs and is already making a positive impact.

In the fall of 2022, the EC surveyed the IWMF community to determine educational needs and satisfaction with our offerings. This survey helped to provide prioritization and recommendations for the IWMF's programs by integrating the patient perspective, WM clinician expertise, and staff/Board member experience.

WM Community Wellness Programs

One of the significant takeaways from this survey and subsequent discussions among the EC was the importance of quality of life and living well with WM to our patient community. To dig deeper into specific programs or other offerings that we should consider, the IWMF staff conducted a follow-up survey to determine interest in expanding our existing WM Community Wellness Programs. Of the 107 folks who responded, 95% said they would like to see the IWMF expand our wellness offerings. With that as our charge, we added Ann Grace MacMullan to the home office staff team as our new Wellness Program Coordinator. Ann is now bringing our "Chair Yoga," "Sound Meditation," "Cardio Flow" and "Yoga Nidra" sessions to an increasing number of patients and caregivers. In addition, 70% of respondents expressed interest in a WM community lecture series. We listened to that customer voice and have since offered wellness webinars addressing several topics, including "Everything You Wanted to Know About Sexual Health and Cancer," "T'ai Chi and Qi Gong for Cancer Care," "Finding Fitness," and "Coping with Fatigue and Sleep Disturbance." In addition, nine wellness topic webinars are already in the works for 2024. These monthly Zoom gatherings will feature notable wellness experts whose mission is to share their knowledge and know-how toward better patient outcomes.

*Each of **you,** as an **IWMF stakeholder,** is the ultimate **judge** of the **quality** and **value** of our **programs** and the **impact** they make.*

Health Care Provider (HCP) Education and Awareness

We grew collaborations that made it possible to adapt and disseminate accurate, up-to-date, and independent information to the global WM community. The IWMF-led "Global Patient Initiative" partnered with other lymphoma patient organizations to provide a forum to work together to ensure that, no matter where patients and caregivers look for the latest information regarding WM, they find the same consistent guidance and information regarding the disease and available treatments. Along with our partner organizations, we identified the need to provide opportunities for health care providers (HCPs) to acquire new knowledge, increase their skill set, and expand their clinical expertise relative to WM. The result should be to improve quality

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of care for people with WM and increase the accessible pool of HCPs knowledgeable about WM. To that end, we created the IWMF's first professional education booklet, "Waldenstrom's Macroglobulinemia Essential Information: A Physicians Guide." It was so well received, we went on to create a comparable resource for nurses, "Waldenstrom's Macroglobulinemia Essential Information: A Nurses Guide." Both are now available in multiple languages. We also partnered with Scientific Education Support, a UK-based medical education provider, to create a WM section of LymphomaHub (*https://lymphomahub.com/*), a highly regarded online resource for health care providers throughout the world. In addition, we are working to expand CME/CE training opportunities to the global health care community.

Success** in today's ever-changing, global environment **depends on agility** and requires a **capacity** for rapid **change** and **flexibility.

International Affiliate Support and Engagement

Our commitment to better serve the global WM community outside the US has never been stronger. Early in 2023, our Board of Trustees agreed to make an investment to hire the IWMF's first employees in Europe. Beth Mitchell and Hannah Syed are now job-sharing our newly created Manager, Affiliate & European Partner Engagement position. They set out to have one-on-one conversations with affiliate leaders to listen to their challenges and begin to strategize about how we could structure our support to best meet their needs.

Just recently, we brought together affiliate leaders from five continents around the globe who met in Amsterdam to talk about how to make the world a better place for members of the WM community. In conjunction with that meeting, we also held the IWMF's first ever European Patient Forum in partnership with WMUK. In total, 233 folks joined us either in one of our two in-person sites (Amsterdam and Birmingham, UK) or virtually. *(See the meeting overview in this issue on pages 9 to 13.)* It was amazing and inspiring to see what can happen when people work toward a common goal!

IWMF/WM-NET Research Partnership

On the research front, we are so excited to support the new WM-NET (led by Dana-Farber Cancer Institute and other institutions) to create a network of clinicians and researchers focused on WM. It is designed to facilitate a more rapid translation of clinical trials and study results into practice, resulting in better treatment options. This $2.5 million commitment is the largest single research grant ever for the IWMF and is our first project outside our long-standing practice of focusing solely on basic science. *(See Dr. Jorge Castillo's article on WM-NET in this issue on page 5.)*

Success in today's ever-changing, global environment depends on agility and requires a capacity for rapid change and flexibility. The IWMF continues its commitment to being just that for the global WM community. As a key stakeholder, please continue to let us know how we're doing. Thank you again for your support that makes all this possible and remember, no matter where you are, with the IWMF, you are never alone!

THE SUN NEVER SETS...

By Ron Ternoway

EUROPEAN WM PATIENT FORUM

IWMF WMuk

As IWMF affiliates from five continents gathered in Amsterdam for the first European WM Patient Ed Forum on October 20, it was blindingly clear that the sun never sets on our quest for a world without Waldenstrom macroglobulinemia (WM).

I was there to represent the WM Foundation of Canada (WMFC), the 21-year-old eldest sibling in this burgeoning international family of WM advocacy and support organizations. There are now more than two dozen IWMF affiliates, representing countries with a combined population of nearly four billion people. That's half the world...and counting!

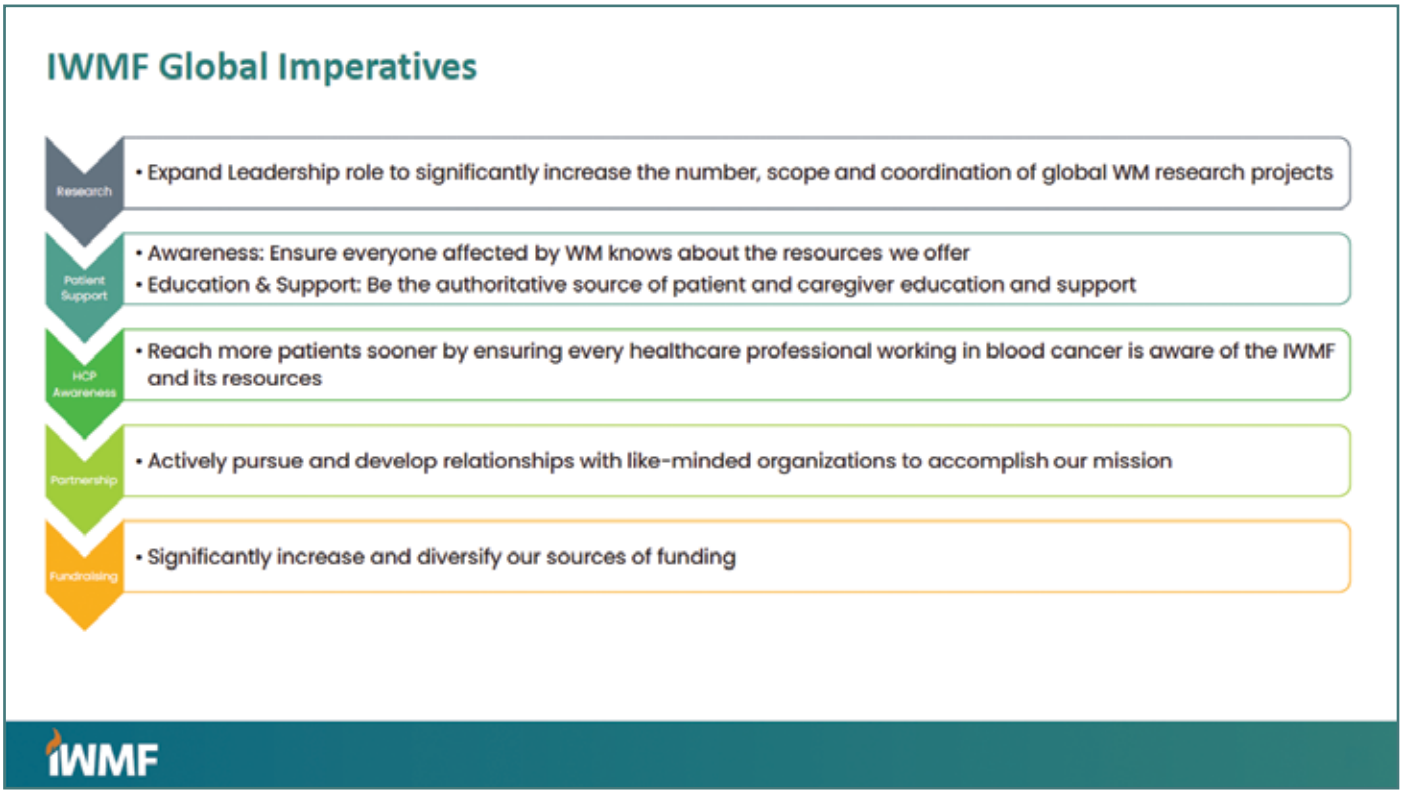
This was the first-ever in-person meeting of these kindred spirits, the fruit of the vision of IWMF Vice Chair Carl Harrington and IWMF Affiliates Chair and WMFC past Chairman Paul Kitchen: the IWMF Global Patient Initiative. It's amazing what past presidents can do when they set their minds to it...

Also in attendance were IWMF CEO Newton Guerin and IWMF Manager, Information and Support Michelle Postek. Newton shared with us the big picture—the IWMF priorities for research, patient support, health care provider awareness, partnerships, and fundraising on a global scale.

As with the IWMF, founded more than 20 years ago by pharmacist Arnie Smokler, most of the current international affiliates were brought to life by "heroes," individual WM patients or family members with a fervent desire to better the lives of those of us living with WM. There is a wide variety in the age and size of our affiliates, ranging from newbies with five members or less to well-established ones with memberships of 800 or more.

As a testament to the IWMF's goal to partner with all and any like-minded organizations, representatives from national cancer support groups in China, South Africa, India, and Portugal joined other local IWMF heroes from around the world.

