IWMF TORCH

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INSIDE THIS ISSUE



# IGM-RELATED AMYLOIDOSIS

By Dr. Shayna Sarosiek

Dr. Shayna Sarosiek

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**Diagnosis of amyloidosis**

Amyloidosis is a disorder characterized by organ dysfunction due to the buildup of a misfolded protein. In amyloidosis, a precursor protein misfolds, forms aggregates, and then forms fibers (called amyloid fibrils) that deposit in organs.

Amyloidosis is diagnosed when a biopsy is performed and demonstrates the presence of amyloid deposits. Since amyloid fibrils are commonly found within the subcutaneous fat (fat just under the skin), most guidelines recommend taking a sample of fat from under the skin of the abdomen to confirm a diagnosis of amyloidosis. Occasionally bone marrow biopsies or biopsies of an affected organ may be needed to confirm the presence of amyloidosis if a fat biopsy is negative.

***AL amyloidosis*** *is the type of amyloidosis most commonly associated with* ***Waldenström macroglobulinemia (WM).***

After a biopsy is performed, the pathologist can use many different techniques to confirm the diagnosis, but it is crucial not only to identify the presence of amyloid fibrils but also to determine the specific type of protein that misfolded to form the fibrils. The type of protein that is present determines not only the origin of the amyloidosis, but also guides treatment decisions. The most common types of amyloidosis in the United States are immunoglobulin light chain (AL) amyloidosis, transthyretin (TTR) amyloidosis, and serum amyloid A protein (AA) amyloidosis.

**Types of amyloidosis**

AL amyloidosis is the type of amyloidosis most commonly associated with Waldenström macroglobulinemia (WM). The origin of the misfolded protein in AL amyloidosis is typically an underlying hematologic or bone marrow disorder. A clonal population of cells in the bone marrow produces an immunoglobulin (antibody) heavy chain (i.e., IgM, IgG, or IgA) and/or

*IgM-Related Amyloidosis, cont. on page 3*

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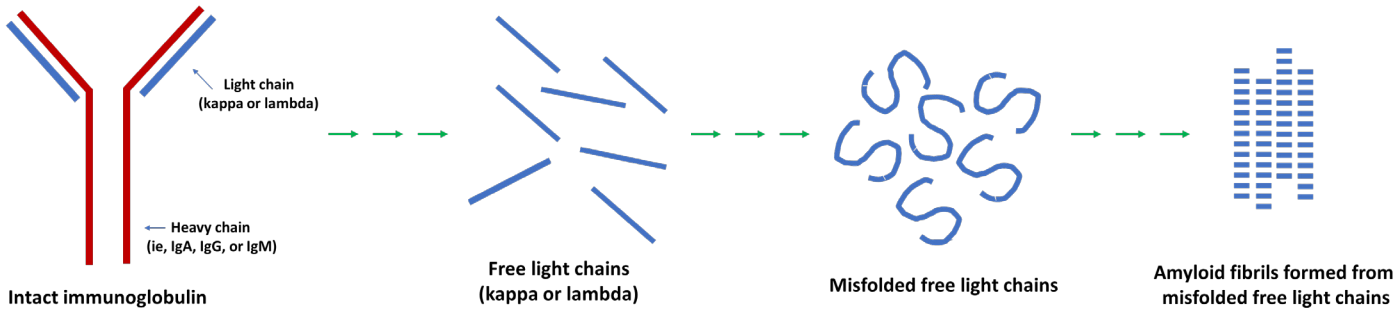



a free light chain (kappa or lambda) which then misfolds and deposits in organs. When misfolded immunoglobulin light chains are discovered as the precursor protein, this is consistent with AL amyloidosis.

In TTR amyloidosis the culprit protein originates from the liver. The TTR protein can be a normal protein that misfolds, or it may be a mutant protein that is the result of an inherited mutation. AA amyloidosis is seen in patients with a chronic inflammatory state, typically related to an uncontrolled medical condition. These latter two types of amyloidosis are not generally associated with WM but have been seen in rare cases, so typing of the amyloid protein is extremely important. Irrespective of the amyloid type, continued production and deposition of the folded protein can lead to severe organ dysfunction and can become life threatening. Therefore, recognition of this rare disorder, accurate diagnostic typing, and administration of an appropriate treatment regimen is incredibly important not only to prevent, but to reverse, organ damage.

