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INSIDE THIS ISSUE

PATIENT PREFERENCES: THE WM-VOICE PROJECT

Interview of Drs. Josephine M. I. Vos and Karima Amaador, Department of Hematology, Amsterdam University Medical Center (UMC), The Netherlands

By Dr. Glenn Cantor, *Torch* Science Editor

Dr. Josephine Vos *Dr. Karima Amaador*

Glenn: Hi, Dr. Vos and Dr. Amaador. Let's start by telling me about yourselves. How did you get interested in hematologic malignancies, and WM in particular? Where are you working now, and what kind of work do you do?

Dr. Amaador: Hi, Glenn, my interest in hematology started early in medical school, because it is a broad discipline that includes both malignant and non-malignant diseases; one day you are treating a patient with leukemia, and another day you are managing thrombotic disorders. WM is a good reflection of this, as it is a fascinating disease where the tumor cells can induce a variety of presenting symptoms, from anemia to rare auto-immune phenomena. I did my PhD on WM at the University of Amsterdam, and I hope to defend my thesis at the end of this year. Currently, I am working as an internal medicine resident at the University of Utrecht (St. Antonius Hospital), where patients with a wide variety of internal medicine disorders (including hematology) are diagnosed and treated.

Dr. Vos: Thanks for inviting us for this interview, Glenn! I have done my medical degree, hematology training, as well as PhD, at the University of Amsterdam. I also had the chance to spend part of my PhD training at the Bing Center for WM at Dana-Farber Cancer Institute, Boston, under the supervision of Dr. Steven Treon. I now work as a senior staff member at the Hematology Department of the Amsterdam University Medical Center (UMC)/University of Amsterdam. My focus both in the clinic as well as in research is on Waldenstrom macroglobulinemia, as well as immunological phenomena related to the IgM paraprotein, including auto-immune hemolytic anemia/cold agglutinin disease and peripheral neuropathy. I also work at Sanquin National Blood Bank and research laboratory. Together with a group of talented PhD candidates, we try to advance the insights and optimal care for these groups of patients. Finally, I am chair of the Dutch WM guideline committee and the Dutch WM working group.

Glenn: Describe the current preferred treatments of WM in the Netherlands. How are treatment decisions made, and what level of discussion occurs between doctors and their patients in choosing treatments?

In the Netherlands, the current preferred and most common first-line treatment is chemoimmunotherapy, and the combination of dexamethasone, rituximab, and cyclophosphamide (DRC) is widely used. Alternatives are rituximab plus bendamustine, proteasome inhibitors such as bortezomib, and BTK inhibitors, such as ibrutinib or zanubrutinib. In our health system, everyone has mandatory health insurance, and reimbursement is the same for all patients (decided on a national level). Treatment decisions within the Dutch health system are made based on the available evidence, informed by national guidelines and the reimbursement status. Generally,

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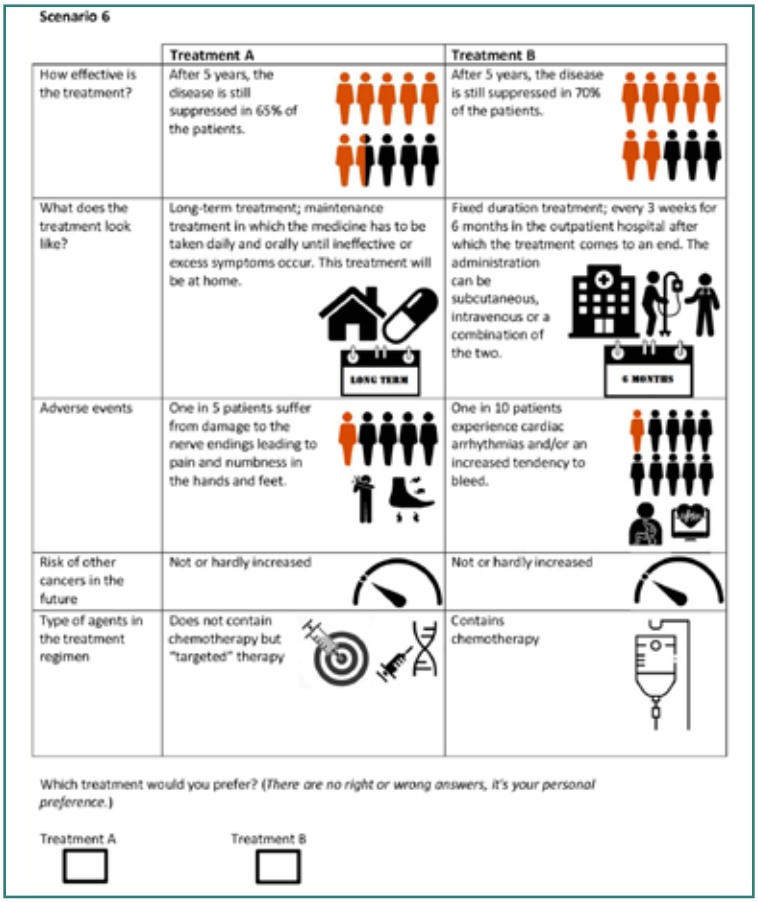


Scenario 6

	Treatment A	Treatment B
How effective is the treatment?	After 5 years, the disease is still suppressed in 65% of the patients.	After 5 years, the disease is still suppressed in 70% of the patients.
What does the treatment look like?	Long-term treatment; maintenance treatment in which the medicine has to be taken daily and orally until ineffective or excess symptoms occur. This treatment will be at home.	Fixed duration treatment; every 3 weeks for 6 months in the outpatient hospital after which the treatment comes to an end. The administration can be subcutaneous, intravenous or a combination of the two.
Adverse events	One in 5 patients suffer from damage to the nerve endings leading to pain and numbness in the hands and feet.	One in 10 patients experience cardiac arrhythmias and/or an increased tendency to bleed.
Risk of other cancers in the future	Not or hardly increased	Not or hardly increased
Type of agents in the treatment regimen	Does not contain chemotherapy but "targeted" therapy	Contains chemotherapy

Which treatment would you prefer? (*There are no right or wrong answers, it's your personal preference.*)

Treatment A ☐ Treatment B ☐

An example of the choice tasks offered to study subjects. By offering a series of this type of choice to each subject, the study investigators could determine which aspects of potential treatments were most important to WM patients. (Reprinted from K. Amaador et al., "Patient preferences regarding treatment options for Waldenström's macroglobulinemia: A discrete choice experiment." Cancer Medicine, https://doi.org/10.1002/cam4.5080, 2022*.)*

the available treatment options (if there are multiple options) are discussed with the patient and their family, with their pros and cons, and, if applicable, a choice is made together.

Glenn: You recently published a study that you performed in the Netherlands of WM patient preferences. What were your goals in the study? What did you hope to learn?

Several treatment options are available for WM, and there is no consensus on optimal first line treatment. There are also some differences between Europe and the US (chemoimmunotherapy is more preferred in Europe versus BTK inhibitors that seem more widely used in US). We were curious about what properties Dutch patients would find important regarding their treatment—for example, a chemotherapy-free regimen, pills versus intravenous medication, or fixed duration versus ongoing treatment. We hoped to get insight into their preferences, since this has never been evaluated in WM patients anywhere. This would help in designing clinical trials and new treatment regimens that match with patients' preferences. The results might also help the discussion about treatment options between patient and physician. We set out to determine how to study these preferences in a more substantial way than just interviewing patients. In a collaboration with our Medical Psychology Department, we learned about a technique called Discrete Choice Experiment (DCE).

Glenn: How did you design the study? What is a discrete-choice experiment? A number of surveys have been conducted before. How does your study differ?

As we mentioned earlier, the treatment preferences of WM patients have not been assessed, and we therefore did not find any literature on this subject. We wanted to know what the treatment preferences of WM patients are without directly asking them their preferences, and that is why a discrete-choice experiment is most suitable. It is a widely used quantitative method in healthcare that reveals the preferences of patients after they have been presented with a series of choice cards, each containing two hypothetical treatments. These scenarios represent two treatment options that have varying attributes and levels. An example of an "attribute" is "mode of administration" and an example of an associated "level" is "oral administration." By choosing between several options in a series of hypothetical treatments, we could afterwards tease out what patients found the most important properties, without directly asking them. There is an extensive statistical approach that makes the results robust. We then worked with our national WM patient group to distribute the online questionnaire via their newsletter and website.

Patient Preferences, cont. on page 4

Patient Preferences, cont. from page 3

To our knowledge this is the first time a discrete-choice experiment regarding treatment preferences has been conducted in WM.

Glenn: Tell me about the results of the study.

First of all, the response was huge: around 20% of all Dutch WM patients participated! As expected, the most important treatment attribute, according to WM patients, for making a treatment decision was its efficacy, which was expressed in a five-year progression-free survival. After that, WM patients preferred a treatment with a low risk of a future secondary malignancy. The third attribute was "adverse events" of which patients wanted to avoid neuropathy the most (more than nausea/vomiting or heart rhythm problems). And patients preferred a fixed duration intravenous/subcutaneous treatment over an ongoing oral treatment. Finally, they preferred a regimen with targeted therapy as opposed to chemotherapy. The combination of these properties does not match a currently available treatment regimen, so definitely food for thought!

Glenn: Were there any surprises to you, such as patient preferences that you would not have suspected when you started the study?

What surprised us was that WM patients would rather undergo a treatment containing intravenous and/or subcutaneous agents at the hospital for about six months as opposed to an ongoing oral regimen at home.

Glenn: Why do you think that is? Why would WM patients prefer the inconvenience of an injectable treatment at the hospital instead of taking pills at home?

Currently there are no oral treatment options that are given for a fixed duration. Therefore, we had to merge the attributes "duration of treatment" with "mode of administration" to avoid unrealistic treatment combinations when designing the choice cards. We believe that patients opted for a regimen containing IV/SC administration because it was the fixed duration option. Patients would rather have a treatment-free interval instead of having to take medication for a long time. This is something we would like to study further in the follow-up project that we are currently working on, a project in multiple countries called WM-VOICE.

Glenn: How do you see the patient preference results being used in the Netherlands? Will they affect individual doctor/patient discussions about treatment decisions? Or will they be more useful at the level of clinical trials, drug development prioritization decisions, or payment reimbursement decision-making?

At the moment, the results are most useful for directing clinical trials. For example, we are working on a new clinical trial with a chemo-free regimen (a bispecific antibody) and the discrete choice experiment results really made us push for a fixed duration approach, knowing how important that is to patients.

Drs. Josephine Vos, Marie José Kersten, Karima Amaador, and Monique Minnema at the IWWM11 meeting, Madrid, 2022

The results were presented at our national hematology conference as well as at the ASH conference in 2021; it was published as a full paper in *Cancer Medicine** and will be made available in the Dutch language in our *Dutch Hematology Journal*. We were also happy to present our results at a national hematology/lymphoma patient symposium. This way we hope to make physicians (and patients!) aware about what aspects should not be left unsaid when discussing treatment options in the WM clinic.

Glenn: Now, you are interested in expanding the Dutch study to other countries. Describe the plan of the WM-VOICE project.

Since the discrete-choice experiment showed feasibility and yielded interesting results in the Netherlands, we wanted to go international and assess whether there are differences or similarities among WM patients from different countries. Also, our experience with the Dutch DCE will help optimize the protocol for a larger study and help answer some questions that were generated. In the WM-VOICE (Views On treatment in International patients Collaborative Effort) project, patients' treatment preferences will once again be assessed by a discrete-choice experiment. Additional or adjusted attributes and levels will be included to account for the differences in health care systems, availability of agents, and so on. The proposal was discussed with WM doctors as well as patients at the recent IWWM11 in Madrid, and everybody was super enthusiastic and supportive! We aim to include the UK, the US, Canada, and Australia, and also make use of the WhiMSICAL and Rory Morrison registries. Patients can participate using a web-based questionnaire.

Patient Preferences, cont. on page 5

Glenn: I can imagine many differences between the health care system and in doctor/patient relations in the Netherlands, compared with the rest of the world. What factors might influence different patient preferences in countries other than the Netherlands?

Firstly, there are factors related to the health care system such as insurance coverage, approved/available agents, and geographic differences (such as distance to the nearby hospital) that influence the patient's preferences. More importantly, cultural differences may influence the communication styles of doctors and patient treatment preferences. For instance, a recent Dutch study showed that Dutch physicians involved in cancer are direct and elaborative in informing patients. However, just in the neighboring country, Belgium, the doctors discuss fewer topics and did not always provide extensive information compared to the Netherlands. We are therefore also interested in the cultural differences among the participating countries in the WM-VOICE project.

Glenn: How many patients would you like to include in the WM-VOICE project. How will you go about recruiting a large number of patients?

For now, we aim to minimally match the response we have gotten in the Netherlands, around 300 patients from each participating country. This would result in a minimum of 1,500 patients. However, we really hope for a massive recruitment, because this would result in more in-depth information and give the results more robustness.

Glenn: I can imagine patient preferences would vary, depending on whether the patients are newly diagnosed and being treated for the first time, or have been treated before, sometimes multiple times, with various drugs. How are you going to dissect which groups of WM patients prefer which treatments?

In our study, we have included some general questions about treatment status, i.e., watch-and-wait, currently being treated, and completed treatment. We did some additional analyses to see if previously treated status influenced the preferences, and it came out negative. This could, however, be attributed to low power (too few people in each group for good statistical analysis), or that additional variables are needed, such as number of prior therapy lines. These are interesting questions that we will assess again during WM-VOICE.

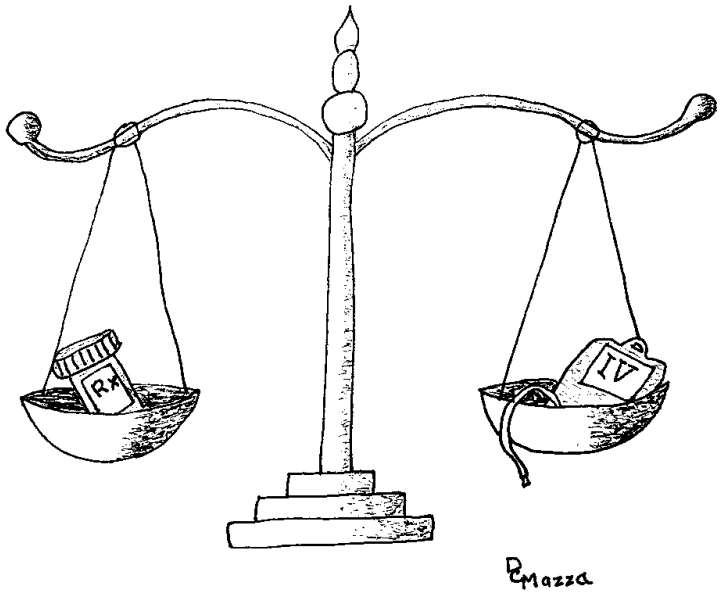
Glenn: This is a fascinating project. How do you see the results being used?

Thank you, Glenn. First, we would love to see the results incorporated at the doctor's office, since these data can help clinicians support shared decision-making with their patients. Furthermore, insight into the treatment preferences of WM patients can aid in the development of new treatment regimens containing these characteristics (e.g., fixed duration, chemotherapy-free, oral options in the best case). Thus, future clinical trials can focus on outcomes that are most important to patients that would otherwise be overlooked. Finally, it might help funding agencies and even governmental approval agencies to set priorities based not only on what professionals think, but also on listening to the WM patients' VOICE (hence the name of our project!).

Glenn: Thank you so much for explaining the WM-VOICE project. And, most importantly, thanks for all the work you do on behalf of WM patients!