We spent most of the day sharing best practices, understanding the unique challenges of each country's health care system,



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Attendees came from all over the world: Europe, including France, Finland, Germany, Sweden, and the UK, as well as South Africa, Chile, USA, India, and China.

and identifying challenges and priorities for 2024. The IWMF announced that there would be funding available in 2024 to support international affiliate priorities. And there are plans afoot for an annual WM Awareness Day.

Ever the visionary, Carl Harrington described how he sees the IWMF, international affiliates, and local support groups working together toward a world without WM:

IWMF responsibilities – global issues
The IWMF should be the acknowledged source for accurate, complete information on WM. Other responsibilities include research, with direct funding to the best research minds world-wide in search of a cure; education for WMers and families; support for people with WM and their families; and primary contact with pharmaceutical companies involved in WM therapies.

Affiliate responsibilities – national issues
The international affiliates should work with their own national healthcare systems; create a directory of national WM experts; give second opinion support to patients; offer information on treatment options, including clinical trials; develop national patient advocacy organization partnerships, and adapt and translate IWMF global documents.

Affiliate responsibilities – regional issues
On a more local level, affiliates should create a directory of community hematologists; act as a support group liaison and offer training to leaders; and gather information about regional hospitals' services for WM patients.

This rewarding and productive meeting was brilliantly planned and executed by Beth Mitchell and Hannah Syed, Managers of Affiliate and Global Partner Engagement for the IWMF. They hit the ground running in April as the IWMF's first European employees. Someone at the IWMF is really, really, REALLY good at hiring the best!

If we thought Beth and Hannah did a stunning job with the international affiliates meeting, just wait for the story of the first-ever IWMF European Educational Forum the

Jeannette Quiroz Gómez, the IWMF affiliate representative from Chile, presented an overview of her patient group.

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next day—an organizational and technical masterpiece featuring simultaneous meetings with WMUK members in Birmingham, England, and those of us in Amsterdam, and live-streamed world-wide!

We in Amsterdam started with a "speed dating" session led by Bob Perry, leader of the Irish WM affiliate and largely responsible for recruitment of the extraordinary faculty who enlightened us from both sites. He kept us moving as we chatted for two minutes with a new person, shuffled left at the bell, repeat...and in 40 minutes I had 20 new friends!

We took a coffee break and time to review three excellent poster presentations on WM research being conducted by PhD students working with Drs. Josephine Vos, Monique Minnema, and Marie José Kersten, all from the Netherlands. Two of the posters proposed evaluating the effectiveness of zanubrutinib for treatment of cold agglutinin disease and of peripheral neuropathy. The third dealt with a novel type of therapy called bispecific monoclonal antibodies (BsAb). This shows great promise as an alternative to CAR T cell therapy. As the name suggests, a BsAb is a protein that can bind to two different antigens. For example, it could take one of our immune system T cells called the natural killer (NK) cell by the hand and lead it over to a WM cell. Once the "handshake" is complete, goodbye WM cell! The significant advantage of this approach over CAR T is that the BsAb is "off the shelf"—rather than the expense and time required to remove, engineer, clone, and reintroduce T cells to an individual patient, the BsAb would work universally without individual customization. Pretty neat!

Back to the Ed Forum—several of the sessions were held simultaneously in both locations, with doctors in Amsterdam and Birmingham co-presenting on topics such as

- WM in the body—what is it, how does it develop, and why do I feel this way?
- Living with WM
- Approaching clinical trials

Susanne Öhrn and Ron Ternoway get acquainted in the "speed dating" session.

Carl Harrington moderated Ask the HCP Panel Q&A session; participants on stage (left to right): Dr. Sarah Dwinger, Dr. Simone Ferrero, Dr. Josephine Vos, Prof. Monique Minnema, Prof. Dr. Marie Jose Kersten; UK speakers on the screen: Charlotte Bloodworth, Dr. Shirley D'Sa, Dr. Dima El-Sharkawi, Isabella Jones

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- Fatigue
- Mental health and active monitoring
- An Ask the HCP Panel

The sessions were recorded and are available here: *https://www.youtube.com/playlist?list=PL8DMfoyQZpOqHTVp4oaZqg14aq-8biJEQ.*

All told, 233 participants enjoyed this premiere event, including nearly 100 online.

For me, there were two aha! moments—new ways of looking at our ongoing adventures with the gremlin called Waldenstrom.

The first one was from Dr. Shirley D'Sa, Doc Star extraordinaire from London. She has replaced the term watch-and-wait for someone not currently in treatment with the phrase "active monitoring." I really like this phrase; it takes us from being passive to active in managing our health.

Attendees find the European WM Patient Forum bags useful.

Saturday morning walkers in Amsterdam - Left to right: Gu Hongfei, Yun Wu, Margaret Hache, Paul Kitchen, Saurabh Seroo

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The second was from Isabella Jones, a refreshingly clear and candid occupational therapist from the Royal Marsden Hospital in the UK, who spoke on the topic of fatigue. Her insight—change your identity and change your point of view. Stop calling yourself a WM PATIENT! WM is just something we live with, not who we are.

So what's next? There will certainly be more growth in the size and number of our international affiliates and, most certainly, another European Ed Forum somewhere next year.

Stay tuned. Although WM is a rare disease, wherever you live on this planet, you are never alone!

Dr. Josephine Vos, Caroline Dippel, Jeannette Quiroz Gómez, and Mateo Rubilar

THE EUROPEAN WM PATIENT ED FORUM – A PERSONAL VIEW

By Bettina Schwethelm

Attending the Amsterdam location of the European WM Patient Ed Forum was really a last-minute decision for me. What literally propelled me to travel from Bonn, Germany (when these days trains in Germany are often very late and may even be cancelled at the last minute) was my immense respect for what the IWMF has been doing for and with people with MGUS and WM and their families. Additionally, what motivated me were the people I would be able to meet in person: Prof. Christian Buske (my second opinion here in Germany), Michelle Postek (Manager of Information and Support at the IWMF), with whom I have had email exchanges, Susanne Öhrn from Sweden, and some of the doctors (e.g., Dr. Shirley D'Sa, who appeared virtually from Birmingham, UK, and who had given a great webinar on peripheral neuropathy for the IWMF a year or two ago).

As an international public health professional, working in English (but living in francophone Switzerland), I quickly found plentiful information on the IWMF website after I received a diagnosis of WM in 2020. I read what I could find on the website and attended many IWMF webinars virtually. What struck me was the welcoming atmosphere and the easy dialogue between patients and well-known specialists in the US, quite different from my experiences in Switzerland (and later in Germany). I could not apply all I learned with success: I thoroughly failed to convince my first haematologist that a bone marrow biopsy was part of a proper diagnostic workup.

My interactions at the European WM Patient Forum started with a dinner the night before. When talking to participants

Bettina Schwethelm in a Belgian spring forest

The European WM Patient Ed Forum, cont. on page 14

from South Africa, England/Ireland, and the US, I realized with excitement that the IWMF truly was going international with some ten countries from four continents participating. This had been a hope during the past two to three years, but I did not expect it to happen at all or to happen this fast.

The next day was packed with information and interactions and went by too quickly. The interphase with the UK Birmingham portion of the Forum was amazing and went pretty much without snags. There are presentations I want to review again when they are online, but here are some of my thoughts after this packed and information-rich day. Let me start with one of my favourite moments:

***Countries** and their **health and insurance** systems **differ** greatly in what **treatments** they **allow** and at what **stage** of the disease.*

Several young Dutch medical professionals working on their PhDs and engaged in WM-related research had been invited to present their research in posters and use the opportunity to talk to patients. Since several were sitting at my table, I had the opportunity to emphasize how important their work is for us. As always, I also "pitched" the need of working across medical specialties and with other health professions in an integrated approach to support the diverse needs of patients with WM. One of the students' research topics on how patients weigh their treatment options is fascinating and should be expanded to more countries (it is currently limited to patients in The Netherlands, US, Canada, and Australia). Decision-making—when? how? with what?—can be truly agonizing when reading about side effects or interactions of available treatments with other conditions. Research findings could help us look at different perspectives when we are weighing our options. It is my recommendation to never lose an opportunity to involve young professionals during patient meetings; thus, I hope that the IWMF organizers make this a routine feature of future meetings.

Some of my other take-aways include:

The session on clinical trials provided a very clear explanation and was thought-provoking. Informed decision-making requires a lot from patients, affected by fatigue and other symptoms, who are not haematologists, oncologists, or neurologists. How can information about clinical trial information be made more accessible to patients and their doctors who may not be part of this research network? Could there be an international, well-explained inventory managed by the IWMF?

Countries and their health and insurance systems differ greatly in what treatments they allow and at what stage of the disease. It is difficult to listen to the treatment landscape and new medications with fewer side effects when such treatments cannot be accessed.

While we are all different in our symptoms and complaints, the IWMF's format of bringing professionals and patients together is comforting. At least during that day, I felt less alone with my condition. The hierarchies and barriers disappear. How could this be expanded?

- Could key faculty for the day bring other specialists and allied health professionals that are supporting WM patients? Could their attendance be supported by sponsors?
- Could there be country/linguistic area meetings (e.g., Germany, Austria, and the German-speaking part of Switzerland)?

A final recommendation: Interpretations of sessions in other languages should be carefully reviewed with native speakers before going on YouTube in languages other than English, as they can misleading if the content has not been translated correctly.

And, yes, my train home was cancelled at the last minute, requiring me to piece my journey home with four regional trains and a lengthy tram ride with more than 50 stops before arriving home. But I had lots to think about.

Videos of the entire Ed Forum can be viewed at: *https://www.youtube.com/playlist?list=PL8DMfoyQZpOqHTVp4oaZqg14aq-8biJEQ*.