**IgM-related AL amyloidosis associated with WM**

Similar to WM, AL amyloidosis is a rare disorder. As mentioned previously, it can be associated with multiple immunoglobulin (antibody) types, such as IgG, IgA or IgM. It is associated with an IgM monoclonal protein in only 4-7% of all AL amyloidosis cases. Additionally, IgM-related amyloidosis is diagnosed in only about 5-10% of patients with WM. AL amyloidosis may be diagnosed at the same time as WM or at a later date, perhaps years after the original diagnosis of WM. There is an increased risk of developing amyloidosis in WM patients who have a free light chain ratio (a ratio of kappa over lambda) equal to or greater than 10.

Patients with WM and AL amyloidosis (or those with AL amyloidosis associated with an IgM monoclonal antibody) have a slightly different presentation than most patients with AL amyloidosis related to other monoclonal antibody types (i.e., IgG). IgM-related amyloidosis more commonly presents with renal (kidney) involvement and neurologic (nerve) involvement. It is less likely to have cardiac involvement compared with non-IgM amyloidosis, although cardiac involvement is still seen in approximately 1/3 to 1/2 of patients. Additionally, lung involvement and lymph node involvement are also seen more frequently in IgM-associated AL amyloidosis.

**Organ dysfunction in IgM-related AL amyloidosis**

There are characteristic signs and symptoms to monitor for in WM patients to ensure that a diagnosis of amyloidosis is not missed. When kidneys are affected by amyloidosis, patients will typically develop proteinuria (elevated protein in the urine). This protein is not the typical monoclonal protein (i.e., IgM) that is seen in WM but is actually an increase in albumin (a healthy protein) that is being spilled into the urine due to dysfunctional kidneys. This loss of albumin can lead to edema (swelling) in the legs or around the eyes. It can also lead to significant fatigue, low blood pressure, and an increased risk of blood clotting.

Nerve damage related to IgM-associated AL amyloidosis can involve both the peripheral nervous system and the autonomic nervous system. The peripheral nervous

| Organs typically affected by IgM-related AL amyloidosis |
|---|
| Kidneys |
| Peripheral and Autonomic Nervous System |
| Heart |
| Lungs |
| Lymph nodes |
| Gastrointestinal/Liver |

*IgM-Related Amyloidosis, cont. on page 4*

system involves the nerves of the arms and legs that affect sensation and movement. With damage to the peripheral nerves, patients can develop symptoms of peripheral neuropathy, such as numbness, tingling, and pain, that begin in the toes and move upward into the feet, legs, hands, and arms. The autonomic nervous system controls the inner workings of the body, including the regulation of blood pressure, the movement of the intestinal tract, and control of the bladder. When the autonomic system is affected, patients may develop orthostasis (symptoms related to low blood pressure such as lightheadedness), new diarrhea or constipation, or changes in urination.

Heart involvement by amyloidosis typically results in thickening of the heart muscle with abnormal diastolic function (difficulty of the heart to relax appropriately). As the amyloid protein builds up in the heart, there is a risk of developing abnormal heart rhythms due to impaired electrical conduction through the heart. Often an electrocardiogram (EKG), echocardiogram (ultrasound of the heart), cardiac MRI, or cardiac enzymes (blood tests of NT-proBNP and troponin) will be abnormal. Patients may experience leg swelling, shortness of breath, or palpitations.

Lung involvement may present with pleural effusions (fluid buildup around the lung). Additionally, patients may develop nodules within the lungs that can be seen on chest imaging. Lymph node enlargement in the area of the lungs or other areas throughout the body are also frequently reported in this patient population. Those lymph nodes are commonly noted to be calcified on imaging studies.

It is important to determine which patients have AL amyloidosis along with a diagnosis of WM so that appropriate monitoring can occur. Patients with WM may be monitored with complete blood counts and IgM levels at follow-up visits, but those with AL amyloidosis also require routine monitoring of free light chains, as well as additional monitoring for possible organ damage.

**Treatment options**

Treatment regimens for patients with WM and IgM-associated AL amyloidosis are vastly different from those used in patients with other types of amyloidosis, and they are also different than those used in patients with non-IgM AL amyloidosis. Determining what treatment to use will depend partially on the bone marrow biopsy findings for each patient.

In non-IgM AL amyloidosis, the bone marrow biopsy will often show a clone of plasma cells, and in that case the therapy can be directed at the plasma cells with therapies that are similar to those used in multiple myeloma (since multiple myeloma is also a plasma cell disorder). A pure plasma cell clone in the bone marrow occurs in most AL amyloidosis, but it is seen in less than 1/4 of patients with IgM-related amyloidosis.