*For the link to the full scientific paper of this work:

Amaador, Karima. "Patient preferences regarding treatment options for Waldenström's macroglobulinemia: A discrete choice experiment" *Cancer Medicine,* July, 2022. *https://onlinelibrary.wiley.com/doi/10.1002/cam4.5080*



Weighing the preferences – by Diane Mazza

THE TORCHBEARER REPORT

By Pete DeNardis, Chair, IWMF Board of Trustees

A PATIENT'S REFLECTION

While we WM patients and caregivers can consider ourselves fortunate today that there are so many treatment options, it was not always that way. And there are still too many of us who have to face the reality of recurrence, of being refractory to the latest novel treatments, and of falling prey to infections that hit us harder because our immune systems have been battered. Yes, for many of us, our "pill" is also our poison. But that "pill" does extend our lives significantly and improves our quality of life while doing so.

Since my initial diagnosis in 2003 and subsequent involvement with the IWMF as a volunteer managing its online discussion list back in 2006, I have personally witnessed the dramatic advancements in treatments for our disease. While I am extremely grateful and consider myself truly fortunate for being able to withstand multiple periods of recurrence, I (like others, I imagine) am carrying in the back of my mind a concern about the next major relapse or serious infection.

Over the years, by being part of the global WM community and an active volunteer, I have met many, many wonderful people who have guided my wife and me on our journey and have been role models for us. Many (too many, in my mind) are no longer with us, but their memory and their life spirit live on in those of us whose lives they touched so caringly and deeply. Mitch Orfuss, who passed away in February 2023, was one of those people, and you will read more about him in this issue of the *Torch*.

As Chair of the IWMF Board for the past two years and as a Board member since 2008, I've had the honor and pleasure of working with many fellow patients and caregivers who also volunteered their talents and time to the cause. They work to make sure that everyone with WM around the world has easy access to the most current information about diagnosis and treatment for WM, along with how best to survive and thrive with it. Board members also strive to find newer and better ways to fund WM-specific research in the global medical community. This research simply would not take place were it not for the generosity of those who donate to the IWMF and for the volunteers, clinicians, and researchers who give of their time to review research proposals. While significant findings have occurred and significant strides have been made, there is still so much to be done! Far too many of us find that even the novel agents do not work well, and many have to contend with the financial toxicity associated with the newer treatments. We (the IWMF Board and IWMF staff) will continue to be on alert for new opportunities to support the WM community and to promote WM-specific research. We will not rest in our quest to fulfill the IWMF's mission to support and educate everyone affected by Waldenstrom's macroglobulinemia to improve patient outcomes while advancing the search for a cure.

Pete and his granddaughter

As I reflect on the tremendous impact the IWMF and members of the global IWMF community have had on my wife and me, I consider myself truly blessed and fortunate that a retired pharmacist who was diagnosed in 1994 took it upon himself to start a support group and reached out to clinicians and researchers about this disease. Arnie Smokler set the wheels in motion for what is now the IWMF, and we all owe him a huge debt of gratitude. Recently, his granddaughter reached out to us just to say hello, and she remembered sitting on his lap as a young child while he was either on the phone with fellow WMers or on his computer typing out messages on the discussion list. It's a bit surreal, almost three decades later, to be writing this article with my own young granddaughter tugging on my leg for attention. As I gaze down at her, I resolve to do whatever I can to ensure that I will be around for her and actively engaged with her for many, many years to come. And I hope that, after I pass away, she will remember and reflect upon this moment, knowing that WM is no longer considered a life-threatening illness, thanks to Arnie and those who have followed in his footsteps.

I encourage all of you to take advantage of the services, support groups, publications, discussion groups, webinars, and seminars that the IWMF provides; they will truly help you improve your quality of life. And, if you appreciate the help and support you receive, consider becoming a volunteer and offering your talents to the cause—and donating so that we can continue to fund much needed research and provide support services to everyone around the world! Together, we can survive and thrive. Together, we can accomplish the vision of "a world without WM"!

Best of health to all.

I raise my glass of homemade wine to celebrate the lives of fellow WMers who are no longer with us, in appreciation to those who are volunteering and giving to the IWMF and in honor of all of you who are travelling the same journey as my wife and me. As I like to say in my email tag lines, *"Vino, amore, salute – cos'altro c'è?"* (Wine, love, health – what else is there?)

US HEALTHCARE LEGISLATION UPDATE

By Bonnie Beckett, IWMF Public Policy Liaison

The past 40 years since the passage of the Orphan Drug Act have seen significant progress in the development of treatments for Waldenstrom's macroglobulinemia and other rare diseases. Continued progress depends on adequate funding for research, as well as ways to make these treatments more affordable and accessible. Recent changes to Medicare offer opportunities for controlling prescription drug costs. With a divided Congress, however, progress could stall if funding appropriated for key agencies involved in the research and approval of drugs is not made available or recently passed changes to Medicare are not implemented.

Celebrating the 40th anniversary of the Orphan Drug Act

In 1983 Congress passed the Orphan Drug Act (ODA) to create incentives for the development of treatments and cures for rare disease patients. Patient advocates, legislators from both sides of the political aisle, researchers, and representatives of the pharmaceutical industry worked together to find a way to encourage manufacturers to invest in research on rare diseases previously viewed as unprofitable. ODA incentives included seven-year market exclusivity for companies that developed an orphan drug, tax credits equal to half of the development costs, grants for drug development, and fast-track approvals of drugs indicated for rare diseases. Before approval of the ODA, only 38 drugs were approved in the United States specifically to treat rare diseases. The ODA has resulted in the development and approval of about 700 new drugs and biologics for rare diseases. But around 95% of the more than 10,000 known rare diseases still do not have therapies approved by the Food and Drug Administration (FDA). The ODA tax incentives for industry have been cut in recent years, and the Orphan Drug Grants Program and other key program components remain critically underfunded.

Key changes to Medicare

The Inflation Reduction Act of 2022 (IRA) included provisions to lower prescription drug costs for people on Medicare and for the federal government. Some changes became effective on January 1, 2023, while other changes will become effective over the next few years. The PAN Foundation has produced an excellent, readable, detailed overview of these changes: *https://www.panfoundation.org/everything-you-need-to-know-about-medicare-reforms/.*

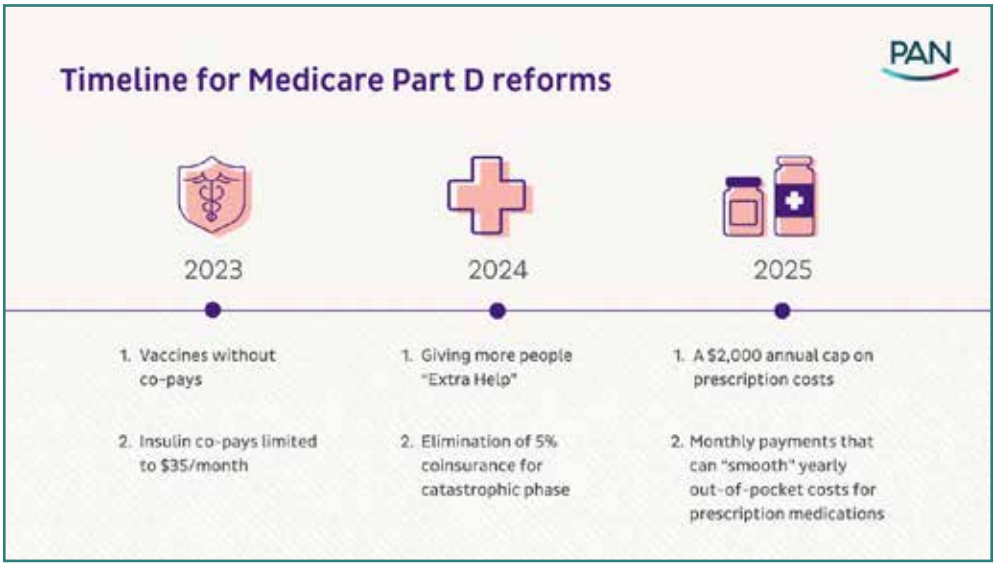
A Kaiser Family Foundation brief provides additional information on the financial implications of these changes nationally and by state*: https://www.kff.org/medicare/issue-brief/how-will-the-prescription-drug-provisions-in-the-inflation-reduction-act-affect-medicare-beneficiaries/.* Here are brief summaries of the new provisions:

2023

- **Vaccines:** Deductible, coinsurance, or other cost-sharing requirements are no longer required for adult vaccines recommended by the Centers for Disease Control and Prevention and covered under Medicare Part D, including the shingles vaccine.
- **Insulin co-pay monthly cap of $35:** Cost-sharing for insulin products covered under Medicare Parts B and D will be limited to $35 per month.
- **Drug company rebates:** Drug companies will be required to pay rebates if drug prices rise faster than inflation.

2024

- **Elimination of the 5% coinsurance for Part D catastrophic coverage:** The current requirement that patients pay 5% of prescription costs once they



PAN Foundation timeline for Medicare Part D reforms

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reach the catastrophic benefit phase will be eliminated in 2024. After paying the initial deductible, a person on Medicare will pay 25% of drug costs with a cap of about $3,250. The cap only applies to covered medications, and Part D plans can opt not to cover certain drugs but are required to cover medications that fall into six protected classes, one of which is drugs to treat cancer. All patients with Medicare Part D will have a cap regardless of their income.

- **Expansion of the federal Low-Income Subsidy (LIS) or Extra Help program:** Beginning in 2024, the partial benefits under the LIS program will provide full benefits that will cover the majority, if not all costs, for prescription medications for low-income patients.

2025

- **Annual limit of $2,000 for prescription drug costs under Part D:** After paying the initial deductible, a person on Medicare will pay 25% of drug costs up to a cap of $2,000 for out-of-pocket costs for a single or multiple medications. A new Inflation Reduction Act provision will allow Medicare patients to continue treatments they have been receiving without switching to a different medication. Before the cap, Medicare patients receiving oral treatments, such as ibrutinib (Imbruvica), under Part D would have to go back to using infusion or injection drugs under Part B because of high out-of-pocket costs.
- **Option to smooth out-of-pocket costs in monthly installments:** All Medicare prescription drug plans and Advantage plans with prescription programs must give their patients the option of paying in monthly installments. Smoothing out the $2,000 cap would result in payments of $166 per month spread over the year.

2026-2029

- **Medicare implements negotiated prices for certain high-cost drugs:** The original legislation that created Medicare precluded negotiation for drug prices. This change represents the first opportunity for Medicare to begin negotiating drug prices, but the limitations on the number of drugs each year means that it may be years before high-priced drugs for Waldenstrom's or other rare diseases become subject to this provision.
  - – 2026 - 10 Medicare Part D drugs
  - – 2027 - 15 Medicare Part D drugs
  - – 2028 - 15 Medicare Part B and Part D drugs
  - – 2029 - 20 Medicare Part B and Part D drugs

In 2023 the Center for Medicare and Medicaid Services (CMS) will begin collecting the pricing and other data necessary to select the first 10 Part D high-expenditure, single-source drugs for negotiation and to develop the negotiation polices. On September 1, 2023, CMS will publish a list of the 10 drugs selected, and negotiations with these manufacturers will be completed by August 1, 2024. CMS will publish a list of the negotiated maximum fair prices for these 10 drugs on September 1, 2024, and the prices will apply beginning on January 1, 2026. The Center for Medicare and Medicaid Services plans to seek public comment from patients, consumers, Part D plan sponsors and Medicare Advantage organizations, drug manufacturers, hospitals and health care providers, wholesalers, pharmacies, and others.

The Inflation Reduction Act further limits Medicare Part D premium growth to no more than 6% per year from 2024 through 2030 and delays to 2032 implementation of the Trump Administration's drug rebate rule that is estimated to increase Medicare spending and premiums paid by beneficiaries. In addition, flexibilities that increased access to telehealth for Medicare and Medicaid participants during the COVID-19 public health emergency have been extended for two years.

Progress on other issues

The fiscal year 2023 spending bill passed at the end of last year included other provisions important to the rare disease community. These included:

- Increased funding for FDA and The National Institutes of Health's (NIH) Advanced Research Projects Agency for Health (ARPA-H) and National Center for Advancing Translational Science (NCATS) for research in the development of new therapies and diagnostics for rare diseases.
- Policies to increase the representation and engagement of diverse and underserved populations in clinical trials supporting FDA approval of drugs and medical devices.
- Authorization of and funding for the Orphan Products Grant Program.
- Accelerated approval reform to improve the pathway used to get innovative therapies to patients sooner.

Outstanding concerns

While significant progress was made on issues important to the rare disease community, concerns remain to be addressed. First, Congress has not yet acted on the Medicare payment cuts scheduled to take effect on January 1. These cuts include a planned 4.5% cut in Medicare reimbursements in 2023 that could jeopardize patients' access to physicians.

Second, the fiscal year 2023 budget passed by Congress included substantial increases for NIH and FDA—agencies critical to rare disease drug development, testing, and approval. However, the impasse over the debt ceiling at the beginning of 2023 has delayed when agencies receive funding increases approved for key programs and staff and could result in funding cuts.

Third, telehealth provisions implemented during the pandemic were popular and have received broad bipartisan

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support. How telehealth can be used more broadly yet safely merits serious analysis.

Finally, confusion about how the Orphan Drug Act's market exclusivity should be awarded remains unresolved. A Circuit Court of Appeals decision in 2021 held that the seven years of market exclusivity under the Act applies to drugs for the entire rare disease or condition, regardless of whether the drug was approved only for a narrower use or indication, such as only for adults who have the disease. The FDA believes that if it approves a drug for a narrower use or indication, then market exclusivity should apply only to that particular use or condition, thereby putting its position potentially at odds with that of the Circuit Court. The National Organization for Rare Diseases (NORD) believes that "the market exclusivity component of the Orphan Drug Act needs clarification in order to remain a useful incentive for manufacturers to study vulnerable populations, such as children."

The next months and years will show whether the funding for research on rare disease treatments and the changes made to Medicare fulfill their promise to make treatments more available, accessible, and affordable for patients with rare diseases and the extent to which other outstanding concerns are addressed.

IWMF-FUNDED RESEARCH: NEW 2022 ROBERT A. KYLE CAREER DEVELOPMENT AWARDS

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

In the October 2022 issue of the *Torch*, we announced the 2022 IWMF research grants, totaling $1,154,000 to seven researchers, and we described the research of Dr. Gareth Morgan, recipient of the IWMF-LLS Strategic Research Roadmap Grant (see *https://iwmf.com/wp-content/uploads/2022/10/N31400-Torch-Oct-2022_web.pdf*).

In this issue, we describe the work of the two 2022 Robert A. Kyle Career Development Awardees. These are two-year awards for up to $157,500 each to young WM investigators who are in a mentoring environment. The strategic intent of the IWMF is to foster a new generation of talented WM researchers who will continue and build on the research accomplishments of the past.

Simone Ferrero,
Hematology Division,
University of Torino,
Alessandria, Italy, on behalf of
Fondazione Italiana Linfomi (FIL).
A multi-omics approach for deciphering the mechanisms of progression in pre-malignant IgM gammopathies: new insights from the FIL BIO-WM trial

Dr. Simone Ferrero

Simone Ferrero, MD, is an Assistant Professor of Hematology at the University of Torino in Italy. Under the mentorship of Prof. Benedetto Bruno, Director of the Hematology Division, he will investigate the biological mechanisms that drive progression from totally asymptomatic IgM monoclonal gammopathy of undetermined significance (IgM-MGUS), a common, non-cancerous disorder; to smoldering WM, "watch-and-wait" WM that does not require treatment; to symptomatic WM.