NEW 2023 IWMF-FUNDED RESEARCH PROJECTS

By Dr. Glenn Cantor, *Torch* Science Editor and IWMF Trustee

Investigator: Jithma Prasad Abeykoon, MD, Mayo Clinic, Rochester, MN, USA

Defining the Prognostic Significance of TP53 Alterations in WM and Exploiting Them for Therapeutic Benefit

Project Period: 2023-2025, $157,500 over two years

Research work in the past 15 years has enabled scientists to understand key gene mutations in WM, including genes called MYD88 and CXCR4. More recently, mutations in another gene, called TP53, have been identified in WM patients. The prevalence and significance of this mutation in WM have not yet been definitively determined because of few studies that included small numbers of patients. TP53, called the "guardian of the genome," is essential because it prevents cancer. Usually, TP53 can tell when cells have damaged DNA or other genomic aberrations, stopping those abnormal cells from growing further and causing cancer. If the TP53 gene is mutated in certain key places, then TP53 can no longer prevent cancer or survey the genome of the cell for errors. With the loss of TP53, a critical control is removed, and abnormal cells can multiply quickly and form cancers.

With some types of cancer, if there is loss of TP53, the cancer is more aggressive and can resist standard treatment. With this two-year Robert A. Kyle Career Development Award, Dr. Abeykoon, an Assistant Professor of Hematology and Medical Oncology at the Mayo Clinic, will test cells from a large number of WM patients to better understand how common TP53 mutations are, whether TP53 mutations are associated with more aggressive disease, and how TP53 mutations affect response to the standard treatments used in WM.

In the second part of the project, Dr. Abeykoon will investigate a new form of therapy for WM patients with TP53 mutations. Using new genetic information and computer tools developed at the Broad Institute at MIT and Harvard, Dr. Abeykoon identified a potential weakness in cells that have mutated TP53. If WM cells lose their normal TP53 function as "guardian of the genome," they are more prone to proliferate rapidly and to have damaged or broken DNA. The WM cells with broken DNA may need to rely more on DNA damage repair mechanisms in order to survive. Dr. Abeykoon hypothesized that this increased reliance on DNA damage repair mechanisms is a critical weakness, making the WM cells with mutated TP53 especially sensitive to drugs that target DNA damage repair pathways. If the WM cells cannot accurately repair their broken DNA, they will likely die. In this project, Dr. Abeykoon will test WM cells in the laboratory and in mice to see if drugs targeting DNA damage repair pathways could be used in the future to treat the subset of WM patients with TP53 mutations.

Investigator: Christelle Vincent-Fabert, PhD, Centre de Biologie et de Recherche en Santé (CBRS), University of Limoges, Limoges, France

Study of Immune Microenvironment and BCR Signalling in WM-Like Mouse Model

Project Period: 2023-2025, $157,500 over two years

A challenge that WM researchers have faced in testing new therapies is the lack of good animal models. Dr. Vincent-Fabert, a WM researcher at the University of Limoges in France, has been working to create genetically engineered mice that develop WM-like disease as tools for WM researchers. With this two-year Robert A. Kyle Career Development Award, she will use the mice that she and her collaborators have created to investigate how WM cells interact with the immune system. Normally, the body's immune system controls the growth of many types of cancer cells. In WM, the tumor cells have developed ways to escape from immune control, enabling them to grow in the bone marrow environment.

*...**mutations** in another gene, **called TP53,** have been **identified in WM** patients.*

Scientists and pharmaceutical companies are discovering and developing many different drugs to prevent tumor cells from escaping the immune system. The exact drugs that are used in any particular type of cancer depend on understanding the specific mechanisms in that type of cancer. Using her mice that develop WM-like disease, Dr. Vincent-Fabert will study the tumor immune microenvironment and then test a variety of drugs to see if they alter the immune response to WM and help control disease.

In the second part of her project, Dr. Vincent-Fabert will focus on a hallmark of WM, the production of excessive IgM in the blood and on the surface of WM cells. She wants to understand why WM cells produce so much IgM, and not other related proteins, such as IgG. If IgM is so important, she hypothesizes that a role of IgM on the surface of WM cells is to send signals to the inside of the cell. These signals could enable the WM cells to grow and to avoid the immune system. Better understanding of the pathways involved in this signaling could lead to selection of specifically targeted drugs in the future.

New 2023 IWMF-Funded Research Projects, cont. on page 16

Investigator: Marion Espéli, PhD, Institut de Recherche Saint Louis, Paris, France

Impact of MYD88 and CXCR4 Mutations on Age-Associated B Cells at Steady State and in the Course of WM

Project Period: 2023-2024, $90,000 during one year

IWMF Research Seed Money Initiative Grants provide one year of funding to allow scientists to test a new idea. If the project is successful, the scientist is then able to use the results to support a larger, multi-year grant to do a more in-depth investigation.

Using a newly developed mouse model of WM which combines a MYD88 mutation and a CXCR4 mutation, Dr. Espéli, a senior scientist at the Institut de Recherche Saint Louis in France, observed an unusual subset of B cells that accumulated before the onset of WM disease. These B cells were seen in mice that had both the MYD88 and CXCR4 mutations, like many WM patients. This cell subset has the ability to become IgM-secreting cells, so this raises the possibility that they could be important in WM. In this Seed Money project, Dr. Espéli and her team will investigate the significance of this B cell population, its role in WM development, and how these cells are affected by drug treatment.

Investigator: Patrizia Mondello, MD, PhD, Mayo Clinic, Rochester, MN, USA

Identifying the Oncogenic Cooperation Between IRF4 and MYD88L265P and Their Impact on Tumor Microenvironment of WM

Project Period: 2023-2025, $480,000 over two years

It is increasingly recognized that WM is not one disease. New research findings from several groups point to the existence of several WM subtypes. In this IWMF-LLS Strategic Research Roadmap project, Dr. Patrizia Mondello, Assistant Professor at Mayo Clinic, will investigate how heritable, pre-existing mutations in a gene called IRF4 may predispose patients to develop one of the subtypes of WM called plasma cell-like WM. She hypothesizes that pre-existing mutations in IRF4 work together with the acquired mutation in the MYD88 gene to drive growth of WM tumor cells and also to reduce the body's immune response to WM cells. This combination of two mutations that work together is called "oncogenic cooperation."

Dr. Mondello and her team will use genetically-engineered WM cell lines and mouse models that combine either too much IRF4 or too little IRF4, together with the MYD88 mutation. They will examine the effects of these mutations on the growth of WM and the immune response to WM in the mice. They will then study the specific ways in which different immune cells and their signals are altered, making the bone marrow environment more hospitable to growth of the WM cells.

Importantly, they will ask if their findings in mice apply to human WM patients. This will be done by examining cells from a large number of WM patients who have donated their bone marrow cells for research projects at Mayo Clinic. In collaboration with Dr. Zachary Hunter from Dana-Farber Cancer Institute (DFCI), these findings will be validated in an independent group of WM patients from DFCI. If IRF4 is confirmed as a critical factor for progression to WM, the investigators propose in future studies to introduce a genetic screening test of IRF4 in patients with the precursor condition of IgM MGUS (monoclonal gammopathy of undetermined significance), to help identify those at risk of developing WM. They also propose to work together with pharmaceutical companies to evaluate drugs targeting IRF4 in their mouse models, with the ultimate goal to identify a novel and more effective therapeutic approach for WM patients.

*A major **dilemma in treating** WM patients is the eventual **development of resistance** to therapy.*

Investigators: Tina Bagratuni, PhD, and Meletios Dimopoulos, MD, National and Kapodistrian University of Athens, Greece

Genomic Characterization of Ibrutinib-Resistant WM

Project Period: 2023-2025, $400,000 over two years

A major dilemma in treating WM patients is the eventual development of resistance to therapy. After initially responding well to ibrutinib treatment, a substantial number of patients eventually develop ibrutinib resistance. Underlying the development of resistance is the ability of the initial population of WM cells in the body to develop or evolve in a number of different directions. As the initial population of WM cells grow, one WM cell might develop an additional mutation. If this mutation allows the cell to grow faster or to avoid the immune system, it will produce daughter cells more rapidly than the other WM cells. Eventually, the descendants of that cell, called a "clone," may become a large proportion of the total WM cells in a patient's body. Meanwhile, another WM cell might develop another mutation. The descendants of the cell with this new mutation may develop yet another clone in the body. WM researchers have become increasingly aware that individual WM patients often harbor multiple different clones of WM cells, each with somewhat different characteristics.

New 2023 IWMF-Funded Research Projects, cont. on page 17

Dr. Maria Luisa Guerrera, Bing Center for WM, prepares samples of cells for flow cytometric analysis. Photo credit: Sam Ogden. Photo courtesy of Bing Center for WM, Dana-Farber Cancer Institute

To unravel this complexity and be able to study multiple clones within the same patient, Dr. Bagratuni, Senior Researcher at the School of Medicine at the National and Kapodistrian University of Athens, and her team will take a large number of WM cells from each WM patient and analyze the cells one-by-one, in what is called single-cell analysis. In this IWMF-LLS Strategic Research Roadmap grant, they will compare results from WM cells before ibrutinib treatment to those from WM cells from patients treated with ibrutinib. They hypothesize that as patients are treated with ibrutinib, multiple clones arise, each with perhaps different ways to avoid being killed by ibrutinib. With this type of specific, cell-by-cell analysis, the investigators hope to better understand the development of ibrutinib resistance and perhaps uncover new therapeutic targets for drug treatment.

Investigator: Maria Luisa Guerrera, MD, Dana-Farber Cancer Institute, Boston, MA, USA

Characterizing the Role of ERK1/2 Regulator WNK2 as a Novel Target in the Disease Progression of MYD88 Mutated WM

Project Period: 2023-2025, $157,500 over two years

Tumor suppressors are proteins that act by preventing cells in the body from becoming cancerous. A mutation in a key tumor suppressor can "remove the brakes" and allow small, early cancers to progress. Dr. Guerrera, Instructor in Medicine at Harvard Medical School and Dana-Farber Cancer Institute, has been working in the laboratory of Dr. Steven Treon. In a prior two-year Robert A. Kyle Career Development Award, she brought attention to a previously little-known tumor suppressor protein called WNK2 that may be important in controlling WM.