*...BTK inhibitors such as **ibrutinib** and **zanubrutinib,** which are often used in patients with WM, are not frequently used in AL amyloidosis.*

In most patients with IgM-related amyloidosis, the clonal population of cells in the bone marrow is made up of plasma cells, lymphocytes (B-cells), and lymphoplasmacytoid cells (cells with features of both lymphocytes and plasma cells). In these cases, the treatment for amyloidosis include therapies that are similar to those used in WM, with some modifications. Hematologic responses in IgM-related amyloidosis may be achieved with bortezomib-based regimens (i.e., bortezomib/rituximab/dexamethasone), alkylating agents with rituximab (i.e., cyclophosphamide/rituximab), and chemotherapy with rituximab (i.e., rituximab/bendamustine). Also, patients with IgM-associated AL amyloidosis may be treated with autologous stem cell transplantation. Previous reports suggest that this treatment option is associated with excellent responses, although patients must be chosen carefully as the mortality risk (risk of death) is higher than expected with other treatment options and varies based on the experience of the institution performing the stem cell transplantation. Overall, autologous stem cell transplantation is generally an effective and safe treatment, but it should ideally be performed at large academic centers with experience treating patients with AL amyloidosis. Another important consideration in the treatment of patients with AL amyloidosis and WM is that BTK inhibitors such as ibrutinib and zanubrutinib, which are often used in patients with WM, are not frequently used in AL amyloidosis. Small studies have shown low response rates and increased risk of toxicity (side effects) with this class of medications. Since additional research is needed, these medications are not typically used in patients with AL amyloidosis.

The goal of treatment in IgM-associated AL amyloidosis is to decrease the free light chain level and the monoclonal protein (IgM) level to prevent additional accumulation of the abnormal, misfolded protein. Patients who are able to achieve a deep hematologic response, such as a complete response or very good partial response, have improved outcomes compared to those who achieve a partial response or have no hematologic response to therapy. By achieving an adequate response, the abnormal protein is no longer available to misfold and deposit in organs. Stopping

IgM-Related Amyloidosis, cont. on page 5

ongoing organ damage often allows for the recovery of the damaged organs. After treatment is completed, continuous monitoring of hematologic markers (IgM and free light chain levels) and organ testing (to ensure there is no more damage to susceptible organs) is a very important part of follow-up.

**Conclusion**

All patients with WM should be monitored closely for any signs or symptoms of the development of AL amyloidosis. If there is any concern for amyloidosis, a tissue biopsy should be performed and, if found, the amyloid fibrils should be typed to ensure an accurate diagnosis. Treatment should then be determined based on the patient's symptoms, the patient's overall health, the extent of organ involvement, and the risk of further organ damage. Achievement of a deep hematologic response is the goal of therapy to prevent further deposition of the amyloid fibrils and to allow organ recovery. Patients with IgM-related amyloidosis will then require lifelong monitoring after treatment is complete to allow for early detection of disease relapse.

# TODAY, TOMORROW, AND BEYOND

BY NEWTON GUERIN, IWMF PRESIDENT AND CEO

**Pay It Forward**

During his opening comments on the last day of our 2021 Virtual Ed Forum, IWMF Chair Emeritus Carl Harrington encouraged us all to think about **four things**:

*Newton Guerin*

#1 - **With the IWMF, you are never alone**. When we need help, we are all just a mouse-click, a phone call, or a posting on Facebook or IWMF Connect away.

#2 - We have seen dramatic advances leading to unbelievable outcomes. **WM patients are living longer, higher quality lives with fewer side effects.** With that in mind, we must invest additional resources for supporting the research which will lead to "A World Without WM."

#3 - During a recent IWMF webinar, Gwen Nichols, MD, chief medical officer of the Leukemia & Lymphoma Society (LLS), began her comments with "**…we have seen incredible progress over the last 25 years.** In 1994, life expectancy for someone newly diagnosed with WM was 3-5 years and today it's 16-20. The number of WM treatment options has increased from four to over forty." Dr. Nichols went on to encourage the entire WM community to continue to support the IWMF-LLS Strategic Research Roadmap, consider a clinical trial if you need treatment, and join the LLS Patient Registry.

#4 - **Pay it forward.** The reason we've seen such progress leading to folks living longer with WM, along with the growth and outreach of the IWMF's information, education, and support programs, is because of those who stepped up to pay it forward with their hard work as IWMF volunteers and their generous financial support. Carl went on to say, "We're living on the backs of those folks who came before. They made it possible to get to where we are today. We all can continue to pay it forward with our financial support of IWMF-funded research and other mission programs. Also, there are many ways to pay it forward that aren't just money. You can pay it forward by participating in a clinical trial, by volunteering for the IWMF, or by soliciting your friends and family to participate in IWMF fundraising events like the Walk for Waldenstrom's, the Giving Challenge, Giving Tuesday, or even an event you create." Paying it forward simply means doing something good for someone in response to a good deed done on your behalf or a gift you received. When we pay it forward, we don't repay the person who did something good for us. Instead, we do something good for someone else.