In a previously IWMF-funded project, a consortium of European investigators from Italy and Spain, coordinated by the Italian Lymphoma Foundation (Fondazione Italiana Linfomi or FIL), enrolled a large number of IgM-MGUS, smoldering, and symptomatic WM patients in an observational project called the "FIL BIO-WM trial" (*https://clinicaltrials.gov/ct2/show/NCT03521596*). The main goals of the trial included development of better non-invasive diagnostic techniques, studying the clonal evolution of WM cells, and evaluating the low level of remaining WM cells in treated patients. As part of the project, biological samples, including bone marrow, blood, and plasma, were repeatedly collected and preserved from 300 patients, along with detailed information on the patients' baseline features and disease progression.

In the present project, Dr. Ferrero will take advantage of this resource. He will do a series of molecular analyses on the samples to better understand why only some people progress from non-cancerous IgM-MGUS to WM and what molecular changes drive this progression.

Some gene mutations such as MYD88 and CXCR4 have been well characterized, yet they do not explain the wide diversity of WM presentations in individual patients, nor do

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Dr. Simone Ferrero and his laboratory group at the University of Torino, Italy. Back row: Daniela Drandi, Michele Clerico, Alessio Lonardo, Giulia Bondielli, Barbara Mantoan, Elisa Genuardi, Michela Borriero, Simone Ferrero. Front row: Simone Ragaini, Aurora Civita, Beatrice Alessandria, Veronica Peri, Martina Ferrante, Mariapia Pironti

they explain why some patients progress to serious disease and others do not. Dr. Ferrero and his team, including Drs. Daniela Drandi and Martina Ferrante at the University of Torino in Italy, will investigate other possible gene mutations that may be involved in the transition to symptomatic WM.

He has proposed a set of genes that are likely candidates, including a gene called PRDM1 that encodes a protein called BLIMP1, which is known to be involved in the transition from B cells to plasma cells. He will also examine another candidate gene called TNFAIP3 (also called A20). Both PRDM1 and TNFAIP3 may encode "tumor suppressors," which are proteins that normally keep B cells from going out of control and becoming cancerous. Tumor suppressor genes are known to be important in other cancers—if the tumor suppressor genes are absent or inactive, normal control is gone, and cells can progress to cancer. Dr. Ferrero's hypothesis is that gene deletions (which are seen in some WM patients) or mutations might result in a deficiency of the tumor suppressors PRDM1/BLIMP1 or TNFAIP3, which would enable B cells to grow without their normal control mechanisms and progress to WM.

As any WM patient knows, it would be desirable if doctors could make diagnoses with blood tests instead of bone marrow biopsies. Better blood tests may also enable doctors to follow progress more reliably. In the second part of the project, Dr. Ferrero, in collaboration with Dr. Philippe Decruyenaere, University of Ghent, Belgium, will examine blood samples from the FIL BIO-WM trial for a type of RNA that circulates in the blood and is called "cell-free RNA" (cfRNA). There are many types of cell-free RNAs, and better characterization may facilitate WM diagnostics and reduce the need for bone marrow biopsies.

The third part of the project is to study clonal hematopoiesis of indeterminate potential (CHIP). CHIP is a common occurrence in older people, in which non-cancerous blood-forming cells in the bone marrow or certain immune cells accumulate mutations that enable them to proliferate and harmlessly accumulate in the body. But CHIP may not be entirely harmless. Dr. Ferrero's team, in collaboration with Prof. Luca Malcovati, University of Pavia, Italy, will investigate genetic changes in these expanded cell populations that might tip them over the edge to become harmful, either in facilitating WM progression or in promoting additional, different blood tumors.

The advantage of using samples that have already been collected from the FIL BIO-WM trial is that any molecular findings can be correlated with information that was collected about the patients' disease characteristics. Using this resource, Dr. Ferrero will consider the rate of progression from IgM-MGUS to smoldering WM to symptomatic WM, the time to disease progression, overall survival, and the rate of transformation to more aggressive lymphoma or development of additional cancers.

By making good use of the large number of patient samples that have already been collected from the FIL BIO-WM study, Dr. Ferrero's project may provide new insights into the underlying molecular changes that initially lead to development of WM. This could open new routes of therapy.

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Signy Chow,
University of Toronto,
Sunnybrook Health Sciences,
University of Toronto,
Ontario, Canada.

Characterization of genomic alterations in treatment-naïve patients with WM through a course of targeted treatment and disease progression

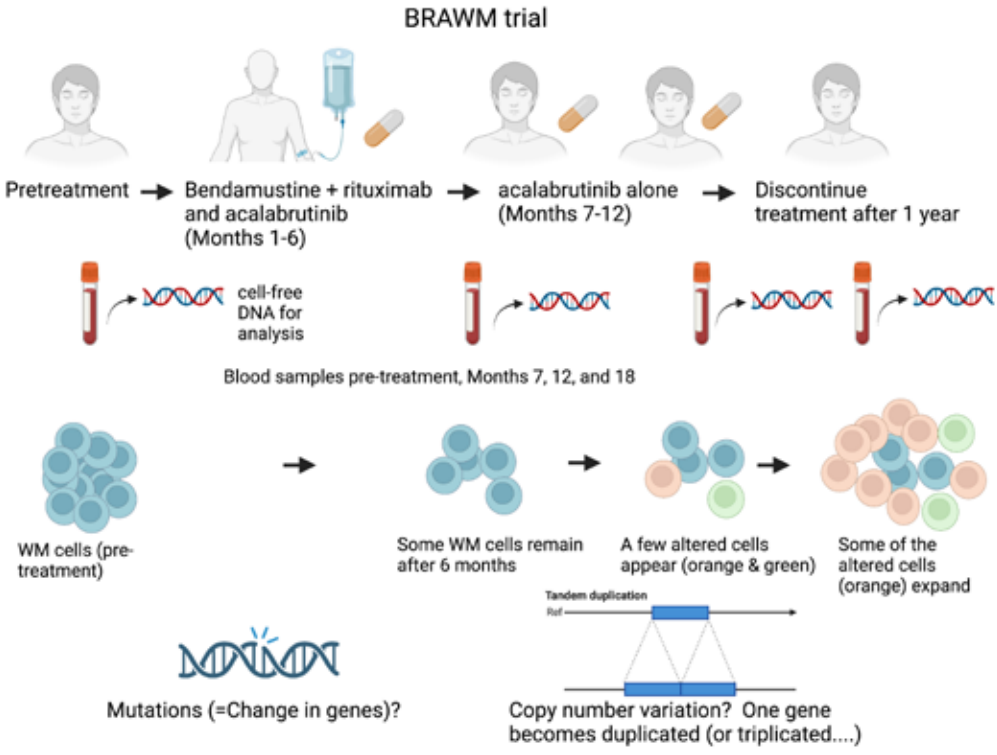
Dr. Signy Chow

Signy Chow, MD, MSc, is a staff hematologist at the Odette Cancer Centre, Sunnybrook Health Sciences, at the University of Toronto, Ontario, Canada. She has considerable experience in multiple myeloma and its underlying DNA abnormalities. Now, she is applying her scientific skills to DNA analysis (called "genomics") of WM.

Specifically, she is examining how the genes of WM cells change with time, starting with cells of patients before they have ever been treated and then examining their cells during treatment. This study of how cancer cells change while under treatment is called "genomic clonal evolution." One can hypothesize that some WM cells develop mutations (changes in DNA in the WM cells) that enable those WM cells to survive treatment with anti-cancer drugs. If the specific mutated genes could be identified, drugs targeted against those particular proteins potentially could be used to help patients who do not respond well or become resistant to drug therapy.

Using cells collected at different times before and during treatment, Dr. Chow will do DNA sequencing on a panel of 27 genes that are known to be altered in WM to look for mutations. By sampling the same people repeatedly during the course of a 1½-year period, she can trace the genetic changes in patients who do not respond well or who become resistant to drug treatment. She will compare genetic changes in these patients with the genetic changes in patients who do respond well to treatment. This analysis can identify if there are new mutations arising during the course of treatment that affect response.

Another genomic change that sometimes occurs in cancers is duplication of genes, even those genes without mutations. Increased copies of particular genes that may drive cell



In the BRAWM trial, previously untreated (first-line) WM patients are treated with six monthly cycles of IV bendamustine and rituximab plus daily oral acalabrutinib (Calquence). After completion of the bendamustine and rituximab infusions, acalabrutinib is continued for another six months (one year total). Blood is sampled before treatment begins and at 7, 12, and 18 months. Dr. Chow analyzes the blood samples for cell-free DNA, as well as mutations and copy number variations in the WM cells. Depicted here is one possibility: WM cells are reduced but not eliminated by the first six months of treatment, followed by emergence of several different types of resistant cells. One of those resistant cells then expands, resulting in recurrence of WM symptoms. The bottom row depicts some of the major changes that Dr. Chow is looking for, mutations (changes in genes) or copy number variation, in which a normal, non-mutated gene becomes duplicated (copied many times), leading to an inappropriately large amount of that particular protein being expressed. (Created with BioRender.com)

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proliferation is a key feature of some cancer cells. This is called "copy number variation." If a gene becomes duplicated, and if the duplicated genes are activated, WM cells could produce twice as much protein as a cell without a duplicated gene. It is not just a single duplication—sometimes, cancer cells make numerous copies of a particular gene, resulting in cells that make ten times (or more) of a particular protein. If that protein happens to be important for making cells survive longer, proliferate more, or resist drug therapy, then the cell population can expand. The duplicated gene may be perfectly normal and be free of any mutations, so an analysis that is confined to looking for mutations may miss this important type of abnormality.

Dr. Chow will also test techniques to obtain WM DNA directly in blood samples ("cell-free DNA"), so that bone marrow biopsies would not be needed for DNA analysis. She is already using this type of analysis in multiple myeloma patients, and there is increasing evidence that WM patients also have cell-free DNA, produced by WM cells, which is circulating in their bloodstream.

To do this work, her study is linked to a large ongoing clinical trial in Canada, coordinated among multiple hospitals across the country (a "multicenter trial"). The trial, called the BRAWM trial, treats previously untreated WM patients with bendamustine and rituximab, in combination with the BTK inhibitor acalabrutinib, a newer alternative to ibrutinib. For details, see *https://clinicaltrials.gov/ct2/show/NCT04624906.* In this trial, patients' blood and bone marrow are sampled before treatment and at 7, 12, and 18 months. Dr. Chow will make use of this rich set of samples for her study. Importantly, she can not only identify genomic changes, but she will also be able to correlate the changes with the clinical response of the trial participants.

The goal of Dr. Chow's project is to better understand why patients respond or do not respond to treatment, and why certain patients become resistant to the drugs they are receiving. With this knowledge, better therapies can be targeted to individual patients.

WATCHING AND WAITING

By Jacob Weintraub, MD, retired

My journey began almost 22 years ago at a Red Cross blood drive. I had donated nine gallons over the years, and this was going to be just a routine donation. However, to my surprise, I was told I was too anemic to donate. They had measured my fingerstick hematocrit at 33% and hemoglobin of around 10-11 g/dL, but told me just to come back in a couple of weeks and try again.

Since I am in the medical field, I knew that healthy middle-aged men don't have hemoglobin that low, so I immediately checked in with my internist, who fortunately was an exceptional diagnostician, and within a month he had discovered an elevated IgM. He requested a bone marrow biopsy at the local cancer center and then called to tell me that I had cancer, Waldenstrom's macroglobulinemia.

This was completely foreign to me, especially since the local oncologist who did my bone marrow biopsy wanted to start treatment immediately. Again, my internist showed his acumen by telling me it seemed strange to start treatment when my lab tests looked so good—venous hemoglobin 13.5 g/dL, IgM 400 mg/dL. So he referred me to Mayo Clinic for a second opinion. I spoke with him on a Tuesday, and Mayo Hematology called on Thursday with an appointment for the next Thursday.

Then I started to worry. Was it because my cancer is so rare, was this much more severe than I thought? This was a little bit of both, plus the doctor I was to see had just finished a fellowship and had openings in his schedule. I remember being disappointed that I was not going to see Dr. Robert Kyle, but realized he was "emeritus" and did not see patients anymore. At that point, I did not know about WM experts, such as Dr. Morie Gertz at Mayo. While the doctor I have been seeing at Mayo is not a WM expert, I have continued to see him for my whole time after diagnosis, and we have almost become family. He was very reassuring that first visit and took a lot of time to talk with me, my wife, and daughter, who lives in Minneapolis and came to the first appointment. I have since learned that the doctors at Mayo consult with each other, and I know the importance of having an expert doctor whose judgment I rely on. Although my watch-and-wait course has been fairly benign, I know that whatever happens, my doctor will give me advice and make recommendations that I will follow, also respecting my preferences, and he will make sure the decisions are good ones.

I think I still hadn't completely assimilated the idea of my having cancer. When I was growing up, a diagnosis of cancer

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almost always meant death. My mother died at age 43 from colon cancer. My stepmother died of breast cancer, as did at least two aunts. The idea of "watch-and-wait" was a foreign concept but clearly recommended by my doc at Mayo, and that has been my course.

One thing I did early on was attend an IWMF Educational Forum in Boston shortly after diagnosis. I was diagnosed at Mayo in August 2001 and attended the Ed Forum in November, not long after the September 11 attacks. The emptiness of Logan airport lent a surreal feeling to my trip. However, that was one of the best decisions I have made. Here were at least a hundred other people with WM, living normal lives with and without treatment. I remember a fundraising project, "RowBobRow," done by Bob Lynch, a WM patient who was going to row a boat from Key West to Miami, FL to raise money. (He raised $30,000!) The presentations were remarkable, comparable to any medical conference I had attended.

I went home reassured. However, as I returned to my day-to-day life, I realized that the specter of having cancer was still with me and would be with me for the rest of my life. My future course was still not fully known. I felt well and looked like my usual self. I spent a lot of time explaining WM to family and friends who knew I had gone to Mayo. I discovered I was being prayed for in at least four different religions. I became amused by the repeated comments of how good I looked, as if having a diagnosis of cancer somehow would turn me into a wasted figure.

Over the next year, it became apparent that my WM progression was going to be very slow, and WM became something I thought less about on a daily basis. I went to work, we went out to eat, visited friends and family, went to local events and places of worship, just like always. However, WM was always there. It was like the elephant in the room. Every decision we made had to be tempered by potential for a sudden course change. Yet, we were able to travel, and that seemed to become more urgent to do. We had other life ups-and-downs that needed to be dealt with.

I had not gone back to my local cancer center after the initial visit for bone marrow biopsy but eventually found another oncologist there. She was good but more than willing to leave the major decisions about my WM up to my doctor at Mayo. I worked into a routine of seeing each doctor once a year, so I was having labs done every six months. After I joined the IWMF-Talk List, now IWMF Connect, I began to realize how fortunate I had been in having a WM course so benign. There were others like me, but many who needed aggressive treatment almost immediately.

I also found other medical conditions that became more important to deal with, always checking with my Mayo hematologist. Cervical spine disc surgery, severe Bell's palsy, when my face suddenly didn't work on one side,

Dr. Jacob Weintraub on the shore of Lake Michigan, Saugatuck Dunes State Park, MI, winter 2023

and finally, a fairly aggressive prostate cancer that needed hormonal treatment and surgery, but from which I appear to have been cured. It was the prostate cancer that finally pushed me to update all my estate planning, which had been started many years before but needed change.

In the end, I have found that although my WM has become a part of my life over the last 21 years, it slowly has been relegated to a feeling of "background noise" that needs to be fully confronted only around the time of my hematology visits. While the COVID pandemic makes me aware of my WM when I go out, even my friends with no medical conditions are at the same level of precautions for that. My recent hemoglobin suggests I am getting to a place of needing treatment, but even that has been variable. It was decreasing for several visits, but now has leveled off again. Granted it is at a level close to the guidelines, but my hematologists assure me that, as has been the preaching throughout my WM life, treatment will depend as much on how I am feeling as it will on lab results. As long as I am maintaining a fairly good quality of life, pandemic notwithstanding, I can continue to watch-and-wait, and that suits me fine.