With this renewal of her Kyle Award, she will continue to investigate the role of WNK2 in WM. WNK2 abnormalities are surprisingly common in WM. Among WM patients, there are a number of different ways that normal WNK2 can go awry. In some WM patients, the WNK2 gene is improperly regulated, and there is too little WNK2 available. This may remove a key restraint and allow WM cells to grow. In other WM patients, however, there is plenty of WNK2, but it is incorrectly formed, so it doesn't function properly. Incorrectly formed WNK2 can also result in too much WM cell growth. Dr. Guerrera's project is to better understand the many different ways WM cells improperly regulate WNK2, and how improper WNK2 regulation can change the WM cells' behavior in the body and impact their growth. Her long-term goal is to develop drugs to correct these defects, restore the ability of WNK2 to suppress WM, and prevent WM from progressing.

Investigator: Zachary Hunter, PhD, Dana-Farber Cancer Institute, Boston, MA, USA

Characterization of Isoform Usage, Novel Isoforms, and Tumor Evolution in WM

Project Period: 2023-2025, $480,000 over two years

In previous, groundbreaking work, Dr. Zachary Hunter and his team at Dana-Farber Cancer Institute have analyzed a large number of genes from WM cells and found a complex variety of abnormalities. Normally, cellular DNA (a gene) is copied into a molecular messenger, called mRNA, which

New 2023 IWMF-Funded Research Projects, cont. on page 18

encodes proteins that a cell needs. But mRNA is not an exact copy of DNA. First, the DNA is copied into a large RNA strand called a transcript. Then specific pieces of the large RNA transcript are cut out and spliced together to create whatever mRNA the cell needs. Dr. Hunter's group discovered that many of the mRNAs made in WM are improperly assembled because of incorrect splicing.

***Venetoclax** is emerging as a **useful** drug that **reduces the survival** of **WM cells**.*

These RNAs are called "alternative isoforms." Sometimes, cells interpret the alternative isoform as gibberish and fail to make a required protein. In other cases, an alternative isoform created by improper splicing results in an mRNA that encodes a new protein different from the original one. In some cases, the new protein can be harmful.

The discovery of so many alternative isoforms in WM cells led Dr. Hunter to ask, in this IWMF-LLS Strategic Research Roadmap project, what the underlying problem is. Why are WM cells prone to making splicing mistakes and improperly assembled RNAs? Is there a way to correct the problem? Additionally, the pattern of alternative isoforms in different kinds of WM cells may be important to know. Dr. Hunter's team has already identified different subtypes of WM, and now they are finding evidence that each subtype has its own pattern of alternative isoforms. By understanding the abnormal proteins that the alternative isoforms encode and how these abnormal proteins interact with each other, it may be possible to identify new targets for novel WM drugs.

Investigator: Marcel Spaargaren, PhD, Amsterdam UMC, University of Amsterdam, the Netherlands

Towards a Rational Targeted Combination Therapy for WM by Venetoclax Sensitizer Crispr Screens

Project Period: 2023-2025, $476,000 over two years

Dr. Spaargaren and his team at the Amsterdam UMC, University of Amsterdam, have been working for a number of years to discover what they call the "Achilles heels" of B cell malignancies, including WM—the weak points that might be exploited by a targeted drug. They try to identify particular proteins which, if inhibited, could significantly keep the cancer cell from growing, avoiding immune cells, or resisting drug therapy. Using a screening technique they developed in their lab, their approach was successful in a previous IWMF-LLS Strategic Research Roadmap project that identified several proteins that could be new drug targets for WM. Some of the proteins they found are important for enabling WM cells to attach to and live in the bone marrow. Others are important for enabling WM cells to resist being killed by ibrutinib treatment. With this knowledge, researchers and physicians can develop better combinations of drugs to avoid ibrutinib resistance.

In the present IWMF-LLS Strategic Research Roadmap project, Dr. Spaargaren and his team are focusing on the drug venetoclax. Venetoclax is emerging as a useful drug that reduces the survival of WM cells. Not all WM patients respond to venetoclax, however, and sometimes, patients respond initially but then become venetoclax-resistant later. Dr. Spaargaren and his team will work on discovering "sensitizers," drugs that can be given in combination with venetoclax to help improve how well venetoclax works for WM patients.

KARIMA AMAADOR OF THE NETHERLANDS AWARDED PHD IN WALDENSTROM'S MACROGLOBULINEMIA

On November 10, 2023, Karima Amaador successfully defended her PhD thesis on the subject of Waldenstrom's macroglobulinemia (WM) at the University of Amsterdam in the Netherlands and was unanimously awarded her PhD degree. According to Dr. Steven Treon of Dana-Farber Cancer Institute, this is only the fourth PhD on WM awarded in the world. Dr. Amaador's thesis title was "Understanding Waldenstrom´s Macroglobulinemia: A Multimodal Approach."

Dr. Amaador's supervisory committee consisted of Prof. Dr. Marie-Jose Kersten, Prof. Dr. Steven Pals, Dr. Josephine Vos, and Dr. Avinash Dinmohamed. The opposing committee, who engaged in critical questioning, consisted of Professors Sonja Zweegman, Arnon Kater, Valery Lemmens, Mette Hazenberg, and Dr. Shirley D'Sa. Dr. Amaador's thesis, which she worked on for almost four years, contains chapters on a clinical trial for relapsed/refractory (R/R) WM with ixazomib, rituximab, and dexamethasone; a study on biomarkers in anti-MAG neuropathy; work on T cells in WM patients; an analysis on trends of WM survival and treatment based on the Dutch cancer registry; and a study on Dutch physicians' knowledge of WM.

She also performed a Discrete Choice Experiment study on patient preferences, which was the foundation for an international project called WM-VOICE that has recently received IWMF funding and was the subject of an article in the April 2023 *Torch* (see *https://iwmf.com/wp-content/uploads/2023/03/N39671-Torch-April-2023_web.pdf*). Her work has been published in prestigious journals such as the *Journal of Clinical Oncology*, and she has twice received a Junior Investigator Award at the International Workshops on WM (IWWM).

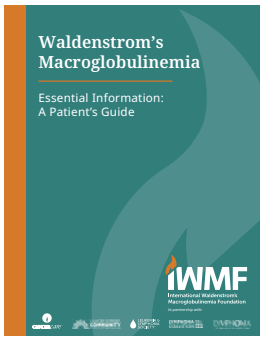
Dr. Amaador, who has an MD degree as well as her PhD, is now an internal medicine resident and has been accepted for a fellowship in hematology at the University of Utrecht in the Netherlands. Her ambition is to work as a clinician in the field of hematology and remain active in research within the WM field.

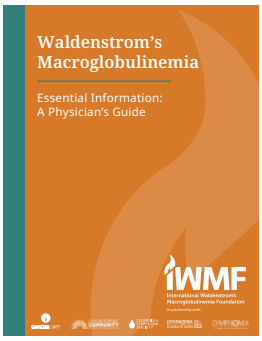
Left to right: Prof. Dr. M. J. Kersten, Dr. Karima Amaador, and Dr. J. M. I. Vos

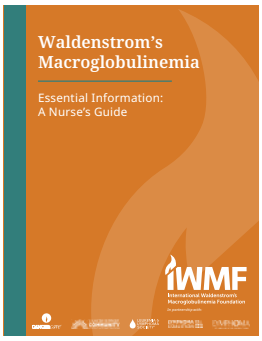
THE IWMF "ESSENTIAL INFORMATION ABOUT WALDENSTROM'S MACROGLOBULINEMIA" SERIES

By Carl Harrington, Vice Chair of the IWMF

You won't want to miss these booklets! Be sure to pass them along!







These booklets are a result of the Global Patient Initiative (GPI). See the October 2022 *IWMF Torch (https://iwmf.com/wp-content/uploads/2022/10/N31400-Torch-Oct-2022_web.pdf,* page 7*)* for a refresher course about GPI. You may have seen the first two booklets above, but the third one is new and completes the series.

These booklets have a few things in common that make them well worth your time:

They are all written by recognized WM experts:

- "Essential Information: A Patient's Guide" was written by Dr. Stephen Ansell of the Mayo Clinic, Dr. Steven Treon of the Dana-Farber Cancer Institute (DFCI), and Carl Harrington of the IWMF.
- "Essential Information: A Physician's Guide" was written by Dr. Shayna Sarosiek and Dr. Jorge Castillo, both of the DFCI.
- "Essential Information: A Nurse's Guide" was written by Dr. Sarosiek, Catherine Flynn, NP, and Dr. Castillo, all of the DFCI.

The guides are all endorsed by our US advocacy partners—a "who's who" of the best cancer advocacy organizations in lymphoma: The Leukemia & Lymphoma Society, Cancer*Care,* Cancer Support Community, Leukemia Research Foundation, and the Lymphoma Coalition.

They are all available in 11 languages: English, French, Spanish, Italian, German, Simplified Chinese, Traditional Chinese, Portuguese, Polish, Norwegian, and Finnish. We did that to make sure as many people with WM as possible can read this information in their native tongue. You know how hard it is to get your head around WM when you are first diagnosed. Imagine if you had to do that in something other than your native language!

As you can see in the illustrations above, the three publications differ in appearance and in target audience. A Patient's Guide has the format that now will be used for all our patient publications, so expect to see them change to this format over time. By the way, this guide is now included in all Info Paks for the newly diagnosed.

The format of the other two will be used for all publications for health care professionals. A Physician's Guide and A Nurse's Guide are the first IWMF publications directed specifically to health care professionals—the first people to know when you have WM. We want health care professionals to refer all their WM patients to the IWMF.

So, what can you do to let others know about these valuable publications? In a word, share them! Everyone affected by WM can benefit from these booklets. And the best way to spread the word is for you **personally** to do it. If we all do, the world will be just a little bit better for WM patients now and in the future.

With the patient version, read it and share it with your friends and family. And if you or they want to go a little deeper, look at our "Frequently Asked Questions" booklet at *https://iwmf.com/publications/*—scroll down to the FAQ booklet. It is also easy to understand and covers key questions like "What did I do to get this?" "Are my kids going to get WM?" "How long am I going to live?" and other burning questions that plague us all, especially when first diagnosed.