We all seem to want the same things in life, including a better world for us and our families, peace, clean water to drink, and cures for so many diseases, especially WM. Paying it forward is how we can all do our part to make these things happen. When we pay it forward, we're thinking of the bigger picture instead of ourselves. We're putting the focus on others.


Paying it forward is not about TODAY, but rather it's about TOMORROW and BEYOND. Above all, the biggest reason we pay it forward is HOPE. Paying it forward brings a renewed sense of hope to us all.

Thank you!

# THE 2021 IWMF VIRTUAL EDUCATIONAL FORUM

By Carl Lisman, IWMF Board Member


While the IWMF had hoped to return to having the Educational Forum in person in 2021, those plans were altered by the continuing coronavirus pandemic. Staff and volunteers had been making contingency plans for a virtual Forum and quickly shifted their efforts to create what participants recognized as an outstanding, fully virtual Ed Forum. As you would expect from this dedicated group, lessons learned from last year's Forum were applied to make this year's event even better. One key change was to create an Educational Month by preceding the Ed Forum with two workshops. All presentations from the early October workshops are available for replay on the IWMF website with slides. Brief summaries follow below in this article. The Ed Forum was held October 28 and 29, and those sessions are also available for replay at *iwmf.com*.

Each session of the Educational Month contained valuable information presented by some of the most prestigious health care professionals working to help the global WM community achieve a high quality of life while we pursue our dream of an eventual cure. The summaries below also provide information on the presenters, and we are indeed fortunate that they took the time to share their knowledge and insights with us. We extend the appreciation and gratitude of the entire WM community to them.

We also owe thanks to the diverse group of IWMF Trustees and fabulous volunteers who not only introduced each of the speakers but also facilitated the Question & Answer segments that followed. Volunteers performing this role were Bonnie Beckett, Julie Richardson, Paula Eastmond, Sharon Rivet, Eileen Sullivan, and Bob Perry. Trustees included Lisa Wise, Meg Mangin, Pete DeNardis, Carl Lisman, Paul Kitchen, and Dr. Tom Hoffmann. You can "meet" each of these individuals in the replays on the website.

On October 6, an "Understanding WM" workshop was held with three presentations. The first was "WM and Basic Terminology" by Dr. Jeffrey Matous, who is medical director of the Colorado Blood Cancer Institute. Dr. Matous's excellent presentation was aimed at making everything related to our WM diagnosis as understandable as possible. He also prepared his audience to better follow the rest of the Ed Forum by providing an explanation of the terminology we hear from our own doctors and would hear in remaining sessions during the Ed Forum.

*Dr. Jeffrey Matous*
*Colorado Blood Cancer Institute, Denver*

The second session on October 6 was "Understanding Your Blood and Bone Marrow Tests" with Dr. Rafat Abonour, professor of medicine at Indiana University. Dr. Abonour went through the significant number of tests we receive as a result of our WM diagnosis. He improved our understanding of each of the tests, how they are interpreted, and how our doctors use this information to provide treatment directed to our specific manifestation of WM. His explanations prepared participants to ask good questions of our doctors and understand the responses we receive.

The final presentation of the first workshop was by Dr. Sikander Ailawadhi from the Mayo Clinic in Jacksonville, Florida. His topic was "Genomics/Science of WM." He presented complex information on the cells and proteins that are present in WM patients with clear explanations and slides. He then talked about drugs being used to treat WM today, as well as those being investigated to provide more effective and tolerable regimens for future WM treatment.

*The 2021 IWMF Virtual Educational Forum, cont. on page 7*

At the close of the first workshop, it was clear the Ed Forum Planning Committee had succeeded in securing an all-star lineup of doctors with tremendous knowledge of WM. The bar was very high for the upcoming days.

On October 13 the "WM and Self Care" workshop contained three additional sessions: "Dealing with the Stress of Medical Uncertainty," "WM and the Eye," and "Infection Prevention Strategies for WM Patients." Julie Larson, licensed clinical social worker, led the second workshop day by dealing with the stress and uncertainty faced by WM patients. She identified leading stressors for WM patients and presented several strategies to cope with them. She made clear that stress can be a normal response, though it is subjective and personal. Her presentation was hailed as both very helpful and wise.

The second session, "WM and the Eye," was delivered by Dr. Maureen Hanley, associate professor of optometry at the New England College of Optometry. She is an expert on the impacts of WM on the eye. In order to ground those listening, she started with a basic understanding of the eye and then showed several of the effects that WM can have. She detailed common consequences of aging and diseases such as diabetes and compared them to WM's impact on the eye. Dr. Hanley discussed the impact of various IgM levels, and while noting that not everyone with WM will have retinal problems, she indicated about 40% will.