MEDICAL NEWS ROUNDUP

By Sue Herms, IWMF Research Committee Member

US FDA Halts Authorization of Evusheld for Prevention of COVID-19 Infection – The US Food and Drug Administration (FDA) has halted authorization of Evusheld in the US for the prevention of COVID-19 infection in the immunocompromised. Evusheld is not active against new COVID variants that are now responsible for more than 90% of infections in the US. The Centers for Disease Control and Prevention (CDC) is urging people with weakened immune systems to wear high quality masks and practice social distancing when it is not possible to avoid crowded indoor spaces and to stay up-to-date on vaccination. If COVID symptoms develop, testing should be performed as soon as possible in order to receive treatment with an antiviral within 5-7 days if COVID-positive. Available antiviral treatments include Paxlovid, remdesivir (Veklury), and molnupiravir (Lagevrio), but patients should talk to their doctors about which treatment is best for their individual situations.

European Consortium of Waldenström's Macroglobulinemia Publishes Consensus Recommendations for Diagnosis of WM – The European Consortium of Waldenström's Macroglobulinemia (ECWM) recently published its consensus recommendations and laboratory requirements for the diagnosis of WM. The article, published in the journal *Leukemia*, can be viewed at *https://www.nature.com/articles/s41375-022-01762-3*.

Australian Medical Group Updates Treatment Recommendations for WM – Updated recommendations for the treatment of WM in Australia have been provided by the Australian Medical Group of the Myeloma Foundation Australia in order to assist Australian clinicians. The recommendations are available on the IWMF website at *https://iwmf.com/wp-content/uploads/2022/09/MSAG-waldenstrom-guidelines-jun22-1.pdf*.

***Evusheld** is **not active** against **new COVID variants** that are now responsible for more than **90% of infections** in the US.*

DFCI Recruiting Participants for Phase 2 Trial of Antibody Drug Conjugate in Relapsed WM – Dana-Farber Cancer Institute (DFCI) has begun recruiting for a Phase 2 clinical trial of loncastuximab tesirine (Zynlonta) in WM patients who have received at least two prior treatments, including an anti-CD20 antibody and a BTK inhibitor. Loncastuximab tesirine is an antibody drug conjugate that is targeted to the CD19 protein found on the surface of B cells; after binding to CD19 on B cells, the drug is brought inside the cells, a toxin is released, and the cells are killed. The trial hopes to include 36 participants, who will be given the IV drug on day one of every 28-day cycle for up to six cycles. Dexamethasone will be given prior to each treatment. The drug has been approved by the US Food and Drug Administration for the treatment of diffuse large B cell lymphoma. On *www.clinicaltrials.gov*, the trial number is NCT05190705.

*The study found that... **(27%)** required a **dose reduction** [of ibrutinib] from the **standard 420 mg** once daily because of adverse events...*

Phase 2 Trial for CAR T Cell Therapy Is Recruiting Patients with Relapsed or Refractory B Cell Cancers Including WM – A new Phase 2 clinical trial called ZUMA-25 is open and recruiting patients with relapsed or refractory B cell cancers, including WM, for a CAR T cell therapy called brexucabtagene autoleucel (Tecartus). Participants must have had at least two prior lines of therapy, including a BTK inhibitor; also, chemotherapy and/or a proteasome inhibitor must have been attempted, with either subsequent disease progression or no response (stable disease). The primary outcome measure will be the combined rate of complete and very good partial responses. This therapy has been approved by the US Food and Drug Administration for relapsed mantle cell lymphoma. The trial number on *www.clinicaltrials.gov* is NCT05537766.

DFCI Publishes Study Examining Impact of Ibrutinib Dose Reductions in WM – An article published in the *British Journal of Haematology* by the Dana-Farber Cancer Institute (DFCI) provided data about the impact on WM patients of ibrutinib (Imbruvica) dose reductions that were required because of side effects. This retrospective study was conducted on WM patients seen at Dana-Farber from May 2012-October 2020 and followed 353 who were treated with ibrutinib over a median time of 64 months. The study found that 96 (27%) required a dose reduction from the standard 420 mg once daily because of adverse events such as musculoskeletal symptoms, cardiac events, dermatologic (skin and hair) changes, cytopenias (low blood counts), and gastrointestinal symptoms. This was higher than demonstrated in the initial ibrutinib trials in WM and CLL but comparable to other recent publications of real-world experiences with ibrutinib. The median time to a first ibrutinib dose reduction was 9.3 months, and it was reduced to 280 mg in all but three patients, in whom the dose was reduced to 140 mg. Dose reductions

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were more common in those 65 years of age or older and in females, with the researchers noting that the reasons for this were unclear and suggesting that more studies are needed for confirmation. Most patients (65%) had improvement or resolution of adverse events after the first dose reduction, but 26% received a second dose reduction. Among those with a second dose reduction to 140 mg, 25% subsequently had improvement or resolution of symptoms. After a median follow-up of three years following dose reductions, the treatment response remained stable or deepened in 79% of patients. The researchers concluded that dose reductions should be considered for patients with adverse effects from ibrutinib, although switching to a different BTK inhibitor may be preferred in some cases.

Mayo Clinic Evaluates Survival Outcomes for Young WM Patients Over Five Decades – A Mayo Clinic study, published in the *American Journal of Hematology*, has evaluated survival trends of young WM patients over five decades. Between January 1960-October 2013, the institution saw 140 WM patients who were 50 years of age or less at diagnosis, representing 11.8% of its total number of WM patients. The young WM patients were matched for time of diagnosis with older WM patients (65 years or more) for comparison. The estimated 10-year overall survival of young WM patients was 74%, with death attributable to WM itself in a higher proportion (91%) than in those who were older at diagnosis (58%). Patients were placed in three groups based on the timing of treatment start: Group 1 was treated between 1960-1977, Group 2 between 1978-1995, and Group 3 between 1996-2013. Among the three groups of young WM patients, there was no significant disease-specific survival difference across the three time periods—although the researchers pointed out that the impact of treatment with BTK inhibitors on survival was not included and remains to be determined. The estimated average years-of-life-lost for young WM patients was 11.2 years from diagnosis, based on the expected survival of a matched normal population. In contrast, the disease-specific survival for older patients incrementally improved over the same three time periods, with Group 1 older patients showing improved survival of 5.2 years, Group 2 older patients of 9.6 years, and Group 3 older patients of 12 years.

***Pirtobrutinib** binds reversibly to BTK at a different location than do several other **BTK inhibitors**, thereby **overcoming** an important means by which the cancer cells develop **resistance** to this drug class.*

Pirtobrutinib Receives FDA Approval for Relapsed or Refractory Mantle Cell Lymphoma – The US Food and Drug Administration (FDA) has granted accelerated approval to the BTK inhibitor pirtobrutinib for relapsed or refractory mantle cell lymphoma patients who have had at least two previous lines of therapy, including a BTK inhibitor. The approval is based on results from the ongoing Phase 1/2 BRUIN clinical trial of patients with relapsed or refractory B cell cancers, including WM. Pirtobrutinib binds reversibly to BTK at a different location than do several other BTK inhibitors, thereby overcoming an important means by which the cancer cells develop resistance to this drug class. The drug has been given the brand name Jaypirca.

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

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*

WM PATIENT INSPIRES GRANDCHILDREN TO PAY IT FORWARD

By Art Brewer

Ken Goldner, an 80-year-old WM patient and resident of Plymouth, MA, and his wife, Carolyn, came up with an inspiring challenge for their five grandchildren this past holiday season. They asked their grandchildren—Olivia, Tyler, Katelyn, Kylie, and Brendon—to select a charity or charities to receive a $500 donation from Ken and Carolyn. As an additional part of the challenge, after performing the necessary research, the grandchildren were required to give a presentation to Ken, Carolyn, and the entire family at Christmas on why the charities were selected and their mission.

The goal of the challenge was to provide the grandchildren an appreciation of the value of charitable giving. "We have been very fortunate in life despite my getting cancer," Ken said. "My wife and I wanted the grandkids to realize how lucky they are and to understand how to pay it forward."

To Ken's delight and surprise, the grandchildren selected the International Waldenstrom's Macroglobulinemia Foundation (IWMF) as the sole charity in Ken's honor. "I cried!" Ken said. "I didn't think they would pick the IWMF. I thought each of them would donate $100 to separate charities."

This "Cousin Charity Project" was a labor of love for the grandchildren, who range in age from 11 to 22. In heartwarming letters to the IWMF, Tyler, 19, and Katelyn, 17, describe how much their grandfather means to them, and why they selected the IWMF as their charity of choice.

Tyler wrote about his grandfather's strength and resolve, and how he wanted to help other WM patients after reading their stories on the IWMF website:

"Papa is the rock of our family and goes above and beyond to keep everyone happy. It was rough when he was diagnosed about two years ago, but he is the strongest person I know, and I am certain he will continue to heal. We cousins read a lot of information about this Foundation, its purpose, and its patients. We were inspired by many of their stories and wanted to help those like our grandfather, or even those in worse condition, as much as possible. We are definitely brainstorming ideas of how we can save more money to make a contribution and help even more people next Christmas season. Thank you for all that you do, and we are all so glad we were able to help others, especially around the holidays."

Katelyn echoed these sentiments:

"When I first found out about my Papa's diagnosis, I was overwhelmed with unknowns and emotions. As time went on, I have watched the strongest man I know overcome all of the challenges of Waldenstrom's while simultaneously supporting our family as he has always done. With his positive attitude and determination, he continues to inspire all of us grandchildren. That is why we wanted to donate to the IWMF—to help others, like our Papa, fight and grow stronger. Our donation will not only honor our Papa, but also help so many other people and spread more awareness. Papa's strength and love have not changed throughout his fight. I love him more than anything, and I know that he can make it through anything that comes his way. Papa has taught our family to always support one another, and that is what we will continue to do for him."

Ken Goldner's grandchildren (left to right) Kylie, Tyler, Olivia, Katelyn, and Brendon

Ken, who was diagnosed with WM in 2019, is no stranger to facing and overcoming challenges. He served in the US Air Force from 1964 to 1969, including service in the Vietnam War from 1966 to 1969. During his career, he clocked over 3,000 flying hours and made more than 100 in-country landings as a navigator on the Lockheed C-141 Starlifter, a retired military strategic airlifter. Since his diagnosis, he has been successfully treated and has become a member of the WM yoga community.

"We are a very close family, and our grandkids are a very caring, thoughtful group of 'rug rats' that we see often and love very much," Ken said. "I hope they will remain close to each other throughout their lives."

LIVING WELL WITH WM
First in a Series of Articles on Quality of Life

By Shirley Ganse, Linda Nelson, and Marcia Klepac
IWMF Education Committee Physical Wellness Subgroup

Many people with WM are now living longer, with relatively healthy lives, so it seems most appropriate to address the concerns they have in wanting to live as well as possible with this indolent disease.

In 2022, the IWMF Board of Trustees formed an Education Committee to investigate how best to serve a variety of patients' needs by conducting a needs assessment survey of our members on the IWMF's education, information, and support programs. Comparing those results to our current offerings soon revealed that people wanted more information about quality of life-related issues than we currently offer. While the Committee's work encompasses a broad range of the IWMF's activities, we decided one way to address this need is to have the *Torch* offer a series of regular articles focused on the physical, psychosocial, and financial issues of dealing with cancer.

In this initial article, we will address physical wellness, the specialized self-care aimed at relieving difficulties like pain and fatigue associated with WM through non-drug management. It is a non-curative, complementary support, which is unrelated to prognosis and designed instead to improve quality of life for patients, their families, and caregivers. While WM has no quick fix, everyone can take some degree of control of their bodies to become stronger and healthier. It has been well documented that frail people do not do as well with cancer treatments as those who are physically strong. Physical activity and optimal nutrition go hand in hand, and both are hallmarks of self-help.

As we later delve into the psychosocial and financial issues, other authors will introduce different aspects of living well after a cancer diagnosis—how people with WM can help themselves live better, healthier lives. If you have interest in a particular aspect of these areas that you would like to see addressed, please contact the *Torch* editor, *shirleyganse@hotmail.com*.

It is common practice for people to use health care approaches that are outside of conventional medicine to enhance wellness and minimize symptoms and treatment side effects. Some of these common approaches include dietary supplements, mindfulness meditation, yoga, tai chi, and acupuncture, among many others. Typically, the terms alternative, complementary, or integrative medicine are noted in reference to these practices, depending on what they are, and how they are used:

Alternative medicine uses a non-mainstream approach in place of conventional medicine. In the US, it refers to forms of medicine that do not have as much scientific evidence to support them as more mainstream methods, and they are not widely accepted or practiced by medical doctors.

Complementary medicine refers to the use of non-traditional approaches in addition to conventional medicine.

Integrative medicine brings together standard or conventional treatments and complementary approaches in a coordinated way. It aims to care for the whole person with well-coordinated, evidence-based treatments among different providers.

Two sources for further discussion of these approaches can be found at:

- *https://www.mayoclinic.org/tests-procedures/complementary-alternative-medicine/about/pac-20393581*
- *https://www.mdanderson.org/cancerwise/integrative-medicine-versus-alternative-medicine-why-its-importa.h00-158596101.html*

Nutrition

The variety and amount of information online about healthy eating are staggering. The problem with any online resource is that you need to make sure the information comes from a trusted source and is science-based. The best way to do that is to use well-known medical research sites, especially those with which you may be familiar through your WM experiences.

https://www.mdanderson.org/documents/Departments-and-Divisions/Clinical-Nutrition/Nutrition-Basics-for-Patients-and-Caregivers.pdf
This link, from the Houston, TX-based MD Anderson Cancer Center, provides a sound basis for nutrition, whether you have cancer or not. The first section of this 64-page booklet covers food and nutrients in general, and the second is specific to the patient and caregiver, with chapters on managing side effects, cancer-related fatigue, and dietary supplements.

https://www.cancercare.org/connect_workshops/492-nutrition_and_healthy_eating_2016-02-01
Nutrition and healthy eating during and after cancer treatments are covered in this one-hour-long video from CANCERcare. In addition to general information similar to that found in the link from MD Anderson, this also includes tips on easy-to-

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prepare foods, guidelines for eating out during and after cancer treatments, and finding an eating plan that works for you.

https://www.youtube.com/playlist?list=PLPLXayOtubE0z9Di6HfdfQGMwh3mlM8zy
The Leonard P. Zakim Center for Integrative Therapies and Healthy Living at Dana-Farber Cancer Institute offers a wide variety of videos for immediate, practical use. You can find recipes, meal plans and ideas, and a wide variety of useful tips for healthy eating. Smoothies? Breakfast veggies? High fiber muffins? Basics of pressure cooking? Peruse the list!

https://www.lls.org/managing-your-cancer/food-and-nutrition
The Leukemia & Lymphoma Society (LLS) provides PearlPoint Nutrition Services® to patients and their caregivers for all cancer types, offering free nutrition education and consultations. Their registered dietitians have expertise in oncology nutrition and provide free one-on-one consultations by phone. Just go to their website and sign up for this important and useful service. You'll find they also offer lots of information other than nutrition for managing your cancer, such as dental health, finances, and home care.