Read the Physician's and Nurse's Guides if you want, but be sure to share them with your health care team. Ask them to share the booklets with others in their medical practice. Also direct them to our first-ever WM continuing medical education (CME)/continuing nurse education (CNE) course. This course was developed with our partner, The Leukemia & Lymphoma Society, and can be found at *https://iwmf.com/treating-indolent-lymphoma-common-and-rare-types/*.

Now complete, this series of booklets is essential information for everyone affected by WM. So, stop and look at them now. And share them!

WM+ME: A UK PATIENT PROJECT

By Kat Tucker, Information and Support Manager, WMUK

Data is the key to improving treatment and care for people living with WM now and in the future. That's why WMUK has launched WM+ME, a ground-breaking study that puts WM patients at the heart of research and in control of their own health.

Over 150 people have signed up to the project, which asks participants to wear a smartwatch (provided for free) and record symptoms and other key data on a specially designed app. This "real world data" is then collected and analysed by our project partner, Sanius Health, to identify trends. It is hoped that these finding can change the way people with WM are cared for and give researchers the vital information they need to find more and better treatments.

The data also helps people on an individual level—giving them the readings and trends in their symptoms and activity that can help them have better informed conversations with their doctors and nurses.

WMUK Patient Trustee Charles Lilley talks more about how the app and data collected helps people on an individual and wider scale in this two-minute film, made for the charity's Christmas campaign: *https://www.youtube.com/watch?v=-WzGiGaLf1Q*.

The pilot project has already collected a huge amount of data, which is being studied. Thanks to the incredible fundraising efforts of our community in the charity's Christmas Big Give campaign, we now have the funds to push the project forward to create an app that will be a "one-stop-shop" for people with WM—empowering them to better advocate for their care.

Anyone diagnosed and treated in the UK can register, as the pilot study is still open to sign-ups. (*Editor's note: as of December 4.)* More detail can be found here: *https://www.wmregistry.co.uk/wmandme.*

MEDICAL NEWS ROUNDUP

By Sue Herms, IWMF Research Committee Member

Retrospective Study Analyzes and Compares First-Line Therapies Used for WM – In the absence of head-to-head clinical trials comparing chemoimmunotherapy regimens, bortezomib-based therapies, and ibrutinib therapies as first-line treatments for WM patients, researchers from Singapore performed a retrospective review and analysis of data from first-line WM trials conducted during January 2007 to March 2023. Response rates, progression-free survival, overall survival, and side effects were evaluated for the eleven Phase 2 and Phase 3 trials included in the analysis. The combined CR/VGPR (complete response and very good partial response) rates for various therapies included: bortezomib, bendamustine, and rituximab (BBR) 47%; bendamustine and rituximab (BR) 46%; bortezomib, dexamethasone, rituximab, and cyclophosphamide (BDRC) 33%; bortezomib, dexamethasone, and rituximab (BDR) 30%; ibrutinib and rituximab (IR) 26%; and dexamethasone, rituximab, and cyclophosphamide (DRC) 15%. The two-year progression-free survival rates were: BR 89%, BBR 89%, IR 82%, BDRC 81%, BDR 69%, and DRC 69%. Two-year overall survival rates were reported for the following regimens: BR 97%, BDRC 94%, DRC 91%; IR 90%, and BDR 80%. In terms of side effects, IR was associated with more moderate-to-severe cardiac events, such as high blood pressure and irregular heart rhythms. Bortezomib-containing regimens were associated with an increased incidence of mild-to-severe peripheral neuropathy although more recent trials using subcutaneous bortezomib reported lower rates of neuropathy. Chemoimmunotherapy regimens were associated with a higher incidence of hematological (blood-related) side effects such as neutropenia (low neutrophil count). Overall, in this analysis, bendamustine-based chemoimmunotherapy regimens resulted in improved response rates and progression-free survival compared with ibrutinib- and bortezomib-based regimens. Notably, however, overall survival did not differ significantly among the treatment groups. This study was published in the online *Blood Cancer Journal*.

Multicenter International Study Reports Survival Outcomes of Bendamustine Dosing in First-Line and Relapsed WM – A multicenter international retrospective study published in the *American Journal of Hematology* looked at the impact of bendamustine dosing on treatment responses and survival outcomes in 250 WM patients treated with bendamustine and rituximab (Rituxan) in both the first-line and relapsed settings. Rates of partial responses or better differed significantly between the first-line and relapsed groups, at 91.4% vs. 73.9%, respectively. The depth of response impacted survival outcomes: the two-year progression-free survival rate after achieving a combined CR/VGPR (complete response/very good partial response) was 96%, compared to 82% for lesser responses. The total bendamustine dose also predicted progression-free survival. In the first-line setting, progression-free survival was superior in the group receiving a total dose of at least 1,000 mg/m^2 of bendamustine to those receiving a total dose of 800-999 mg/m^2; in the relapsed group, those who received a total dose of at least 600 mg/m^2 of bendamustine had better progression-free survival outcomes than those who received a total dose of less than 600 mg/m^2.

*...**bendamustine-based** chemoimmunotherapy **regimens** resulted in **improved response** rates and **progression-free survival**...*

Analysis Looks at Single Agent Rituximab Vs. Ibrutinib as First-Line Treatment for Older WM Patients – Despite its relatively modest effectiveness, single agent rituximab (Rituxan) is commonly prescribed as first-line treatment for symptom control in older WM patients. In clinical trials, single agent ibrutinib (Imbruvica) yielded durable outcomes and was well tolerated by older or frail patients; however, real-world evidence comparing outcomes of the two therapies in older WM patients remains scant. This retrospective study from Dana-Farber Cancer Institute, reported during the Society of Hematologic Oncology 2023 Annual Meeting, looked at both agents in the first-line setting among Medicare beneficiaries treated between January 2014 and December 2019. In this study, 1,871 received single agent rituximab and 783 received single agent ibrutinib. The average age of patients in both groups was 77.2 years, and common co-existing conditions at the beginning of treatment included high blood pressure, other cardiovascular diseases, and atrial fibrillation. The study found that within twelve months, patients treated with ibrutinib were 23% less likely to move to a next treatment than patients treated with rituximab, indicating a significantly longer time-to-next-treatment with ibrutinib.

UK Researchers Report Phase 2 Trial Results of BCR Therapy in WM by Using Novel Flow Cytometry Approach to Assess Response – A study from the United Kingdom evaluated a bortezomib-based first-line therapy in WM by developing a sensitive flow cytometry assay to assess blood and bone marrow response to the treatment instead of the conventional method of using IgM levels to assess response. Sixty treatment naïve WM patients were enrolled in this Phase 2 clinical trial and randomized to receive cyclophosphamide and rituximab (Rituxan) with either subcutaneous bortezomib (Velcade) or with

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fludarabine as a control arm. The combination of bortezomib, cyclophosphamide, and rituximab (called BCR) was chosen because it targets both the B cell and plasma cell components of WM. An overall response rate of 97.6% was observed in those who received BCR, exceeding the trial's target rate of at least 80%, while two- and three-year progression-free survival rates were 92.7% and 80.5%, respectively. Two patients withdrew from the trial after four cycles of BCR because of neuropathy. Using their sensitive flow cytometry assay to detect the presence of identifying markers on the surface of WM B cells in the blood and bone marrow, the researchers noted that three-year progression-free survival was markedly longer in patients without WM B cells detected following treatment (94.7%) than in those detected with persisting WM B cells (63.2%). The trial results were reported in *ResearchGate*.

In the process of ***transformation,*** *the* ***LPL/WM cells*** *acquire additional gene* ***mutations*** *that lead to the* ***development*** *of* ***DLBCL****.*

Italian Study Analyzes Characteristics of WM Diagnosed in the Very Elderly – Italian researchers reported results in the journal *HemaSphere* from their retrospective study of WM in the very elderly—those diagnosed at 75 years of age or more—compared to those diagnosed at less than 75 years of age. The study, conducted at the Azienda Ospedaliera University of Padova, reviewed the records for 153 patients diagnosed with WM between 1990 and 2022, with 33 patients belonging to the very elderly group at the time of their diagnosis. This group displayed a higher frequency of kidney dysfunction compared with younger patients (42.4% vs 25.0%, respectively) and a trend toward the coexistence of other cancers (37.9% vs 22.3%, respectively). The frequency of peripheral neuropathy was similar between the two groups. The very elderly had a tendency toward higher levels of monoclonal IgM and significantly higher levels of beta 2-microglobulin, along with lower levels of albumin. Chromosome abnormalities, such as 6q deletion, were more frequent in the very elderly patients, as was wild-type (unmutated) MYD88. No significant differences between the two groups were observed in terms of the need for therapy, dose intensity, or reduction in treatment cycles in the first-line treatment setting. The overall response rate to first-line therapy in the very elderly was 65%, compared with 80% in the younger group. Very elderly patients also displayed a higher rate of progressing disease. Median overall survival was shorter in the very elderly, at 79 months, compared to 198 months in the younger group.

Dutch Researchers Investigate Transformation of LPL/WM to Diffuse Large B Cell Lymphoma – About 2-10% of patients with lymphoplasmacytic lymphoma (LPL)/WM develop diffuse large B cell lymphoma (DLBCL), mostly resulting from transformation of the LPL/WM clonal cells to this more aggressive lymphoma. In the process of transformation, the LPL/WM cells acquire additional gene mutations that lead to the development of DLBCL. Occasionally, however, DLBCL can also independently arise in LPL/WM patients, without being clonally related to the LPL/WM cells. Researchers from the Netherlands looked at 13 LPL/WM patients who developed DLBCL to investigate the incidence of transformation and the gene mutations contributing to it. In this group, the MYD88 L265P mutation was present in 73% of patients who were analyzed for the mutation, while CXCR4 mutations were observed in 55%. The researchers noted that wild-type (unmutated) MYD88 was present at a higher incidence than typically seen in LPL/WM and is in line with previous findings indicating that wild-type MYD88 is associated with a higher risk of developing DLBCL. In 11 of the 13 patients, genetic studies indicated that the occurrence of DLBCL arose from additional mutations acquired by their LPL/WM cells and was, therefore, presumed to be a result of transformation. These mutations were in the genes BTG1, BTG2, CARD11, CD79B, PIM1, and TP53. Upon diagnosis, the patients in this study were treated with chemoimmunotherapy, and the five-year overall survival was 38%. The study was published in the journal *HemaSphere*.