The final presentation for the second workshop featured Dr. Andrew Branagan from the Massachusetts General Hospital Cancer Center. Dr. Branagan explained how WM suppresses our immune system and reviewed common infections encountered by patients with WM. He discussed how WM patients can avoid infections and presented a novel influenza vaccination strategy for WMers. Dr. Branagan concluded by discussing efforts to study and improve immune responses to COVID-19 vaccination in WM.

At the end of the second workshop, all participants were pleased with the information delivered by this knowledgeable and caring group of health care professionals. This second day completed the Planning Committee's work to establish a solid foundation to build upon during the two days of the virtual Ed Forum. Expectations were high, and no one was to be disappointed.

After the built-up anticipation from the two workshop days, the opening of the 2021 Ed Forum finally arrived on October 28. There were 1,146 registrants from 19 countries for this virtual event. Attendees were able to select events across all of the Education Month, and over 3,857 attended sessions over the four days!

The 2021 Walk for Waldenstrom's kicked off the day. The IWMF office led a walk across the Ringling Bridge in Sarasota in order to raise funds for the Foundation and to create awareness about WM. A video of the Sarasota walk is available on the IWMF website. More importantly, there is still time to donate to the Walk if you haven't yet had the chance to demonstrate your support of this vital initiative.

Opening the first day, IWMF Board Chair Peter DeNardis welcomed everyone and introduced Laurie Rude-Betts. Laurie serves as the founding honorary chairperson of the Ben Rude Heritage Society, named after her husband, who was president of the IWMF for over four years before he passed in 2005. Laurie spoke about the Society and its importance in supporting the IWMF in both research and member services. She encouraged everyone to contact the IWMF for more information about including the Foundation in estate plans.

Pete then announced Michael Farbman as the winner of the Judith May Volunteer Award in recognition of his long-term work for the IWMF, helping to craft many of the communications produced by the Foundation. Michael offered his thanks for the recognition and displayed the trophy he received.

*Dr. Stephen Ansell –*
*Mayo Clinic, Rochester*

Pete's next duty was to introduce Dr. Stephen Ansell to deliver the important update on "Current Treatment Options for WM Patients." Dr. Ansell is an IWMF Trustee and well known to WMers for his work at the Mayo Clinic in Rochester, Minnesota. Reflecting the interest of the Ed Forum participants, Dr. Ansell's presentation was the most attended of the entire month. He was especially skilled at presenting very technical information in a manner that helped prepare participants to understand treatment options and the timing considerations they may face in their own care.

For the second topic of the day, Dr. Jorge Castillo of the Dana-Farber Cancer Institute spoke on "Novel Treatments and the Importance of Clinical Trials." Dr. Castillo is also well known to the IWMF community

*The 2021 IWMF Virtual Educational Forum, cont. on page 8*

for his generous contribution of time and talent to Ed Forums and various IWMF support groups. His presentation addressed potential new treatments for WM, with an emphasis on clinical trials that further the research to advance them. He explained how clinical trials work, summarized the broad range of trials ongoing and upcoming, and encouraged WM patients to consider if a clinical trial could be right for them.


*Dr. Shirley D'Sa – University College London Hospitals, United Kingdom*

The final portion of the first day of the Ed Forum consisted of three mini-sessions. The first of these was by Dr. Shirley D'Sa, from the University College in London, speaking about WM and peripheral neuropathy (PN). Dr. D'Sa presented coping strategies and treatment options for living with PN, and her presentation included excellent slides which helped to distinguish WM-caused PN from treatment-caused PN.

The second mini-session featured Kate Mimken, nurse practitioner at Colorado Blood Cancer Institute, delivering a comprehensive review of WM and dermatology issues. She provided an overview of the variety of conditions that affect some WM patients. She distinguished symptoms caused by the disease from those associated with treatments.

The final mini-session was on WM and fatigue, pre-recorded by Larisa Patacchiola, a social worker from the Dana-Farber Cancer Institute. She explained that fatigue from WM can be different from the typical tiredness associated with daily activities, and it can be long lasting with many possible causes. She presented methods to reduce and manage fatigue to improve quality of life.

With the mini-sessions wrapped up, day one of the Ed Forum was complete. Participants gained an enormous amount of information for consideration. You can replay these sessions on the IWMF website to refresh your memory or listen for the first time if you missed one that might be helpful to you.