Dietary Supplements
Many cancer patients take dietary supplements to help minimize side effects of treatment or for general wellness. It is very important to be aware that some of these supplements may interact with your cancer treatments and increase or lessen the effect of the treatment. Some integrative medicine programs offer supplement consultations by pharmacists who have expertise on popular supplements and how they interact with medicines. Always consult with your doctor about any dietary supplements that you may consider taking.

https://www.mayoclinic.org/departments-centers/integrative-medicine-health/sections/overview/ovc-20464567
Mayo Clinic Integrative Medicine and Health offers services for patients' physical, emotional, spiritual, and mental health and well-being. Here you can make an appointment with Mayo Clinic for a variety of integrative programs, such as acupuncture, massage, yoga, dietary supplements, wellness coaching and meditation. During a botanicals and supplements consultation, you would talk with a pharmacist who is an expert on these popular products and learn about how their potential risks and side effects might affect your health and well-being. Check with your insurance to find out if these appointments are covered.

https://www.mskcc.org/cancer-care/diagnosis-treatment/symptom-management/integrative-medicine/herbs
Memorial Sloan-Kettering Cancer Institute has a one-hour video presentation on "Herb and Drug Interaction in Cancer Care." It covers the challenge of determining whether herbs, vitamins, and other over-the-counter dietary supplements would be helpful or harmful to you. Will a substance work as the label states it will? Is it likely to interact with your cancer medicines? Is it worth the cost? In addition, a link beneath the video opens their "About Herbs" database, which you can browse for herb information using the alphabetically arranged list. Each herb includes links for its mechanism of action and its potential interactions.

Physical Fitness
It is not surprising that people who stay active have a greater chance of being healthier than those who do not. Physical activities can include walking, running, dancing, biking, swimming, performing household chores, gardening, resistance exercises, yoga, and engaging in sports. But with a cancer diagnosis and treatment, it often becomes difficult to continue one's regular activities, so finding alternatives is a good idea. Many websites offer scientific rationales for staying active, but fewer offer specific things to do to help you work around the physical abilities that might be curtailed by your cancer fatigue and treatment. As always, consult with your doctor before starting any new physical activity.

Early morning walkers at the Ed Forum in Philadelphia, 2018

https://www.cancer.gov/about-cancer/causes-prevention/risk/obesity/physical-activity-fact-sheet
This site's information falls into the category of "That's good to know," but it doesn't answer "Now what do I do about it?" Reading good background information about exercise and cancer in general is a good place to start if you need convincing that it's something you should do to feel healthier.

https://www.acsm.org/search-results/all-blog-posts/certification-blog/acsm-certified-blog/2019/11/25/acsm-guidelines-exercise-cancer-download
This American College of Sports Medicine site has a very interesting graphic about the effects of exercise on health-related outcomes for those with cancer. It shows the amount ("dose") of aerobic or resistance exercise or a combination of the two suggested for various outcomes, including helping alleviate cancer fatigue, anxiety, and depression.

https://www.youtube.com/playlist?list=PLPLXayOtubE10vhpmu_XjacPRUtwRofH5
The Zakim Center at Dana-Farber (also listed above in nutrition) offers dozens of videos for various exercises, from tai chi to cardio workouts, yoga, stretching, and strength training. There is something here for everyone of all ages and abilities, and if you need to relax at the end of your workout, you can meditate to a music video as well.

https://anngraceyoga.com/cancer-care/
If you are into yoga, the IWMF offers a program by Ann Grace MacMullan that includes 45-minute classes on cardio flow, chair yoga, meditation, and more. You can sign up with a link on the website above or contact Michelle Postek in the IWMF office at *mpostek@iwmf.com*.

So, here's your chance to be proactive in your quest to feel better, by seeing if any of these resources might fit your interests and needs. It's up to each of us to decide how much effort we want to make to improve our physical quality of life, and these links can help. Make sure to look for more information in succeeding *Torch* issues on living well with WM.

Meanwhile, eat well and stay active!

RIDING "AROUND THE WORLD" WITH TOR OLOFFSON

By Pete DeNardis, Chair, IWMF Board

Sixteen years ago (a couple years after his initial diagnosis with WM in 2003), Tor Oloffson began riding a bicycle as a form of exercise. Biking became a passion for him, and he's now nearing his goal of riding "around the world" in terms of distance—40,070 kilometers! The double challenge of dealing with his WM diagnosis and teaching his non-athletic body to consistently ride long distances gave Tor a new lease on life.

Tor was born and raised in Sweden and worked for several years as an electronic engineer in sales and marketing and management of customer accounts for telecom companies. His career led him to other countries, and he even worked on the introduction of mobile telephony in Brazil and in Portugal, where he currently resides.

Shortly after diagnosis, he began to pursue other activities, which included biking, consulting, and even teaching Swedish to Portuguese citizens wishing to learn the language. Tor has a strong belief that those whose native tongue is Portuguese have a natural affinity for picking up other languages, such as Swedish, so his job is easy. Of course, it could be the teacher who makes learning the language easy too!

Diagnosis of WM

Tor's journey with WM began in November 2003 at the age of 57. He had recently left a leading Swedish international corporation, and he had been feeling unhealthy for a few years. His symptoms at the time were weakness, frequent infections in the airways, and redness in the eyes. One doctor initially diagnosed him with chronic lymphocytic leukemia (CLL), but after further testing (including a bone marrow biopsy), a hematologist in Sao Paolo, Brazil, diagnosed him with Waldenstrom macroglobulinemia. At the time, the doctor's prognosis included the statement that "The bad news is that it's incurable, but the good news is that it's treatable." Yet, when he returned home, he immediately Googled the illness and found that, at the time, the prognosis for five-year survival was 50% and for ten-year survival was 10%. Today, 20 years later, Tor is still going strong and looking forward to more "pearls" to be found in his future.

At the time of the diagnosis in 2003, he was living in Rio de Janeiro and happened to have a book written by Dr. Andrew Weill called *Spontaneous Healing,* which he had not yet opened. Tor read it with much attention and took home three points that he decided to focus on:

- Exercise regularly.
- Try to ensure healthy living with good food and supplements.
- Focus on positive things.

And then his biking with WM journey began.

Tor Olofsson

Biking journey

Tor admits that as a boy and young man, he was always weak at sports, and at 57, he could not run because of his knees. What he could do was inline skating, so he skated for two years.

In 2006, he bought himself a new bike and began logging his biking trips on a mobile phone app. His goal was to bike at least four times a week, doing 15-25 kilometers each day. A year later, Tor's brother and three friends agreed to help Tor fulfill a biking dream of his—to bike all the way from Lisbon to Algarve (250 kilometers). They ended up extending the ride even further, going all the way to Spain (600 kilometers). It felt fantastic.

Since then, he's logged over 38,000 kilometers in total, and by the time this article is published, he'll have reached his goal of biking a distance equivalent to traveling around the world (over 40,000 kilometers).

His longer bike trips (250 to 600 kilometers each) have included:

- 2007 Lisbon to Ayamonte, Spain
- 2011 Ayamonte, Spain, to Tangier, Morocco
- 2012 North of Finland to Northcape, Norway
- 2015 Lisbon to Santiago de Compostela, Spain
- 2016 Madrid to Lisbon
- 2017 Bilbao, Spain, to Santiago de Compostela, Spain
- 2018 Setubal, Portugal, to Cabo Sao Vicente, Portugal (southwestern-most point of Europe), with son and grandson
- 2019 Setubal to Cabo Sao Vicente again, this time with daughter and grandchildren

Riding "Around The World" with Tor Oloffson, cont. on page 20

Tor continues to ride 14-18 kilometers several days a week along less-travelled roads, enjoying the city sights and countryside along the way.

Healthy living

Since diagnosis, Tor has tried to focus on living a healthier life. He does his best to increase the number of vegetables in his diet (such as broccoli, onions, and garlic) but does admit to still having a sweet tooth. He also limits his alcohol intake to a glass of gin and tonic three times a week and a glass of red wine two-three times a week.

With regard to supplements, after reading a lot about the beneficial impact of antioxidants, he also takes one capsule of resveratrol every morning and tries to eat blueberries or blueberry powder every day.

Other aspects of his life (besides biking and a healthy diet) that he finds have helped him improve his quality of life for the past 20 years include:

- A supportive wife and family.
- Three grandchildren who have been born since he first noticed something was wrong with his health.
- Staying active and involved. Besides biking, for the past 12 years he's pursued a new activity as a teacher of the Swedish language in Lisbon and finding it to be a very positive and rewarding activity. For Tor, spending 8 to 16 hours per week with positive and motivated Portuguese people, ranging in ages from 16 to 72 years, is exciting and invigorating.
- Excellent care at a well-run medical facility (the Portuguese Institute of Oncology in Lisbon).

Currently, besides biking, he takes Nordic-style walks with his wife, using walking poles. He likes to bike with his children and grandchildren, who live in Stockholm and Holland, when he has the opportunity.

Tor's advice for others who, like him, are not athletically inclined but want to try biking, is to find a road or path that is enjoyable—one that has not too much traffic and has nice surroundings and scenery—and it can be on a trail or in a city. Then gradually work your way up to doing between 10-20 kilometers per day for multiple days per week. It benefits both your physical and mental health.

The take-aways for Tor's secret to thriving and surviving the past 20 years? Healthy eating, pursuing your passions, having a strong support network, being treated at a quality medical facility that provides quality care to cancer patients, and having a positive perspective on life.

Editor's note: Just before going to press we learned that Tor has completed his goal!

LAWN BOWLING

By Ron Ternoway

When I took up the sport of lawn bowling this past summer, I had no idea I was connecting to an ancient obsession of humans rolling eccentric spheres along the ground.

I was so fortunate to discover the Saint Mary's Lawn Bowling Club in my hometown of Halifax, Nova Scotia, Canada. A beautiful seaside location, wonderful facilities, friendly, helpful members, and a top-notch teaching and coaching program have me totally in love with my new avocation.

And I'm doubly fortunate to have connected with The Villages Lawn Bowling Club in Florida—a wonderful collection of retired folks from around the world. You are just as likely to hear an English or Scottish or Canadian accent as an American one, and everyone has been warm and welcoming, so welcoming that they have allowed me to be on the winning team in the pairs tournament and to win the singles competition. Beginner's luck...

Archaeological findings support the theory that a game with biased (unevenly weighted) stone balls was played almost 7,000 years ago by the ancient Egyptians. The Romans picked up the game, and carried it to the four corners of their Empire. Records exist of lawn bowls being played in England in the 12th century.

The increasing popularity of bowls in England led to a string of kings and queens passing laws restricting its play. The concern was that lawn bowls were taking too much time away from men practising archery. This was important as bowmen were an integral part of any army, and any drop in their effectiveness in battle would have major implications for king and country. It was only in 1845 that Queen Victoria rescinded all the anti-bowling laws.

As the British Empire spread, it brought lawn bowls with it. This introduced the game to new territories such as the US, Canada, New Zealand, and Australia. While interest in the post-Empire, now Commonwealth, countries around the world has remained strong, the popularity of lawn bowls in America diminished after 1776. It was rekindled by 19th century Scottish immigrants, and today there are some 150 lawn bowling clubs in the US, including my winter home in The Villages.

Lawn bowling is played on a large, square, flat area of tightly-mown grass, very similar to a golf green. The objective is to roll the bowls (not balls) towards a target, with the closest bowls scoring points.

Sounds straightforward, but there are a couple of curves. First, the bowls curve because they are biased. Second, the target can move. This target, a ball called the jack, can be struck by a rolling bowl and moved to a different position on the green. Makes for interesting strategy!

It's very exciting and rewarding for me to discover a new sport in my dotage, at the age of 71. I encourage you to give lawn bowling a try—here is "Lawn Bowling 101," a video to tell you more about it: *https://www.youtube.com/watch?v=II_FRVw15Wk*. If you want to find your closest club, click here: *https://www.bowlsclub.info/*.

Ron and his winner's trophy for the Singles Competition in Florida
Left - Jeanne Homan, President, The Villages Lawn Bowling Club
Right - David Grimshaw, Ron's opponent in the singles final

ABSTRACT SUMMARIES FROM THE 64TH ASH ANNUAL MEETING

By Sue Herms

The following are summaries of selected abstracts about clinical trial results, prognosis, and survival trends specific to WM or its associated conditions that were presented at the 64th American Society of Hematology (ASH) Annual Meeting held in New Orleans, LA, on December 10-13, 2022. The abstracts can be searched online at *https://ash.confex.com/ash/2022/webprogram/start.html*.

Efficacy of Pirtobrutinib, a Highly Selective, Non-Covalent (Reversible) BTK Inhibitor in Relapsed/Refractory Waldenström Macroglobulinemia: Results from the Phase 1/2 BRUIN Study (Abstract 229) – This multicenter international abstract reported on the first sizeable group of WM patients from the BRUIN study of pirtobrutinib (Jaypirca), a non-covalent BTK inhibitor that has demonstrated promising efficacy in patients with poor prognosis following prior therapy, including prior covalent BTK inhibitors like ibrutinib (Imbruvica). Because pirtobrutinib binds reversibly at a different location on BTK, the BTK mutations that make WM cells resistant to ibrutinib do not have the same effect on pirtobrutinib, thereby making pirtobrutinib particularly useful in patients who have developed ibrutinib resistance. Of the 78 WM patients in the BRUIN study, 61 had received prior BTK inhibitor therapy, with 40 of these having discontinued prior therapy because of disease progression. Overall, the major response rate (partial responses or better) for the 72 evaluable patients was 68%, including 24% very good partial responses and 44% partial responses. In the subset of 55 evaluable patients with prior BTK inhibitor therapy, the major response rate was 64%, including 24% very good partial responses and 40% partial responses. The most frequent adverse events of all grades for all patients with B cell malignancies were fatigue, diarrhea, and bruising. The incidences of moderate-to-severe adverse events included neutropenia at 20%, hypertension at 3%, hemorrhage at 2%, and atrial fibrillation/flutter at 1%. Overall, 2% of patients discontinued pirtobrutinib because of adverse events.

Ibrutinib and Venetoclax in Previously Untreated Waldenström Macroglobulinemia (Abstract 231) – Dana-Farber Cancer Institute reported results for the highly anticipated Phase 2 trial of this combination treatment, which enrolled 45 participants. Ibrutinib (Imbruvica) was begun at 420 mg daily, starting on cycle 1; on cycle 2, venetoclax (Venclexta) was started at 100 mg daily for one week, then 200 mg daily for week, followed by 400 mg daily for two weeks. Both agents were given together to complete 24 four-week cycles. Responses rates included very good partial responses in 40% of patients, partial responses in 53%, and minor responses in 7%, for an overall response rate of 100% and a major response rate of 93%. The median time-to-major response was longer in CXCR4-mutated patients, and the very good partial response rate was lower. With a median follow-up of 11 months, one patient progressed with transformation to aggressive lymphoma and two patients died of cardiac arrest/ventricular arrhythmia. Other moderate to serious adverse events included neutropenia (low neutrophil count), mouth sores, and tumor lysis syndrome. The estimated 12-month progression-free survival rate was 92%. In January 2022, a third cardiac arrest/ventricular arrhythmia was reported, and in April 2022, one participant developed ventricular tachycardia while undergoing a stress test, prompting a full clinical hold on the trial. No further patients will be recruited for the trial, and all active participants stopped therapy and are in follow-up.

***Ixazomib** is an oral **proteasome inhibitor** being investigated as an alternative to bortezomib because it causes **less peripheral neuropathy**.*

Zanubrutinib Plus Ixazomib and Dexamethasone for Newly Diagnosed Symptomatic Waldenström Macroglobulinemia: A Prospective, Phase 2 Study (Abstract 1559) – This Chinese study enrolled 20 patients, who received 160 mg zanubrutinib (Brukinsa) twice daily; 4 mg ixazomib (Ninlaro) on days 1, 8, and 15; and 20 mg dexamethasone on days 1, 2, 8, 9, 15, and 16 in four-week cycles for up to six cycles. After that, zanubrutinib was continued twice daily, with ixazomib and dexamethasone administered as maintenance therapy every three months for two years. Ixazomib is an oral proteasome inhibitor being investigated as an alternative to bortezomib because it causes less peripheral neuropathy. The primary endpoint was deep remission (very good partial responses or better) after six cycles. Of 19 patients who were available for analysis after six cycles, the overall, major, and very

Abstract Summaries, cont. on page 23

good partial response rates were 100%, 94.7%, and 42.1%, respectively. Insomnia was the most frequently reported adverse event. Serious adverse events of rash and neutropenia (low neutrophil count) were observed in 10% of patients. With a median follow-up of 12.3 months, all patients are alive, but one has experienced disease progression. The study is ongoing, and future results will be reported.