Multicenter International Study Evaluates Stem Cell Transplantation Outcomes in Patients with Transformed WM – A multicenter international study, published in the journal *Hematological Oncology*, evaluated outcomes after autologous or allogeneic stem cell transplantation in WM patients whose disease had transformed into a more aggressive lymphoma, such as diffuse large B cell lymphoma. Patients who received stem cell transplantation between January 1996 to December 2021 were identified from a multicenter database of 285 with transformed WM, with 46 receiving autologous transplant (with their own stem cells) and 10 receiving allogeneic transplant (with donor stem cells). The three-year estimates for overall survival and progression-free survival for those with an autologous transplant were 57% and 44%, respectively, and for those with an allogeneic transplant were 50% and 50%, respectively. In the group with autologous transplant, a complete response following transplant was found to be associated with superior overall and progression-free survival; superior overall survival was also seen in those who received less than two lines of therapy to treat their transformed disease prior to transplantation.

Iopofosine I-131 (Formerly CLR 131) Granted Priority Medicines Designation for Relapsed or Refractory WM by the EMA – The European Medicines Agency (EMA) has granted Priority Medicines designation to iopofosine I-131

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(previously called CLR 131) for WM patients who have already received at least two treatment regimens. Priority Medicines designation (called PRIME) enhances support for the development of medicines that target an unmet medical need so that their evaluation takes place on an accelerated basis. Iopofosine I-131 delivers radioactive iodine directly to cancer cells, thereby killing them, through the use of a small phospholipid carrier molecule, and is currently in clinical trials for WM.

Study Describes Characteristics of Monoclonal IgM in Patients with Type 1 Cryoglobulinemia – Type 1 cryoglobulinemia is defined by the presence of a monoclonal antibody that precipitates at temperatures below that of body temperature (37 degrees C) and redissolves upon rewarming. The precipitated antibody can block blood flow in the smaller blood vessels located in areas of the body exposed to cold temperatures. An article in the *British Journal of Haematology* described several characteristics of IgM-associated type 1 cryoglobulinemia, which can occur in WM patients. In this study by researchers from the United Kingdom and the Netherlands, 534 patents with monoclonal IgM disorders were screened from 2013 to 2022, and 134 patients with IgM-associated type 1 cryoglobulinemia were identified. Of these, 76% had WM, 5% had another non-Hodgkin's lymphoma, and 19% had IgM MGUS (monoclonal gammopathy of undetermined significance). In addition, 31% had a co-existing monoclonal antibody condition (such as peripheral neuropathy, Schnitzler's syndrome, or amyloidosis) or had Bing Neel syndrome. Half of all patients were exhibiting symptoms at the time of cryoglobulinemia detection, and 16 of the 134 patients required treatment for their symptoms at a median of 38 days from detection. The most common symptoms included: vasomotor symptoms (cold intolerance, white and bluish discoloration of the fingers and toes in the cold—known as Raynaud's syndrome) in 22% of patients; cutaneous symptoms (skin ulcers, purple patches from bleeding under the skin, necrosis or gangrene) in 16%; hyperviscosity syndrome in 9%; joint pain in 7%; and inflammation of the kidney tubules in 1%. With a median follow-up of three years, cryoglobulinemia treatment-free survival was 77%.

Phase 2 Trial in Europe to Investigate Zanubrutinib for the Treatment of Cold Agglutinin Disease – A Phase 2 clinical trial investigating the effectiveness and safety of zanubrutinib (Brukinsa) for the treatment of patients with cold agglutinin disease (CAD) is anticipated to begin in February 2024 at several medical centers in the Netherlands, Belgium, Norway, and Denmark. Cold agglutinin disease is a rare autoimmune disease characterized by the presence of high concentrations of circulating cold-sensitive antibodies, usually IgM, that are targeted against one's own red blood cells, causing them to agglutinate or clump and be destroyed, with anemia and acrocyanosis (persistent bluish skin discoloration) as a result. This condition is known to occur in patients with WM and IgM MGUS. The researchers will enroll 25 participants, who will receive oral zanubrutinib for at least six months, and responders to treatment will continue the drug for up to three years. The study is referred to as HOVON 169, and more details can be found on *www.clinicaltrials.gov* under trial identifier NCT06067048.

Paxlovid,** Pfizer's oral medication to treat COVID-19 disease, is set to move **to commercial sales** in the US after **government stockpiles** run **out.

Zanubrutinib and Rituximab Combination to Be Evaluated in the Netherlands for Treatment of IgM MGUS-Related Neuropathy – A trial in the Netherlands will evaluate zanubrutinib (Brukinsa) in combination with rituximab (Rituxan) for the treatment of neuropathy associated with IgM monoclonal gammopathy of undetermined significance (IgM MGUS) in patients whose neuropathy is the result of anti-MAG (myelin-associated glycoprotein) antibodies. The Phase 2 trial, referred to as MAGNAZ, plans to include 42 participants for at least a six-month treatment period; responding participants will be treated for an additional six months, and those with a hematological VGPR (very good partial response) at 12 months will remain on treatment. The total study period will be three years. The trial identifier on *www.clinicaltrials.gov* is NCT05939037.

Phase 1 Trial Data of BTK Inhibitor Nemtabrutinib for Relapsed or Refractory CLL and NHL Is Released – An article in the journal *Cancer Discovery* reported Phase 1 dose escalation results from the Phase 1/2 trial of the BTK inhibitor nemtabrutinib in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and B cell non-Hodgkin's lymphoma (NHL). Among 47 treated patients, 29 had CLL, one had WM, and 17 had other NHLs. Nemtabrutinib was dosed from 5-75 mg doses once daily. Results in CLL patients demonstrated an overall response rate of 75% with a 65 mg daily dose, and this dose was recommended for the Phase 2 expansion part of the trial. Moderate-to-severe adverse events occurred in 89% of patients, most commonly neutropenia (low neutrophil count), febrile neutropenia (low neutrophil count with fever), and pneumonia. Nemtabrutinib, formerly known as ARQ 531, is a reversible inhibitor of BTK and is thought to be effective in those with C481S mutations that lead to resistance to several other BTK inhibitor therapies.

Paxlovid to Move to Commercial Sales in the US in 2024 – Paxlovid, Pfizer's oral medication to treat COVID-19 disease, is set to move to commercial sales in the US after government stockpiles run out. Pfizer announced that its US price for the five-day course of Paxlovid will be approximately $1,400,

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but that price does not include rebates and other discounts to insurance companies and pharmacy benefit managers. The drug is expected to remain free to all patients until the end of 2023, although an agreement with the US government will allow the drug to remain free to Medicare and Medicaid recipients through 2024 and to uninsured and underinsured patients through 2028.

The author gratefully acknowledges the efforts of Grete Cooper, Peter DeNardis, Julianne Flora-Tostado, Tom Hoffmann, Richard Savoy, 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.*

FROM THE FACEBOOK WM SUPPORT GROUP: WINTER 2024

By Betty Ann Morton

As friends generally do, members of the Facebook Waldenstrom Macroglobulinemia Support Group talk about what's on their minds. Not surprisingly, symptoms of WM are frequently discussed. For many, troubling symptoms led to tests with atypical results, then a diagnosis of WM, and sooner or later treatment to eliminate or at least alleviate those troubling symptoms.

Some, including **JMS**, were diagnosed early, at a time when they were feeling well and did not need treatment for years. "I came across this site as it was mentioned in the *Torch*. I have learned so much in the short time I have been on it. I was diagnosed in 2005 and have been on watch-and-wait until now. My symptoms, specifically anemia and weight loss, have resulted in upcoming treatment." Eighteen years of watch-and-wait may be a record, but WMers have learned to listen when our expert doctors counsel that immediate treatment may not be necessary. **JMS** closed by saying, "I met with my oncologist today, and we are going to go the BR (bendamustine and Rituxan) route."

Several people have recently mentioned needing treatment because of eye issues. **KD** wrote, "In March this year I had my routine eye exam. My ophthalmologist found a retinal hemorrhage in one eye. He sent that info to oncologist. That started my BR treatment."

RT also started WM treatment because of vision concerns. "Hyperviscosity symptoms may occur when IgM is over 4,000 (mg/dL) in the US or 40 (g/L) in the rest of the world. A dilated fundoscopy may reveal the classic 'sausaging' of the retinal capillaries. It was this exam that prompted my hematologist to treat me for the first time 17 years ago." *(Note: US measurements of IgM are typically in mg/dL, while most of the world uses g/L. To convert from mg/dL to g/L, divide by 100. To convert in the other direction, multiply by 100.)*

I recently asked the Facebook WM Support Group what their goals had been when they first had treatment and how that had turned out. Here's my own experience: When I had my first treatment back in 2009, it was because IgM was very high and viscosity was rising. My doctor and I were concerned about damage to organs and even possible stroke. I'm delighted to report that the treatment was successful. I have not had a stroke, nor any retinal damage, etc. For me, as for many, the treatment was successful.

***WMers** have learned to **listen when** our **expert doctors counsel** that immediate treatment may not be necessary.*

A similar experience was reported by **RP**. "Eight years ago, high IgM and high viscosity meant high risk of stroke, heart attack, or both. Straight on to eight sessions of BR, brilliant response, now on six month checks, and living an amazing life as I approach 70. I pay particular attention to my physical fitness and have rediscovered the joy of cycling."

RF had similar concerns about possible consequences of high viscosity. "For me…anemia, slight foot pain, but mostly my IgM was over 10,000, and my viscosity was at 5 (or maybe higher, I have to check). I was at risk of stroking out."

SJ posted, "I was diagnosed in 2019 and on watch-and-wait; I finally went to a different doctor. He told me with my numbers I would have a heart attack or stroke in only months, so I went ahead and had the chemo. With some adjustments with the pre-meds, I was done—IgM still in the 800s, my viscosity normal, and I'm feeling much better. IgM was close to 6,000 mg/dL before!"