Day two of the Ed Forum began with the familiar face of Board Chair Emeritus Carl Harrington offering welcoming comments, as well some keen insights and historical perspectives. Not surprisingly, he reminded everyone of the progress that has been made in understanding and treating WM through efforts funded by contributions of all sizes from friends of the IWMF. He encouraged us all to "pay it forward" by contributing as we are able. Carl then introduced Trustee Tom Hoffmann, MD.

Dr. Hoffmann had the privilege of introducing the first recipients of the Dr. Robert A. Kyle Career Development Award. This award was established to recognize the vital importance of providing funding to support the career development of next-generation researchers for WM. The award is named in recognition of Dr. Kyle's 50+ years of contributions to WM research. The first recipients are Dr. Maria Luisa Guerrera and Dr. Romanos Sklavenitis-Pistofidis, both of the Dana-Farber Cancer Institute in Boston, MA. Both recipients offered remarks and thanked the IWMF for the recognition and support.

Friday's session then continued with a discussion of familial WM delivered by Dr. Mary Lou McMaster from the National Cancer Institute. As we learned from Dr. McMaster, the question of whether WM is inherited is a complicated one. She clarified what is meant by "familial" as opposed to "genetic predisposition." She provided clear explanations of this complex topic, as well as what is known and what areas need more research.

The next topic on Friday afternoon was recorded by Dr. Steven Treon from the Dana-Farber Cancer Institute. Dr. Treon is well known in the IWMF community for both his research and his support of the IWMF's efforts to educate everyone with WM about this rare disease. Dr. Treon reviewed the National Comprehensive Cancer Network (NCCN) Guidelines for WM. NCCN is an alliance of 31 leading cancer centers which provide clinical practice guidelines for WM, useful for health care providers treating the disease. He explained differences in treatment regimens, the potential value of newer regimens, and the reasoning behind recommendation differences.

*The 2021 IWMF Virtual Educational Forum, cont. on page 9*

The culmination of the Ed Forum was the highly anticipated "Ask the Doctors" session moderated by Dr. Hoffmann, with a powerhouse panel including Dr. Stephen Ansell, Dr. Andrew Branagan, Dr. Christian Buske of Germany, Dr. Jorge Castillo, Dr. Mary Lou McMaster, and Dr. Steven Treon. Always a highlight of the Ed Forum, this year's panel was no exception. It is impossible to capture the value of this session in a paragraph or two; all I can do is strongly suggest that you watch the video to appreciate the tremendous information this group of talented, caring doctors provided.

With the Ed Forum completed, we should once again thank the presenters, the amazing IWMF staff, the Ed Forum Planning Committee members, and all who contributed to make the 2021 Ed Forum a success.

Next year's "live" Ed Forum (with a virtual option) will be August 26-28 at the Hyatt Regency Lake Washington in Renton, Washington. Hope to see you all there!


*View of Seattle across Lake Washington from the 2022 Ed Forum hotel restaurant in Renton, WA*

# MEDICAL NEWS ROUNDUP

By Sue Herms, IWMF Research Committee Member

**NCCN Adds Venetoclax to List of Other Recommended Regimens for Previously Treated WM/LPL Patients** – The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines for WM/LPL (lymphoplasmacytic lymphoma) has just added venetoclax (Venclexta) to the category of Other Recommended Regimens for previously treated patients. This category consists of treatments that are appropriate but may be less effective, more toxic, based on less mature data, or less affordable for similar outcomes when compared to treatments in the Preferred Regimens category. The inclusion of venetoclax is based on Phase 2 clinical trial results recently published in the *Journal of Clinical Oncology*. A summary of those Phase 2 trial results appears later in this column.

**BeiGene Announces Approval of Zanubrutinib for Treatment of WM Patients in the European Union** – BeiGene announced that the European Commission has approved zanubrutinib (Brukinsa) for the treatment of WM patients who have received at least one prior therapy or for first-line treatment of patients unsuitable for chemoimmunotherapy. The approval is applicable to all 27 European Union member states, plus Iceland and Norway, and follows a positive opinion granted in September by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), based on results from the multicenter Phase 3 ASPEN trial comparing zanubrutinib to ibrutinib.

**Zanubrutinib Also Approved for WM Patients in Australia** – Meanwhile, zanubrutinib (Brukinsa) is now approved in Australia for the treatment of WM patients for the same indications—that is, for patients who have received at least one prior therapy or as first-line treatment for those who are unsuitable for chemoimmunotherapy. Following registration of zanubrutinib with the Therapeutic Goods Administration, patients will have immediate access to the drug through a BeiGene-sponsored post-approval, pre-reimbursement access program.