PEMBROWN: Results of a Multi-Centre Phase 2 Trial Investigating the Safety and Efficacy of Rituximab and Pembrolizumab in Relapsed/Refractory Waldenström's Macroglobulinaemia (Abstract 1574) – A multicenter trial from the United Kingdom combined intravenous pembrolizumab (Keytruda), a PD-1 immune checkpoint inhibitor, with rituximab (Rituxan) and is the first trial designed to specifically investigate immune checkpoint inhibition in WM. The principle behind immune checkpoint inhibition is to decrease the ability of cancer cells to evade detection by one's own T cells. Participants were eligible to receive eight doses of intravenous rituximab and 18 doses of intravenous pembrolizumab. The trial originally planned to enroll 42 relapsed/refractory WM patients but was closed early, in part because of low recruitment during the COVID pandemic, and finished with 17 patients. The median number of lines of previous treatment was three, and the majority of participants had a BTK inhibitor as their last treatment. The overall response rate at 52 weeks post-treatment was 36.4%, with 9% very good partial responses, 27% partial responses, and no complete responses. Median progression-free survival was 12.6 months, and median overall survival was not reached. The majority of adverse events were mild-to-moderate, the most common being anemia, fever, infusion-related reactions, and increased creatinine levels. The authors suggested that a randomized study comparing this combination to rituximab alone would be required to evaluate what benefits are added by PD-1 inhibition in this combination.

Long-Term Follow-up of Bendamustine Plus Rituximab Regimen in 69 Treatment Naïve (TN) Patients with Waldenström Macroglobulinemia, a Study on Behalf of the French Innovative Leukemia Organization (FILO) (Abstract 1575) – Participants in this study received a bendamustine and rituximab (Rituxan) regimen for a maximum of six cycles, and at the time of this report, the median observation time following treatment was 68.5 months. The overall response rate was 97%, with a cumulative very good partial response rate or better increasing over time (47.8%, 53.6%, 55%, and 56% at six, 12, 18, and 24 months, respectively). The median overall survival was not reached, and the median progression-free survival was 82 months. Categorized by genomics, the median overall survival for patients with mutated MYD88 was not reached vs. unmutated MYD88 at 72.8 months; the median overall survival for patients with mutated CXCR4 was 70.2 months vs. not reached for unmutated CXCR4. Sixteen of the 69 participants relapsed, and 12 (17.6%) developed a second cancer within 66 months: nine solid tumors (pancreatic, gastric, colon, pulmonary, breast, and skin) and three treatment-related myeloid blood cancers, including two fatal cases of acute myeloid leukemia.

*The principle behind immune checkpoint inhibition is to **decrease** the ability of **cancer cells** to **evade detection** by one's own T cells.*

Phase 2 Study of Ibrutinib in Combination with Ixazomib in Patients with Waldenström Macroglobulinemia (WM) (Abstract 4203) – A Mayo Clinic trial attempted to improve the depth of treatment responses by combining ibrutinib (Imbruvica) with ixazomib (Ninlaro) in 24 WM patients who were either treatment naïve or relapsed/refractory to prior treatment. The primary endpoint was a complete response rate greater than 5%. Participants received 4 mg of ixazomib on days 1, 8, and 15 and 420 mg of ibrutinib daily in four-week cycles for a maximum of 24 cycles. At the time of this preliminary analysis, only three patients had completed the planned two years of therapy, three are still in treatment, and 18 discontinued therapy because of adverse events, progressing disease, patient withdrawal, and other reasons. Of the 21 patients analyzed, the overall response rate was 76.2%, with no complete responses, 23.8% very good partial responses, 52.4% partial responses, 14.3% minor responses, and 9.5% stable disease. The overall response rate was higher (83.3%) in patients with mutated CXCR4. The median time-to-progression was 25.7 months. Common adverse events were anemia, fatigue, nausea, thrombocytopenia (low platelet count), and vomiting. The researchers noted that the trial failed to meet the primary endpoint, as no patients achieved a complete response, although they also pointed out that most of those enrolled had relapsed or refractory disease.

Next Generation BTK Inhibitor Acalabrutinib with Bendamustine-Rituximab in First Line Waldenstrom's Macroglobulinemia: The BRAWM Study (Abstract 4223) – The main objective of this ongoing multicenter Canadian trial is to determine the complete and very good partial response rates of this fixed-duration combination therapy, as it is theorized that adding six monthly cycles of bendamustine and rituximab (Rituxan) to one year of daily acalabrutinib (Calquence) treatment will result in deeper responses than either treatment used alone. The trial intends to recruit 59 participants—this abstract

Abstract Summaries, cont. on page 24

reported early results for the first ten. Although adverse events occurred in all patients, moderate-to-serious adverse events occurred in 10.9%, including neutropenia (low neutrophil count), transaminitis (high liver enzyme levels), atrial fibrillation, and infection. There were seven drug interruptions related to adverse events; of those, six patients restarted acalabrutinib, one with a dose reduction. With a short median follow-up of five months for the eight patients who have completed six treatment cycles, all achieved a very good partial response. Additional analyses will occur over the course of the trial.

All patients who ***developed [COVID] infection*** *had* ***received three or fewer*** *vaccinations.*

Clinical Effectiveness and Long-Term Serologic Responses of COVID-19 Vaccination in Patients with Multiple Myeloma and Waldenström Macroglobulinemia (Abstract 535) – In this clinical trial at Dana-Farber Cancer Institute and Massachusetts General Hospital Cancer Center, multiple myeloma and WM patients were vaccinated with Moderna, Pfizer, or J&J COVID-19 vaccines and followed up for 12 months to assess spike protein antibody responses; studies of T cell responses to vaccination are ongoing and will be reported later. What follows is a summary of the 50 WM patients who were participants. Following primary vaccination, the antibody response rate after 28 days was 57.1%; however, the rate of adequate response, defined as greater than 250 U/mL, was 26.5%. Following the first booster, the antibody response rate was 60.9%, and the second booster increased the response rate to 88.8%. A one-year antibody assessment was available for 38 WM patients, with 86.8% achieving an adequate response of greater than 250 U/mL. Surveillance of vaccinated WM participants during the 12-month period was also performed to determine the rate of COVID infection, which was 8.1%. No severe infections leading to hospitalization or death occurred. All patients who developed infection had received three or fewer vaccinations.

Type 1 Cryoglobulinemia Associated with Waldenström Macroglobulinemia, IgM MGUS, or Non-Hodgkin Lymphoma (Abstract 1586) – Type 1 cryoglobulinemia associated with WM, IgM MGUS (monoclonal antibody of undetermined significance), or other non-Hodgkin's lymphomas is defined by a monoclonal IgM antibody that precipitates at temperatures below body temperature and redissolves on warming; depending on its severity, it may cause a range of symptoms. This study from the United Kingdom and the Netherlands is the largest of its kind, analyzing the incidence and characteristics of type 1 cryoglobulinemia in 98 patients, the majority diagnosed with underlying WM. There was a kappa light-chain predominance in 85%. An MYD88 mutation was present in 90% of WM and 38% of IgM MGUS patients with type 1 cryoglobulinemia, while CXCR4 was mutated in 38% of WM patients. Coexisting IgM-associated disorders, such as cold agglutinin disease, Bing Neel syndrome, anti-MAG antibodies, and Schnitzler syndrome, were present in 25 patients. Those with coexisting cold agglutinin disease were more significantly associated with IgM MGUS and unmutated MYD88 than with WM or other lymphomas. Symptoms were present in 49% at cryoglobulinemia diagnosis and included skin/vasomotor, neuropathy, hyperviscosity, joint aches, and renal involvement. No cases had cardiac or pulmonary involvement. With a median follow-up of 2.4 years, the two-year overall survival was 89%, and the estimated five-year overall survival was 73%.

Skin Punch Biopsy Findings in Patients with IgM MGUS and Waldenström Macroglobulinemia Presenting with Peripheral Neuropathy (Abstract 2896) – Peripheral neuropathy can be associated with a monoclonal IgM antibody and typically results in slowly progressing weakness, numbness, and/or pain, beginning in both feet and progressing upward to affect both hands. Establishing the specific cause of IgM neuropathy can be difficult. Dana-Farber Cancer Institute, Brigham & Women's Hospital, and Massachusetts General Hospital performed full-thickness skin punch biopsies of the abdomen and lower extremities on 136 participants with symptomatic neuropathy to evaluate for the presence of monoclonal antibody and to reveal the cause of the neuropathy. Of these, 31 had been diagnosed with IgM MGUS (monoclonal gammopathy of undetermined significance) and 105 with WM. Non-IgM-associated causes of neuropathy were also evaluated in each participant. Of the total, 83 participants showed no evidence of malignancy, monoclonal protein, or amyloid deposits in the dermis of the skin, blood vessels, or nerves; however, 53 did have evidence of monoclonal protein presenting in the following manner: monoclonal protein deposition in the blood vessels, accumulation of lymphoplasmacytic cells, monoclonal protein deposition in the dermis of the skin, and monoclonal protein deposition in the nerves. Additionally, five participants were diagnosed with amyloidosis, a disorder in which protein fragments of immunoglobulin light or heavy chains are misfolded and deposited in tissues, interfering with their normal function. A higher serum IgM level was seen in those who had monoclonal protein deposition in their skin biopsies as compared with those who had negative biopsies. The researchers suggested that the use of skin

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punch biopsies can be useful, even for the diagnosis of amyloidosis, with the advantage that they can be easily performed in the outpatient setting.

Waldenstrom Macroglobulinemia and the Clinical Implications of Acquired von Willebrand Syndrome (Abstract 4216) – Rarely, WM patients can develop acquired von Willebrand syndrome, a disorder that results in heavy bleeding or bleeding that will not stop. The Mayo Clinic assessed the prevalence of this condition and explored its clinical manifestations and outcomes. From a total of 2,210 patients diagnosed with WM at Mayo between January 2002-January 2022, 3% received lab testing for von Willebrand's factor (VWF), and the condition was diagnosed in 0.5% (11 patients). The most common underlying reason for testing was bleeding, followed by pre-surgical screening and routine screening. Recurrent nosebleeding was the most-observed bleeding site, with others including spontaneous hematoma (a pocket of localized bleeding), gastrointestinal bleeding, retinal hemorrhage, and subarachnoid hemorrhage (bleeding between the brain and its membrane covering). Treatments included surgical intervention to stop blood flow, administration of Factor VIII/VWF complex (a clotting factor), a drug called desmopressin, intravenous immunoglobulin, and prednisone. It was noted that 67% of patients with bleeding symptoms showed improvement after treatment directed against their WM, while the remainder did not respond to WM-directed therapy and had no improvement in their bleeding symptoms.

***IgM MGUS** had a relative **survival** slightly **higher than** that of a matched **general population** during the first ten years after diagnosis...*

Progression Risk and Long-Term Survival Trends of 915 Patients with Asymptomatic IgM Monoclonal Gammopathy (Abstract 104) – Researchers from 13 medical centers in Spain looked at the use of several biomarkers to develop a model for determining which patients with IgM monoclonal gammopathy of undetermined significance (IgM MGUS) and with smoldering WM (SWM) are most at risk of progressing to symptomatic WM. In this study of 915 patients, 462 IgM MGUS and 453 SWM were included. MYD88 L265P mutation testing results were available for 465 patients, with the mutation detected in 54% of IgM MGUS and 81% of SWM. After a median follow-up of six years, disease progression was documented in 250 patients—16% in IgM MGUS and 39% in SWM. By performing continuous testing over this period, the researchers selected four factors to use in their prognostic model for progression: IgM equal to or greater than 10 g/L; albumin less than 3.5 g/L; IgG/IgA less than 6.8 g/L and 0.6 g/L, respectively; and bone marrow infiltration equal to or greater than 20%. Each of these factors was assigned a point, so that low-risk (score of 0-1), intermediate-risk (score of 2), and high-risk (score of 3-4) groups were established. More IgM MGUS patients were categorized as low-risk, while SWM accounted for the majority of intermediate- and high-risk scores. The researchers looked at relative survival, which is calculated from the proportion of observed survivors in a group of cancer patients as compared to the proportion of expected survivors in a comparable group of cancer-free individuals. IgM MGUS had a relative survival slightly higher than that of a matched general population during the first ten years after diagnosis, with a subsequent decline after 20 years. SWM had a relative survival lower than the general population, with the difference observed from the first 10-15 years after diagnosis.

How Age, Comorbidities, and Concomitant Medications Influence Ibrutinib Management and Survival in Waldenstrom Macroglobulinemia (Abstract 2905) – The aim of this multicenter Italian study was to evaluate which fitness parameters are significant for treatment outcome and management in WM patients receiving ibrutinib (Imbruvica) in clinical practice. From August 2016 to April 2022, 206 patients were included in the analysis. After a median follow-up of 26.6 months, 139 remained on ibrutinib. Temporary treatment interruption occurred in 29.6%, while dose reductions were required at least once in 25.7% of participants, followed by permanent dose reductions in 19.4%. Overall, 32.6% of the 206 patients permanently discontinued ibrutinib because of the following: progressive disease (14.6%), toxicity (11.2%), and other reasons (6.8%), with the most common toxicity being recurrent atrial fibrillation. Median progression-free survival, event-free survival, and overall survival at two years were 73.3%, 54.1%, and 85.3%, respectively. The factors that negatively predicted all survival outcomes included age greater than 75 years; poor ECOG Performance Status (a set of guidelines from the Eastern Cooperative Oncology Group that determines a cancer patient's ability to perform daily living activities); creatinine clearance greater than 50; and nephropathy (kidney disease). Among baseline disease characteristics, the presence of a CXCR4 mutation was the only factor independently associated with disease progression. The study did not identify the concurrent use of multiple medications or any particular type of medication that interfered with ibrutinib management.

Oligosecretory Waldenström Macroglobulinemia Patients Exhibit Excellent Treatment Response and Outcomes (Abstract 4184) – WM patients typically

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present with elevated IgM, but some have relatively low IgM levels; in these cases, it can be difficult, if not impossible, to make an accurate assessment of response to treatment. Chinese researchers used the database of the Chinese Registration Network for Waldenstrom Macroglobulinemia to find WM patients with low IgM, which they defined as within twice the upper limit of normal and called oligosecretory WM. Out of 1,274 patients, 80 (6.3%) met this criterion. Compared with typical WM, oligosecretory patients had a higher proportion of thrombocytopenia (low platelet count), a lower proportion of hypoalbuminemia (low blood albumin), and a lower proportion of elevated serum beta2-microglobulin. The researchers identified four ways to evaluate tumor burden in these patients: flow cytometry of bone marrow, percentage of bone marrow infiltration by WM cells, splenomegaly (enlarged spleen), and lymphadenopathy (enlarged lymph nodes). They found that oligosecretory WM patients were more likely to have a bone marrow infiltration greater than 50%, compared to the typical WM group of patients, even though their IgM levels were low—the other factors were not significantly different between the two groups. The percentage of patients who did not require treatment was significantly higher in the oligosecretory WM group (6.1%) vs. the typical WM group (1.0%). If treatment was necessary, the percentage of oligosecretory patients who achieved a complete response after treatment was also significantly higher (14.7%) vs. the typical group (5.4%). Progression-free and overall survival at three years were higher in the oligosecretory WM patients.