From the Facebook WM Support Group, cont. on page 26

JL wrote, "I was diagnosed in 2017 because of PN (peripheral neuropathy), which had been very slowly increasing over about 8-10 years. At first I was diagnosed with both multiple myeloma and WM. Specialist changed this to WM only. I was treated with Rituxan. PN improved somewhat, and IgM went down from high of 2,400 mg/dL to about 650. This lasted five years. I was treated again with Rituxan last winter after PN had increased, beginning night sweats, and kidney issues. My IgM high was 3,700, currently around 900."

Peripheral neuropathy seems to be particularly difficult to treat. **DM** responded, "My IgM was 1,000 mg/dL. I was treated almost two years ago in the hopes that it would improve or stop the progression of my anti-MAG negative, axonal peripheral neuropathy. Unfortunately, I don't believe the treatment has improved it, but it may have stopped the progression."

Some WMers have multiple symptoms. **DPT**, for example, noted, "I was diagnosed in 2011. Neuropathy was the first issue. Blood tests showed high IgM. Neuropathy was worsening along with a kidney issue, so I was given Rituxan for eight rounds but it did nothing to help. A bone marrow biopsy showed the treatments didn't change anything, so stopped. Watch-and-wait for several years as things progressed. Kappa light chain increased, developed vasculitis, stage 3 CKD (chronic kidney disease), etc. My symptoms were worse, especially PN, autonomic neuropathy, diarrhea, and fatigue. Fast forward to a new doctor who trained under Drs. Castillo and Treon! How fortunate I was. He immediately put me on Imbruvica and symptoms improved. Diarrhea went away. CKD gone. Neuropathy quit growing, even improved a little. Unfortunately, two years later, my diarrhea is back. I will need to let him know. But, for the most part things have been good."

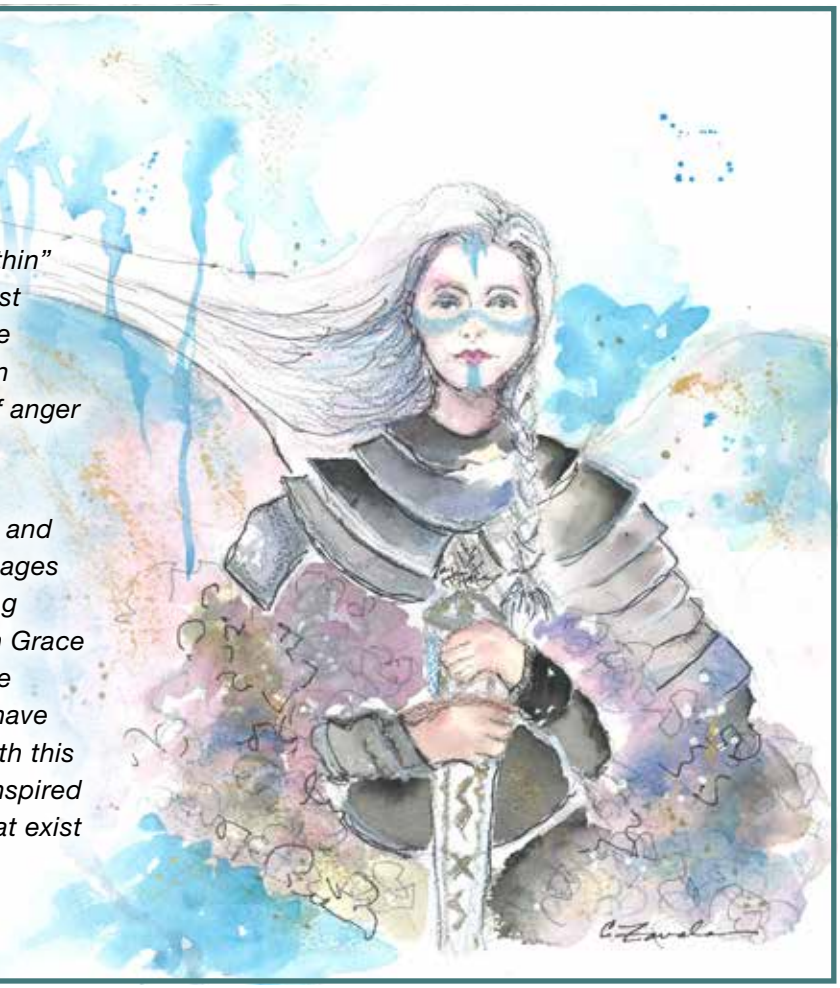
JR posted, "Diagnosed in 2020 at 45 after two years of acute anemia, multiple upper respiratory infections, and then, closer to diagnosis, soaking night sweats and then stomach pain, which led to the discovery of swollen lymph nodes all across my abdomen. I did four rounds of BR, and I have been treatment-free since; however, in September, I began regular IVIG infusions (every 4-5 weeks) after another year of multiple upper respiratory infections, one of which landed me in the hospital for four days with pneumonia and

The Warrior Within

Watercolor painting by Carole Zavala

I had a tough time finding any "warrior within" when I was initially diagnosed with WM just before my 80th birthday five years ago. The journey has been challenging, and I was in denial and initially with no small degree of anger and frustration.

Thanks to the fine resources, information, and support from the IWMF, my "warrior" manages to work her magic (as did the mythic Viking female warriors) fairly frequently now. Ann Grace McMullan, her powerful programs, and the wonderful "warriors" who meet regularly have helped me embrace and move forward with this unique medical issue. This painting was inspired by the support and loving camaraderie that exist among us during those weekly sessions.



From the Facebook WM Support Group, cont. on page 27

sepsis. My numbers are otherwise looking good, though. I do bloodwork every three months, but only see my oncologist every six months, unless something is wonky with the bloodwork. And, especially since starting IVIG, I feel better than I have in years."

At first** I was like **"I HAVE CANCER!"** **Now** most days I am like **"Hmmmm, I have cancer?"

SS is one of those WMers whose symptoms were first thought to have other explanations. "I was diagnosed in 2021 and started Brukinsa (zanubrutinib) immediately because of high viscosity and 5,500 IgM. My only symptoms were rapid weight loss and a little bit of tiredness. I attributed my tiredness to PTSD resulting from the Texas power grid failures during the ice storm of 2021 and the COVID pandemic. I was quite surprised when my annual physical resulted in a referral to my oncologist with a possible diagnosis of smoldering multiple myeloma. I was relieved that my issue was WM, not MM! Brukinsa treatment has been successful with minimal side effects and a current IgM of 427."

MZS's path to diagnosis and treatment had twists and turns. "I knew something was wrong during COVID, but it was hard to get a diagnosis at that time because doctors and the world were dealing with a pandemic. I advocated for myself and continued to go from doctor to doctor to ERs. I experienced doctors who thought I had a mental health issue, very difficult time. Eventually the pieces came together and a bone biopsy revealed my diagnosis. My symptoms were PN with my IgM at 2,400 and biopsy approximately at 15% and anti-MAG positive. My hematologist was OK to watch-and-wait, but I wanted to treat because of my PN symptoms that I felt were worsening. My doctor and I discussed treating with rituximab. I am pleased with the results, IgM is down and PN has greatly improved, and I am not as fatigued. I felt relief when I received my diagnosis, and I shared my diagnosis with all the doctors and hospitals. They had never heard of Waldenstrom macroglobulinemia."

CBP described symptoms, "Two eye strokes six weeks apart, vertigo, nausea, numbness in hands and one foot, and anemia. The retina specialist and my primary doctor both said there was something wrong with my blood. Further tests with a hematologist and a hematologist/oncologist showed high IgM (5,489), high lambda/kappa ratio (50), high viscosity, high M-spike and high B2M (beta 2-microglobulin). The bone marrow test showed B cell lymphoma. Further testing showed MYD88 and CXCR4 mutations, 30-40% bone marrow involvement, and 80-90% hypercellularity. I am doing much better after Rituxan treatments, but do tire out easily still. I just received a second opinion from Mayo Clinic, and my first diagnosis is confirmed. I think attitude is everything with this, so I keep walking, keep drawing, and surround myself with so many good and loving people. I'm grateful for so much."

Although treatment for WM in most cases does not eliminate all of our troubling symptoms, the majority of WMers feel significantly better after treatment. **CP** concluded, "Although I was in denial at the time, BR made me feel so much better once I was through. At first I was like 'I HAVE CANCER!' Now most days I am like 'Hmmmm, I have cancer?'"

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.*

DRUG ADVOCACY FOR NEW ZEALAND WALDOS

By Lea Hullett, Affiliate Leader, New Zealand

Several positive things have happened for the Waldos (*https://waldos.kiwi*) since I wrote in 2021.

Our number of members for the entire country has risen from 43 to 51 since July 2021. There will be many more who either do not know about us or who prefer to go it alone on their journey with Waldenström. Maybe some just don't want to think about WM and leave it to their physicians to do the right thing for their treatment. This is not good when we have a small population of about five million, with our haematologists unlikely to see many patients with WM; they may or may not be up to speed on the pitfalls of treating our rare blood cancer. This leaves us without a specific person with the knowledge needed to offer a second opinion when uncertainty occurs on the way forward.

I mentioned before that in a report by PharmaDispatch, dated June 2020 and commissioned by Medicine New Zealand, we ranked last in the list of twenty countries for publicly funded access to new medicines.

Therefore, it is good to have a growing organization established in 2020, called Rare Disorders New Zealand (RDNZ) (*https://www.raredisorders.org.nz),* an umbrella group for rare disorders. It aims to provide a strong common voice to advocate for an equitable health care system that works for the 300,000 Kiwis (New Zealanders) with a rare condition. Mel Arnold (more about her later) very kindly agreed to liaise for us with RDNZ.