**US FDA Authorizes Injectable Evusheld for Pre-Exposure Prevention of COVID-19 in the Immunocompromised** – The US Food and Drug Administration (FDA) has issued emergency use authorization for AstraZeneca's drug Evusheld for the pre-exposure prevention of COVID-19 infection in adults and children over 12 years of age who are moderately or severely immunocompromised and may not mount an adequate immune response to COVID-19 vaccines or who have a history of severe adverse reactions to the vaccines. It is only authorized in those who are not currently infected with COVID-19 or who have not recently been exposed to an infected individual. Evusheld consists of two monoclonal antibodies, tixagevimab and cilgavimab, which are targeted to different parts of the coronavirus spike protein. One dose of Evusheld is administered as two separate, immediately consecutive intramuscular injections and is expected to be effective for six months, at which point it can be repeated. In individuals who have received a COVID-19 vaccine, Evusheld should be administered at least two weeks after vaccination. The data supporting the authorization are from the ongoing Phase 3 PROVENT trial, in which 3,441 participants received Evusheld and 1,731 received a placebo. Evusheld recipients had a 77% reduced risk of developing COVID-19 infection compared to those who received the placebo, and this effectiveness increased to 83% in an updated analysis at six months. Side effects included hypersensitivity reactions, bleeding at the injection site, headache, fatigue, and cough. Serious cardiac adverse events were uncommon but occurred more often in those receiving Evusheld than placebo; it was noted that these individuals had a history of, or risk factors for, cardiac disease. AstraZeneca is studying the impact of the new Omicron variant on the effectiveness of Evusheld, and the company believes the drug will be effective based on early results. The US government has an agreement with AstraZeneca to buy 700,000 doses, which will be available at no cost to eligible patients, and the first doses should be distributed within a few months. The FDA emphasized that this treatment is not intended to be a substitute for vaccination.

*...the European Commission has* ***approved*** *zanubrutinib (Brukinsa) for the treatment of WM patients who have received* ***at least one*** *prior therapy...*

**CDC Updates Guidelines for Additional COVID-19 Vaccination in Immunocompromised Adults in the US** – At press time, the US Centers for Disease Control and Prevention (CDC) published on its website the following updated recommendations for additional COVID-19 vaccination in moderately and severely immunocompromised adults: 1) those who have received the initial two-shot Pfizer or Moderna vaccine series **should receive** a third shot of Pfizer or Moderna at least 28 days following the second shot—and the Moderna dose should be the full volume of 100 µg in 0.5 mL; 2) those who have received three shots of the Pfizer or Moderna vaccine **should receive** a single COVID-19 booster shot of Pfizer, Moderna, or J&J at least six months after completing their

*Medical News Roundup, cont. on page 11*

third shot—and the Moderna dose should be a reduced volume of 50 µg in 0.25 mL; and 3) those who have received the initial single dose J&J vaccine **should receive** a booster shot of Pfizer, Moderna, or J&J at least two months after receiving their initial shot—and the Moderna dose should be a reduced volume of 50 µg in 0.25 mL. Because of concerns about rare blood clotting problems associated with the J&J vaccine, the CDC currently prefers Pfizer and Moderna vaccines over J&J, although the latter is still available. There are special recommendations for those who have received CAR-T cell therapy or hematopoietic stem cell transplant. **Note that CDC terminology does not refer to a third Pfizer or Moderna shot for the immunocompromised as a booster, which is an important distinction when selecting the appropriate Moderna dose.** The CDC also recommends that the immunocompromised continue to follow COVID-19 prevention measures and that close contacts should be strongly encouraged to get vaccinated. The full recommendations can be viewed at *https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#considerations-covid19-*.

*It was noted that there was still a* ***large percentage*** *of patients who may remain at risk of* ***breakthrough infections****, even with the additional third dose.*

**LLS Presents Analysis of Third Primary Dose of COVID-19 Vaccination in Blood Cancer Patients** – The Leukemia & Lymphoma Society (LLS) has presented new data on the production of antibodies following a third primary dose of COVID-19 mRNA vaccines in patients with blood cancers. While one in four blood cancer patients in an earlier study did not produce detectable antibodies after their first two doses of Pfizer or Moderna, 43% of them did produce antibodies after a third dose of either vaccine; data on responses to the J&J vaccine were not included. The analysis, the largest of its kind to date, included 699 patients who received a third COVID vaccination from June-September 2021, and was weighted to include more patients with blood cancers that deplete the immune system's B cells, which are responsible for making antibodies. It was noted that there was still a large percentage of patients who may remain at risk of breakthrough infections, even with the additional third dose. As reported in previous studies by LLS and others, B cell-depleting treatments such at BTK inhibitors and anti-CD20 antibodies blunted the immune response while patients were on therapy and even for several months after therapy was completed. LLS continues to encourage blood cancer patients to use additional precautions, such as mask wearing and social distancing. The analysis was just presented during the 2021 Annual Meeting of the American Society of Hematology (ASH).