Determinants of Overall Survival (OS) of Waldenstrom Macroglobulinemia (WM): A National Cancer Data Base (NCDB) Analysis of Over 14,000 Patients Treated Between Years 2004 and 2017 (Abstract 4204) – This analysis from the Cleveland Clinic in Florida used the National Cancer Data Base to identify variables affecting the overall survival (OS) of 14,295 WM patients diagnosed and treated during 2004-2017. Older patients, male sex, Black race, lower income, and multiple comorbidities (coexisting medical conditions) were significantly associated with lower OS. Patients with access to private insurance and academic centers had better OS. In terms of disease-specific factors, patients with higher tumor burden and those requiring therapy rather than observation had worse OS than patients with lower tumor burden and those observed without therapy. Interestingly, patients diagnosed between 2011-2017 had superior OS compared to those diagnosed between 2004-2010, likely due to advancements in therapy over time.

Use of Ibrutinib in Real Life Settings in France: Results from a Retrospective Observational Study Using the SNDS Database (OSIRIS) (Abstract 4443) – A group of French researchers used SNDS, the French national health insurance database, to look at the use of ibrutinib (Imbruvica) in real life settings in patients with B cell malignancies. The study population, whose data were collected from August 2017-December 2020, consisted of 6,083 patients with chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), WM (which was 13.8% of the total), and unclassified. At treatment initiation, 68.3% of all patients had significant comorbidities (coexisting medical conditions), including 47.6% with cardiovascular disease in the preceding year and 21.5% with at least one solid tumor. Ibrutinib was second-line or later treatment in 94.5% of the WM patients. After a median follow-up of 15.2 months, the probability of permanently discontinuing ibrutinib or dying at 12 months was 29% (including 10.7% deaths) in WM patients. Safety data were only reported for CLL patients: of 2,771 included in the study, 8% were hospitalized for a cardiovascular or bleeding event during follow-up, but more than half of these continued to receive ibrutinib after hospitalization.

Second Primary Malignancy in Waldenström Macroglobulinemia: Insights from a Population-Based Analysis (Abstract 4925) – The development of a second primary cancer in WM patients is based on many factors, including the indolent nature of the disease, associated immune system dysfunction, environmental factors, and treatments used for WM. An international retrospective study to determine the frequency and types of second primary cancers was performed on WM patients diagnosed between 2000 and 2018 and included in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database. For this study, a second primary cancer was defined as another malignancy appearing at least one year after WM diagnosis. Of the 4,112 WM patients identified, 17% received a diagnosis of a second primary cancer; this was 53% higher than in the general population. The second primary cancer risk was higher in WM patients who were Caucasian but not in those who were African American or other races. The risks for WM patients younger than 50 years were not increased. Significantly increased risks for cancers in WM patients aged 50-74 years were of the lungs and bronchus, skin, vulva, thyroid, nodal non-Hodgkin's lymphoma, extranodal (outside the lymph nodes) non-Hodgkin's lymphoma, acute non-lymphocytic leukemia, and acute myeloid leukemia. WM patients age 75 years and older had significantly increased risks for cancers of the cecum, colon, soft tissues, nodal non-Hodgkin's lymphoma, extranodal non-Hodgkin's lymphoma, acute non-lymphocytic leukemia, and acute myeloid leukemia.

Spotlight ON SUPPORT GROUPS

EDITOR'S NOTE:

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

KANSAS/MISSOURI IWMF SUPPORT GROUP HAS IN-PERSON MEETING

By Co-leaders Jack Honaker and Tom Shyver

Editor's Note: REMEMBER, each IWMF support group leader has responsibility for their local support group and decides how best to lead their own meetings. Although in-person meetings are now permitted, they are in no way mandatory. Meeting in-person, virtually, or in a hybrid model will depend on each support group leader's choice and the group's interest; the need for any restrictions, such as being vaccinated and wearing masks, is a group decision.

The first in-person meeting of the Kansas/Missouri IWMF Support Group since COVID began was held on January 14, 2023, at Tallgrass Creek in Overland Park, KS. It was wonderful to finally see members in person again. Everyone was required to wear a mask and be fully vaccinated. In attendance were eight patients and three caregivers. Three other patients and their spouses would have been there also but, unfortunately, had prior commitments. Two of the patients in attendance were recently diagnosed, and this was their first meeting.

Members gave updates on their current medical status, and much discussion was held concerning local oncologists already treating and having experience with Waldenstrom's. There was also a conversation concerning the importance of getting a second opinion from one of the Waldenstrom's experts, especially at Dana-Farber Cancer Institute in MA and at Mayo Clinic in MN.

A discussion about the preferred type of meetings in the future ensued. All in attendance expressed their preference for meeting in person. The group was advised that there is a possibility of doing combined in-person and Zoom meetings. Co-Support Group Leader Tom Shyver's company has recently installed new equipment which may permit this. Testing with this equipment will be done to ascertain if this is, in fact, a possibility.

Back Row L to R: Mary Stang, Keith Bottorff, Tom Shyver, Tam Vincent
Front Row L to R: Jack Honaker, Gianfranco Pezzino, Dennis Wyatt, Mary Lynn Cate

The IWMF Educational Forum in April in St. Louis was also covered at length. Those who had attended in person in the past expressed that these Forums were extremely helpful and worthwhile. Co-Support Group Leaders Tom Shyver and Jack Honaker told of their experiences of meeting in San Diego at a Forum for the first time, and they have since become best friends.

Staying distanced in the meeting

Spotlight on Support Groups, cont. on page 28

Spotlight on Support Groups, cont. from page 27

NEW SUPPORT GROUP LEADERS

JAN WIECZERZAK
(South Florida Support Group)

Jan comes to the group with a background in technology product and program management, working for telecommunications companies including Comcast, Time Warner, Digicel, and Breezeline.

He moved from the Philadelphia area to South Florida in 2018 and immediately discovered how valuable it was to have a support group and peers in the area as he struggled to find the right doctors and medical groups to manage his WM journey. As the new support group leader, Jan is looking to provide information and support to help others manage the medical, financial, and logistical elements of the disease.

SHARON PIOTROWSKI
(Sarasota Support Group)

Sharon has lived in Lakewood Ranch, FL, for five years after relocating from NJ. She has been married for 36 years and has two adult daughters. As a personal trainer for over 12 years, she carries her passion for healthy living into daily life, with road biking, running, and weightlifting.

She was diagnosed with WM in July of 2019, and since she was highly symptomatic, she had treatment right away. The IWMF has been a lifeline to help her cope and learn to live with this rare chronic cancer. She says "I thrive to educate myself about WM as much as possible to be my own best advocate. I am so happy to help in any way to assist the IWMF with their mission to help people with WM."

CORDELIA STEARNS
(Santa Barbara Support Group)

Cordelia is from the East Coast, although she and her husband now live in California. Almost 10 years ago, after a long overdue blood test, she was shocked to eventually learn she had WM and was treated.

"I feel extremely lucky to have been diagnosed early; I saw top doctors in WM and connected with the IWMF. I went to several Ed Forums and found out about the NY support group led by Mitch Orfuss, who was an excellent leader—he was welcoming, pleasant, informative, and always kept the meetings on track. I miss Mitch and the group, but I'm in Santa Barbara now, and there was no support group within a large radius." So Cordelia volunteered to start one, a boon to others with WM in her area.

Spotlight on Support Groups, cont. on page 29

Spotlight on Support Groups, cont. from page 28

WM FLOATS OUR BOAT!
WHY WE LOVE THE WATER – SUPPORT GROUP REFLECTIONS

COMPILED BY LISA WISE, SUPPORT GROUP CO-LEADER AND IWMF BOARD MEMBER

The Eastern PA and Southern NJ Support Group discovered during a recent meeting that we had several sailors in our midst. We decided to draft a group article exploring why we love being on the water so much. We considered: Did it enhance our sense of well-being? Is it healing? Or is it just plain fun? Whether sailing, kayaking, canoeing, rafting, paddle boarding, or floating, our folks had plenty to share about how water enhances our sense of well-being and how transformative it can be to enjoy water play. We hope you enjoy and decide to jump in! The water's perfect…

Lorraine, NY, diagnosed March 2019

"How is it that I find myself in the middle of the Hudson River in a kayak at dusk? On a river smooth as glass, waiting for the moonrise? Enjoying the unseasonably warm weather, breathing in the sweet autumn air, and feeling at one with nature? Well, you listen to someone like the brilliant anthropologist Jane Goodall, who is adamant: 'Nature can save us.' And while I already know that, I want to reaffirm my feelings. Still, it's with some trepidation that I sign up for a two-hour kayaking tour of Cornwall Bay—even though I haven't kayaked since I broke my wrist a dozen years ago—and I'm not sure I can last five minutes. All right. I'll try. I'm only 74. LOL. And so, here I am. I never admit to being old, achy, or afraid. Never wonder out loud if I'm out of my league with these kids half my age. Or worry that I'll ruin their tour if I can't keep up. I just put on my game face and pick up the paddle. The Hudson River is ALL mine."

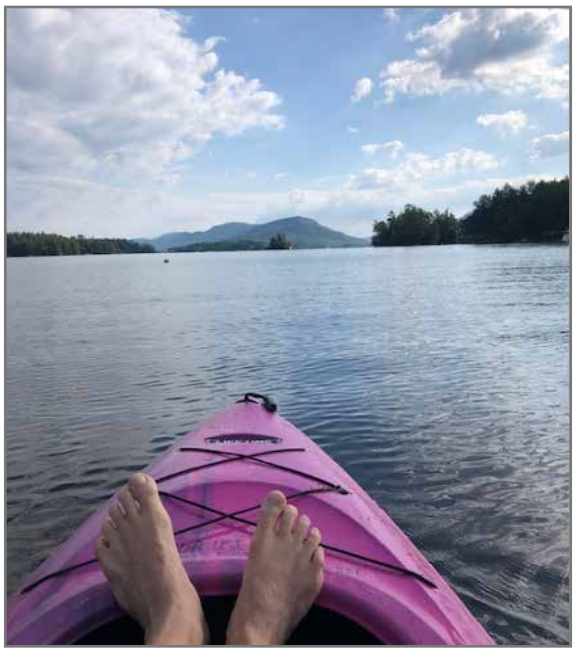
Ross Schmucki, Swarthmore, PA, diagnosed July 2013

"My most powerful and enduring memory of water is swimming in New Hampshire at my grandparents' summer cottage between 1960-1998. Visiting my grandparents, I would swim in Gilmore Pond near Mt. Monadnock (see photo). When I wish to be calm, no matter where I am, I recall floating peacefully on my back in the middle of the pond, feeling the warm sun, seeing the endless blue sky above, floating like a leaf suspended on the surface, feeling the water supporting me as if I were floating in air. Pure joy."

Judie and Lawrence Elliott, Philadelphia, PA, Lawrence diagnosed January 2020

"The day is as warm as the sun is long. We pull up to see the water looking like glass. Within minutes we cast off to the cool breeze the Delaware River has to offer. Once we are underway, we look for that special place of solitude where we are free of thought, just doing and not thinking, just living in the moment, not just existing. Songs in the background, the glistening water in front of us, the shoreline to the side exposing its glory; all bring excitement to the experience. When pulling up the anchor, we always know just how special the day truly was!"

Spotlight on Support Groups, cont. on page 30



Lisa Wise, Philadelphia, PA, diagnosed November 2010
"After surviving COVID in June 2022, I went online and bought a cherry red inflatable standup paddle board in celebration. I threw it in my car trunk and spent the summer seeking lakes, rivers, and creeks to float on. A peaceful stillness fills my spirit when I am on water. As an infant, I spent my first summer of life sleeping in a bassinette on the porch of our family's rented cabin on Lake George, NY. Gently lapping waves filled the air day and night, and that sound is the music of my soul. Water is my place to reconnect, refresh, and recharge. At 57 years old, I find that being in a kayak, floating on a raft, boldly balancing on my red paddleboard makes me feel fearless in the face of uncertainty. On the water, I am free. Nothing—not even WM—can catch me."

Randy Schonour, Leesport, PA, diagnosed January 2015
"Among fly fisherman there is a saying that a stream is water in its most beautiful form. A few years ago, I was able to spend an entire day alone in the White River Canyon in the Bob Marshall Wilderness in Montana. The White River Canyon is as remote from a road as any spot in the lower 48. This was part of a 10-day backpacking trip, one of 25 or so I have done in the Continental Divide area. Going on these strenuous hikes was my incentive for maintaining a high aerobic capacity. When I was diagnosed with WM eight years ago, I considered stopping. However, listening to my fellow WMers about their discomfort from low red blood counts, I decided to continue my activities and monitor my blood count, and perhaps increase my hemoglobin with aerobic activity. So far, I have not experienced shortness of breath or had a below-normal hemoglobin reading. I remain on watch-and-wait. I was greatly influenced by a story the IWMF ran about a world class marathon runner from Iceland and how he maintained his level of performance with WM. Here is a photo from that very special day."

Cheryl Frustieri, Flemington, NJ, diagnosed June 2010
"I am drawn to the water. Whether sailing, kayaking, or paddle boarding, it is a time I come into the peace and tranquility of nature. It is freeing, magical, and rejuvenating to my mind, body, and spirit. I never lose the feeling of being in absolute awe of the magnificence of all nature's beauty surrounding me when I am gliding on the water or just taking a break and gently rocking back and forth, as I take it all in. My favorite time to be out on the water is during sunsets when the day is winding down and the sky transforms into a beautiful palette of colors. I am filled with a sense of calm, tranquility, and gratitude. Nature is God's gift to us all, and it is the place that I can escape to and experience a deep sense of connection, not only to nature, but to all living beings and to the greater world around me."

Spotlight on Support Groups, cont. on page 31

IN MEMORY OF MITCH ORFUSS, LEADER OF THE NEW YORK CITY METRO AREA SUPPORT GROUP

BY SUE HERMS

"The highest tribute to the dead is not grief but gratitude."
– Thornton Wilder

The IWMF community has learned with much sorrow about the recent passing of the beloved, long-time leader of the New York City Metro Area Support Group, Mitchell (Mitch) Alan Orfuss.

A lifelong New Yorker, Mitch was an advertising executive at Grey, J. Walter Thompson, Ogilvy, and Harte-Hanks and also taught at New York University's School of Professional Studies. After his diagnosis of Waldenstrom's, Mitch embarked on his "third career" as a mentor and supporter of others with our disease.

Mitch was a very active support group leader, holding meetings of his group twice monthly. He also volunteered for the IWMF at one time or another in other capacities—as a member of its Fundraising and Website Design Committees and as a LIFELINE volunteer.

As a mentor for new patients, Mitch was unsurpassed. One of his support group members wrote to him during his last illness, "When I was diagnosed in 2010… I was saved by two things: going to a conference and meeting the top doctors…and coming back to NYC and, thanks to you, meeting with fellow patients to compare notes. You helped build and sustain a community that felt safe and comforting..." Another newly diagnosed member wrote, "Thanks so much for being there for me when I first reached out. Your advice based on your accumulated wealth of knowledge was unparalleled and greatly appreciated."

Mitch was also greatly admired by other support group leaders, with Marcia Klepac of the Eastern OH, Western PA, and West Virginia Group noting, "It has been a privilege to share the WM journey with you as a fellow WMer and support group leader. Your compassionate manner of reaching out to WMers is an inspiration to all of us."

Peter DeNardis, Chair of the IWMF, added that Mitch "has been an important guiding force for others with WM. In fact, personally, when I was first diagnosed in 2003, he was among my initial contacts with anyone else with WM. His words and guidance meant more to me than you can imagine and helped my wife and me immensely on the start of our WM journey. He proved to be an invaluable resource for me and others."

Preceded in death by his wife, Kate Stringfellow, Mitch is survived by his sister Leslie, daughter Kathryn, son Stuart, granddaughter Carter, and several nieces and nephews.