In September 2022, I was informed that Pharmac, the government agency that manages the Schedule of Medicines in New Zealand, was considering funding a BTK inhibitor, specifically ibrutinib, for non-Hodgkin's lymphoma. But it was only for CLL, and WM was to be left out. Three people provided me with advice about how to help our members write to the CEO of Pharmac with our stories and evidence about why they needed to include Waldenström along with CLL. As time was short, we needed to write with urgency, and a good number of our members did so and told their stories of the impact of living with WM, the lack of treatment options available, the difficulty of accessing a BTK inhibitor, and the prohibitive cost—without funding, very few people can afford to purchase ibrutinib from overseas. The government does not fund ibrutinib for WM and applies tax on top as well. Private health insurance is very expensive. I was told later by my advisors that our efforts were very good. Sometime later we each received a generic letter from Pharmac, which basically said that they didn't want to hear from us until the funding application reaches the under consultation status. I wrote more letters, as my advisors suggested, in order to keep in touch with Pharmac anyway. No replies came directly from the CEO but from various others.

Fast forward to June 2023, and a bright spark in the way of a new member, Mel Arnold, joined Waldos. You may have read about Mel, a young mother of four children, whose story is featured on the IWMF website: *https://iwmf.com/stories-of-hope/from-new-zealand-mels-story/*. Mel had worked in public health policy and knew a bit about presenting submissions. Had she known, she said she would have written earlier along with the rest of us. Mel had received treatment with BR (bendamustine and rituximab), but unfortunately it only gave her a short 18 months before she relapsed. She immediately got into action and submitted a 39-page comprehensive report with her own story, feedback from our WM members on what their lives are like living with WM, updated WM evidence, and the reasons why we needed funding. She actually received a reply from the CEO, which was amazing, as the CEO is not generally known to respond personally. Mel is continuing to correspond, and we are hopeful this will hurry things along. We will provide updates of our progress in the next *Torch* issue.

Lea Hullett in her garden

WELCOME TO NEW SUPPORT GROUP LEADERS!

By Sharon Rivet, Support Group News Editor

As 2023 came to a close and we reflected back on the year, there was a flurry of activity in our support groups. Many groups are reconnecting again with in-person meetings, from picnics to Walk for Waldenstrom's meet-ups. The Facebook WM Support Group continues to increase in membership, and new groups have been formed. We also have several new support group leaders, four of whom are profiled below. Other new leaders include Tom Gamble of the Minnesota/Western Wisconsin Support Group and Christine (Chris) Parmelee of the Connecticut Support Group.

LISA FOUST

Co-leader, Arkansas/Mississippi/Tennessee (AR/MS/TN) Support Group

Lisa was diagnosed with WM in November of 2022, and she says of the IWMF, "I am so impressed. I've gotten more information here than from my oncologist in the last year!" Lisa responded to the request to become a support group co-leader because she thinks it's important for people to be able to share their experiences with this disease, especially since it is so rare.

Lisa still works full-time for her state utility commission and is less than two years away from having 30 years of service and being able to semi-retire. To recharge, Lisa likes to plant flowers in the summer and watch them grow and go to the beach a couple of times a year. She also loves spending time with her first grandchild, who was born in August.

PAULA ADAMS

Co-leader, Arkansas/Mississippi/Tennessee (AR/MS/TN) Support Group

Paula was diagnosed with WM three years ago. She learned about the IWMF via emails and webinars. She started attending webinars to learn more about WM and was impressed with the sessions. "It was so exciting to finally meet other WM patients and family members. I volunteered to become a group leader to support the wonderful work the IWMF does. WM is such a rare disease, the need for support and collaboration is important. I am thrilled to be a part of the IWMF."

Paula recently retired, and while she loved her work, she felt it was time to "move on" from 43 years in clinical and corporate work to a new chapter. During this time, she worked in oncology and led an American Cancer Society "I Can Cope" support group that she describes as a wonderful experience.

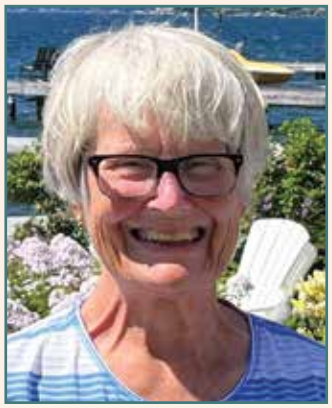
Paula golfs, power walks daily, watches and attends college football games, enjoys spending time with family and friends, and traveling. She has two grown

Welcome To New Support Group Leaders, cont. on page 30

Welcome To New Support Group Leaders, cont. from page 29

sons and two grandchildren in California and visit frequently.

Paula said, "I am looking forward to working with Lisa Foust in our leadership for the AR/MS/TN group and to meeting all of you."



NANCY F. NELSON

Co-leader, NW/Seattle Area Support Group

Of her diagnosis with WM in February of 2020, Nancy says, "Of course I'd never even heard of it! When I was almost done with treatment, I decided I needed to learn more about it. I've been treated at Fred Hutch in Seattle and was given a list of things to read. Once I started reading the IWMF information, I knew I'd found exactly what I needed. I also realized I wasn't alone. Like so many others, I never heard of WM, didn't know anyone with WM, and didn't know anyone who knew anyone with WM."

Nancy placed a call to Shirley Ganse, the NW/Seattle Support Group leader. "Shirley was the first person I spoke with who had WM. I couldn't believe I was talking to someone like me! Next, I attended a Zoom support group meeting and saw and heard more people with WM. I mostly listened because I was learning so much."

Last summer Nancy met WM patients in person at a support group picnic she and her husband Mark graciously hosted at her home. She says that knowing she's part of a community of people like her is very meaningful.

Nancy has lived in Seattle since 1989. The thing she likes most about the area is all the water, and her favorite thing to do is go for an open water swim in Lake Washington. She and her husband have two adult children, both married, and two grandchildren.

JULIE YEOMAN DAM

Indiana Support Group

Julie was diagnosed with WM in the summer of 2019. "The IWMF has been a fantastic resource for me. Over the past four years I have used many of the IWMF resources, and I am so thankful that we have so much information available. I like that all of the research articles are available to us in real time!"

She appreciates the Indiana Support Group and recognizes how important it is to continue this established group. "It is my hope that anyone can receive good reference materials, good friendship from others who understand, and life-giving hope for the future."

Julie is married with three grown children and ten grandchildren.

WHAT AN AMAZING YEAR FOR THE WALK FOR WALDENSTROM'S! THANK YOU FOR ALL YOUR SUPPORT!

We are thrilled to announce that more than a dozen Walks took place in September across the globe in support of our 2023 Walk for Waldenstrom's initiative. It is heartwarming to see the community come together to raise awareness and funds for WM. Thanks to the unwavering support of individuals like you, we have raised more than $191,000 toward the cause. Our goal is to reach $200,000 by the end of the year, and we are confident that with your continued support, we can achieve this target. Let us continue to spread the word and make a difference in the lives of those affected by this disease. Your contribution, big or small, can help make a significant impact. Thank you for being a part of this journey. Let's keep walking toward a brighter future!

A very successful Walk took place in San Diego, California, that raised $12,275! Karen Fiorello shared her experience at the Walk:

"The San Diego Walk for Waldenstrom's took place on Sunday, September 10, and was a tremendous success. Since being diagnosed with Waldenstrom's, I have participated in every Walk, including those that took place at the Educational Forums. Speaking of Ed Forums, I want to encourage everyone who is able to attend next year. I have attended every one since I was diagnosed and not only have I learned more each time, but I have met some wonderful people.

(Editor's note: You will also be able to attend virtually.)

"There were sixteen of us on our Walk in San Diego, including my oncologist, a radiology oncologist, and the oncologist of another Waldenstrom's patient who came to cheer us on. Our official mascot, my dog Noodles, walked all the way. She has also attended all the Ed Forums since 2013. We started our mile distance with stretching, and afterwards we shared pizza, half of which was donated by a local restaurant. We provided water and chocolate chip cookies. All in all, it was a fun morning."

The San Diego Walk for WM had lots of participants!

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:

RONALD ALLEN
ANONYMOUS
JEAN-MARC* AND SARAH AUDIBERT
PAUL AWES
C. EDWIN BAKER
JACK BAKER
JANET BAUSSER
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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:

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

- 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 targets for therapy*
- Brad H Nelson PhD & Julie S Nielsen PhD, Deeley Research Centre, *Mutant MYD88: A target for adoptive T cell therapy of WM*

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

- Dr. Marzia Varettoni, Fondazione Italiana Linfomi Onlus, *Non-invasive diagnostics and monitoring of MRD and clonal evolution 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 combinational therapies for Waldenstrom's Macroglobulinemia*
- Shahrzad Jalali, PhD, Mayo Clinic, *Modulation of T-cell function by metabolomic signature of the bone marrow microenvironment in 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 Waldenstrom's Macroglobulinemia and to design genetically driven human-like experimental models*
- Dr. Gareth Morgan, New York University Grossman School of Medicine, *Using mutographs to define the molecular landscape and cell of origin of Waldenstrom's Macroglobulinemia*

Hamberg Family Research Fund of the IWMF

Robert Douglas Hawkins Research Fund of the IWMF

The Lynn M. Fischer Research Fund of the IWMF

Michael and Rosalie Larsen Research Fund of the IWMF

Leukaemia Foundation of Australia 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*
- Gareth J Morgan, PhD, New York University Grossman School of Medicine, *Using mutographs to define the molecular landscape and cell of the origin of Waldenstrom's Macroglobulinemia*

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

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

Carolyn K. Morris Research Fund of the IWMF

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

- 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*

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

- 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

Waldenstrom's Macroglobulinemia Foundation of Canada 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*
- Zachary Hunter, PhD, Dana-Farber Cancer Institute, *Characterization of Isoform Usage, Novel Isoforms, and Tumor Evolution in WM*
- Patrizia Mondello, M.D. PhD, Mayo Clinic, *Identifying the oncogenic cooperation between IRF4 and MYD88 L265P and their impact on the Tumor Microenvironment of Waldenstrom Macroglobulinemia*

Robert and Nadeline White 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*

Marcia Wierda Memorial Research Fund of the IWMF

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*

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 Annette Preston, Director, Donor Engagement, *apreston@iwmf.com*.

BETWEEN SEPTEMBER 1, 2023, AND NOVEMBER 30, 2023, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN MEMORY OF

Sai Baba
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Lori Cabrera
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