The comments above are just a small sampling of the many tributes that were received during Mitch's recent illness and after his death. He will be remembered long and very gratefully by the many WMers whose lives he touched.

FROM THE FACEBOOK WM SUPPORT GROUP: SPRING 2023

EDITED BY BETTY ANN MORTON

Since WM is the focus of the Facebook Waldenstrom Macroglobulinemia Support Group, it's not surprising that choosing a treatment is a frequent topic of discussion.

ED posted, "For those of you who received treatment after watch-and-wait, what triggered the decision to start treatment? I was diagnosed 'by chance' and am worried that the recommended treatment is a knee jerk reaction from doctors unfamiliar with WM's nuances." **ED** does not live in the US, and DRC treatment (dexamethasone, rituximab, and cyclophosphamide) has been suggested, but he intends to discuss bendamustine/rituximab (BR) at his next appointment. **ED** noted that his main symptoms are fatigue and very severe cyanosis, or bluish skin tone from lack of oxygen, and that they are a result of hemolytic anemia. He is planning to contact the specialists at Mayo for a second opinion.

NAD's experience was common: "When my hemoglobin was heading towards 9 g/dL, I was started on BR. My platelets were about 60,000 per mcL (or K/mm^3) too, so on both counts it was time. My IgM was very low, so that wasn't an issue. I was very tired, although I was used to it so couldn't really see it." She has three kids and had been working full time, including every evening and weekends. As she said "I expected to be tired. Now I see I was a zombie!"

PJ replied, "My IgM was 5,000 mg/dL after 1.5 years of trying to get a diagnosis. Twenty-six years ago at 42 years of age, I saw five specialists and then had five different chemo drugs over the years. Numbers are escalating (1,000) again after 4.5 years of remission."

Often ***newly diagnosed*** *WMers are* ***afraid of treatment*** *and its potential* ***side effects****.*

Often newly diagnosed WMers are afraid of treatment and its potential side effects. **SJ's** recent post summarized her original reactions. "So in 2019 I went in for some lab work at my primary doctor, because I was always so tired. He called me in to discuss the results. I was horrified when he sent me to an oncologist! In my mind I was like 'Wait, isn't that for cancer?'" She went to the oncologist, who wanted to start chemo immediately, but she found our Facebook Group, did some research, and realized that this doctor was not right for her.

SJ thought she could heal herself with a better diet and supplements. Two years later, she went back to her primary doctor for some blood work. Her numbers were sky high, and she felt terrible. She said, "I told my primary I need to find another oncologist, and he led me to someone else… He wasn't a WM specialist, but he was willing to find out all he could about WM. He listened to me and was so compassionate. He told me if I didn't start treatment, I would probably have a heart attack or stroke within months. So, I agreed. Now in my head I'm thinking I'm going to be sick like all the stories you hear about chemo… The doctor assured me I would get pre-meds to help with the stomach sickness…"

SJ ended up having six treatments with bendamustine and rituximab. She recently posted, "Well, here I am finished with the six treatments. My hair did not fall out; in fact, it has grown so much it's amazing. I need a haircut! My nails are growing so fast, and I don't need a million naps throughout the day anymore! My viscosity is in normal range now, my IgM is still not normal but has come down greatly from almost 6,000 mg/dL to 857. I feel much better." **SJ** advised newbies not to fear chemo but to go into it with a positive attitude. With the help of the Facebook WM community, **SJ** went from being afraid of treatment to a person who has been successfully treated.

GB was another person who had doubts about starting treatments, as well as worries about unwanted effects. "I am new to this group, and I don't really understand what I have or what the proper treatment should be for my WM condition. I had one oncologist who recommended the wait-and-see process, and if I ever developed any symptoms, then I would start ibrutinib (Imbruvica) treatments. I have no symptoms and no issues at all. It was a fluke that they even found the tumor. Unfortunately for me, he left the cancer center that I go to, and they assigned me to a new doctor, who wants to start treatments immediately. I don't understand his thinking or suggestions.

"I have a large retroperitoneal mass or tumor in the mesentery area of my stomach, and he wants to reduce the size of the tumor to prevent any complications… Right now I am not having any issues. So why should I start the rituximab and bendamustine?"

Among the many empathetic and supportive responses to **GB** were a number of links to IWMF videos and written materials. **ES** wrote, "I would insist on a biopsy of the tumor and, unfortunately, a bone marrow biopsy as well. The tumor could be WM, but how would they know without a biopsy? You'll definitely want to see a WM specialist! You

From the Facebook WM Support Group, cont. on page 33

could let the WM doc do the BMB, so that they can do a thorough analysis."

More recently **GB** posted, "It's amazing what you learn in a short period of time once you hear the "C" word...and this type is so rare that a lot of cancer doctors don't really know what to do. It's not their fault. It's just a rare type of cancer that they are not exposed to. Thanks for reaching out." **GB** is currently undergoing BR treatments and responding well.

Frequently, WMers or their care partners request information about a treatment they are about to start. Here's a typical request, this one from **DF**: "My husband is starting Brukinsa (zanubrutinib) today. I am worried about side effects—the list is quite long and scary. What are other people's experiences with this drug?"

DC responded, "I've taken 'zan' for the last four months with almost no side effects, but I do feel much better. Right now I'm sold on zan, and my IgM has gone from 1,985 mg/dL to 234 since I started." **PR** explained, "They have to list all the possible side effects. Yes, it's scary, but it doesn't always happen. Keep close observation, and if anything happens, contact the doctor. They might reduce the dose. Many people have good results with minimal and manageable side effects."

*"It's amazing what you **learn** in a short period of time **once you hear** the **'C' word**..."*

EHM posted in Spanish, *"Hola nuevamente a este hermoso grupo. Tengo una duda para quienes toman ibrutinib, después de cuánto tiempo empezaron a sentir una mejoría y a ver resultados favorables!? Es decir que su hemoglobina y plaquetas subieran y su IGM bajara? Muchas gracias por leerme y que tengan un feliz domingo.*" Although Facebook's translations are not always smooth, WMers worldwide understand each other and converse. **EHM's** post was, "Hello again to this beautiful group. I have a question for those who take ibrutinib: After how long did they start to feel improvement and see favorable results? So your hemoglobin and platelets went up, and your IgM went down? Thank you very much for reading me and have a happy Sunday."

RT responded, "My hemoglobin increased and IgM dropped within a month. Stayed on the drug for six years with minimal and manageable side effects. Your genomics will determine your response rate. MYD88 mutation and no CXCR4 mutation is the combination that gives the quickest and deepest response to ibrutinib."

SAP responded to a caregiver who was worried, as her family member was starting treatment with a BTK inhibitor. "Worry is something I think most of us felt when diagnosed with cancer and thinking how will the drugs affect me." I decided not to read the side effects, as I knew I needed something to make me feel better.

*"**Worry** is something I think **most of us felt** when **diagnosed** with cancer and thinking how will the drugs **affect** me."*

"I had some issues on Imbruvica, which is also a BTK inhibitor drug like Brukinsa. Then I was put on Brukinsa when I relapsed. I was glad to hear from this support group that people had a better response. I did get some minor issues with itching and rashes like I did on Imbruvica, so I didn't panic. They went away and Claritin helped too. I didn't get A-fib like [I had with] Imbruvica... I started Brukinsa last June; however, by December my neutrophil numbers went down to a critical low. I didn't know what that meant until I posted on the Facebook page (and also wrote my oncologist). The Brukinsa side effect was the reason. It was recommended I go to a half dose. Within two weeks everything went back to normal. I was more scared my symptoms would come back. So far so good.

"If you want more information from WM people here, do a search on Imbruvica in the upper left hand corner of this (Facebook) page, and you should see that many WM patients do very well on it. I hope your husband gets relief from his symptoms soon."

By the way, if you're a person who likes numbers, you might be interested to know that between February 2022 and February 2023, our Facebook WM Support Group membership increased from 4,500 to 5,500, or about 22% growth. There's still plenty of room for more.

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*.

INTERNATIONAL SCENE

EDITED BY ANNETTE ABURDENE

CANADA

By Betty McPhee, WMF Canada

There's a lot happening at the Waldenstrom's Macroglobulinemia Foundation of Canada (WMFC)!

We are very excited to announce that our WM Patients Educational Video Series for newly diagnosed patients will soon be available. These four whiteboard videos, each approximately five minutes long, will be handed out to doctors for distribution across Canada and be made available on our website for all our viewers. This is possible through the generosity of BeiGene (Canada) pharmaceutical company.

The WMFC has also been actively promoting Canada's BRAWM trial (bendamustine, rituximab and the BTK inhibitor acalabrutinib) for newly diagnosed WM patients across Canada. This groundbreaking trial, led by Dr. Neil Berinstein in Toronto, has obtained exciting results to date. In further Canadian WM research, Dr. Signy Chow from Sunnybrook Hospital in Toronto has received a prestigious Robert A. Kyle Career Development Award from the IWMF. She will be evaluating the evolution of WM cells during treatment in the BRAWM trial. *(Editor's note: Dr. Chow's project is described in this issue of the* Torch *on page 11.)* The WMFC has agreed to fund 50% or $100,000 of this award over the next two years. Congratulations, Dr. Chow!

In the past year, the WMFC organized, and BeiGene (Canada) funded, a three-lecture series by Dr. Steven Treon to members of the Canadian Hematological Society, updating doctors on current treatments and research in WM. The WMFC financially supports research in Dr. Treon's lab.

The WMFC has also signed a partnership agreement with the Leukemia & Lymphoma Society of Canada (LLSC) to jointly fund WM research in Canada.

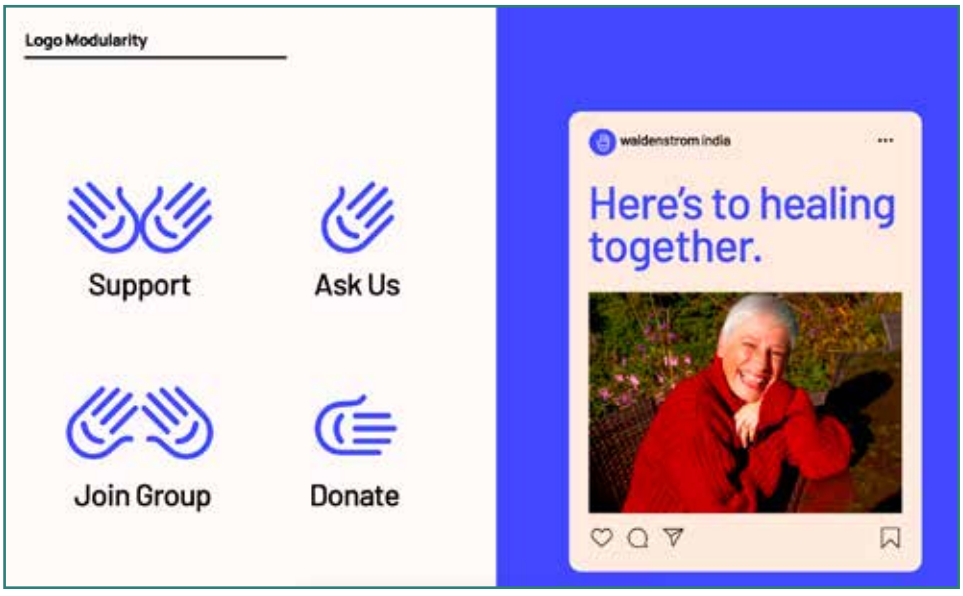
The WMFC continues to host support groups across the country from Vancouver to Halifax. We are very thankful to all our support group leaders for everything they do. On March 20, at the WMFC National Support Group Zoom meeting, Catherine Caule from the LLSC gave a presentation on "Getting a Second Opinion," followed by a Q&A.

And finally, the WMFC Board acknowledges that none of this would have been possible without the efforts of Cam Fraser, our Board Chair. He has assembled a team that works together and well. We know that he puts in a great deal of volunteer time and effort—some visible, but mostly invisible—to keep us moving forward. Thank you, Cam!

INDIA

By Saurabh Seroo, India Affiliate Leader

After several months of development, WM India completed work on its redesigned online presence. The effort included all aspects of our member-facing outreach such as our logo, brand guidelines, and website flow. It was important to design our logo and website with a fresh visual identity system that eschewed the often staid and unapproachable norms and conventions followed by cancer support groups in India. Our aim was to rethink common emotions or attributes that patients and caregivers can occasionally associate with WM, attributes such as disease or illness. Instead, our goal was to invoke a different set of emotions and attributes, such as trust, hope, safety, warmth, and care.



A page from Waldenstrom India's new website – www.wmindia.org

International Scene, cont. on page 35

We are excited to reveal our results and new visual identity and hope that our redesigned online presence and better patient outreach and analytics will help us attract and support more patients and caregivers across India.

GERMANY

Meeting of the Waldenström Support Group in Ulm February 9 to 11, 2023

By Jürgen R. Goetz, Waldenstrong Germany

Is it appropriate to talk already about tradition, when a second meeting of the Waldenström Group takes place in the same city, Ulm, as in May 2022, and the agenda looks like a copy and paste approach from that meeting? Sure, some of the participants at the meeting in May 2022 were seen again. However, since the Waldenström group doubled its number of members within six months, newcomers attended the reunion in February of this year. Taking this into consideration, one hesitates to talk about tradition.

Nevertheless, starting with meeting in a restaurant, even for first timers, it was again like seeing good old friends. It seems that having similar health problems and exchanging frankly very personal messages on our WhatsApp group brings people faster and closer together, creating an atmosphere of mutual respect and common understanding. This experience provokes the question of why this approach seems to be so rarely successful elsewhere, despite the fact huge challenges are threatening the survival of mankind in an unseen way.

Let's leave this philosophical side trip and come back to Ulm, this old medieval city situated in the southern part of Germany on the banks of the river Danube, where a charming, humorous Daniela took us on a tour through her city. Here we recognized another copy and paste approach—or call it tradition. But to our surprise Daniela had sufficient new historical details for those of us who had already enjoyed her talents during her May 2022 tour.

The afternoon of February 10 saw us finally at the University of Ulm in a meeting following the tradition with Prof. Dr.

Meeting with Prof. Christian Buske and Mrs. Lisa Maria Kaiser at the University of Ulm

Christian Buske and his assistant Mrs. Lisa Maria Kaiser. It was a question-and-answer session also set up as a video conference for those who could not attend in person. The title of a list of topics and questions previously collected in our WhatsApp group was "Symptoms of Waldenström Macroglobulinemia" or "What Are the B-cells Causing in Our Bodies?" Prof. Buske patiently took us through a detailed story of Waldenström disease. He explained complex medical knowledge in an astonishingly clear and easily understandable way. We learned a lot and were grateful students of this extraordinary teacher. He explained how the treatment of our disease in the future could look. We left the meeting with remarkably increased knowledge, with curiosity and hope for the future. Later we enjoyed dinner in a restaurant with Prof. Buske and Mrs. Kaiser, where the fruitful discussion about our questions did not stop.

The official part of the Ulm meeting is available as a podcast on the German Waldenström website, following the tradition from the first meeting in May 2022. Since tradition is not a bad thing at all, we shall see each other again in Ulm to gather information and perspectives of our disease. Furthermore, personal exchange and contact is what carries us through life.

The group near Ulm Cathedral

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:

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

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

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

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

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

The Lynn M. Fischer Research Fund of the IWMF

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

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

The Michael and Rosealie Larsen Research Fund of the IWMF

The 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*

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

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

The Carolyn K. Morris Research Fund of the IWMF

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

- 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*

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

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

The Paul and Ronnie Siegel Family Research Fund of the IWMF

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

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

The Marcia Wierda Research Fund of the IWMF

The WMFC has supported the following research projects:

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

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

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

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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*.

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