**Phase 3 Trial to Evaluate REGEN-COV as Treatment to Prevent Symptomatic COVID-19 Infection in the Immunocompromised** – A Phase 3 randomized trial will evaluate the effectiveness and safety of the COVID-19 monoclonal antibody treatment casirivimab and imdevimab (REGEN-COV) as pre-exposure prophylaxis to prevent symptomatic infection in immunocompromised patients. Currently, this treatment is used in patients who have recently tested positive for COVID-19 infection and are at risk for severe disease. The study is now recruiting and hopes to enroll 8,752 immunocompromised individuals across the US at 51 trial locations. Enrolled participants must be fully vaccinated against COVID-19 or deemed medically ineligible to receive a full course of vaccine, have a documented negative antibody response to the COVID-19 spike protein, and have tested negative for the virus. Participants will receive either REGEN-COV or a placebo subcutaneously at different dosing regimens. The trial identifier on *www.clinicaltrials.gov* is NCT05074433.

**Results Published from Phase 2 Study of Venetoclax in Previously Treated WM** – After a median follow-up of 33 months, the *Journal of Clinical Oncology* published data from a multicenter Phase 2 study of venetoclax (Venclexta) in 32 patients with previously treated WM. Venetoclax was dose-escalated from 200 mg to a maximum of 800 mg daily for up to two years. All patients were MYD88 L265P-mutated, and 17 had mutations in CXCR4. The overall, major, and very good partial response rates were 84%, 81%, and 19%, respectively. Median progression-free survival was 30 months. The median time to minor and major responses was 1.9 and 5.1 months, respectively, but previous treatment with BTK inhibitors was associated with a longer time to achieve response. CXCR4 mutations did not affect treatment response or progression-free survival. The only recurring moderate to severe treatment-related adverse event was neutropenia (low neutrophil count) in 45% of participants. A laboratory case of tumor lysis syndrome (a potentially serious event caused by massive tumor cell die-off and the release of large amounts of potassium, phosphate, and nucleic acids into the blood) occurred in one patient, but without clinical symptoms.

**Three Common Fixed-Duration Treatments Compared in Mayo Clinic Retrospective Study of Treatment Naïve WM** – The Mayo Clinic retrospectively evaluated 220 treatment naïve WM patients seen in clinic November 1, 2000 - October 31, 2019, to compare three commonly used fixed-duration therapies for WM. The therapies studied included rituximab and bendamustine (R-Benda); dexamethasone, rituximab, and cyclophosphamide (DRC); and bortezomib,

*Medical News Roundup, cont. on page 12*

dexamethasone, and rituximab (BDR). The median follow-up was 4.5 years. The R-Benda cohort demonstrated a superior overall response rate of 98%, in comparison to DRC at 78% and BDR at 84%. Similarly, longer progression-free survival and time-to-next-therapy favored R-Benda, while overall survival was similar in all three groups. Patient outcomes in any of these three regimens were unaffected by MYD88 status. The study was published in the *American Journal of Hematology*.

**DFCI Presents Final Report from Phase 2 Study of Ibrutinib in Treatment Naïve WM** – Dana-Farber Cancer Institute (DFCI) has presented the final report in the journal *Leukemia* on its Phase 2 trial evaluating ibrutinib (Imbruvica) in 30 treatment naïve WM patients. With a median follow-up of 50 months, the overall, major, and very good partial response rates were 100%, 87%, and 30%, respectively. The four-year progression-free survival rate was 76%. Median time to a major response was 1.9 months, although longer (7.3 months) in those with mutated CXCR4. CXCR4 mutations also appeared to negatively impact attainment of very good partial responses and four-year progression-free survival, although the data were not statistically significant. Six patients experienced disease progression. The most common treatment-related adverse events were fatigue, upper respiratory infection, and hematoma (localized seepage of blood from capillaries into surrounding tissues). Atrial fibrillation occurred in 20% of patients.

**Researchers Publish Final Analysis for European Phase 1/2 Trial of IRD Therapy in Relapsed/Refractory WM** – Final analysis of the multicenter European Phase 1/2 HOVON124 trial combining oral ixazomib (Ninlaro) with subcutaneous rituximab (Rituxan) and dexamethasone in relapsed/refractory WM has been published in the *Journal of Clinical Oncology*. The dose level of ixazomib in Phase 1 was established as 4 mg for the Phase 2 part of the trial. This combination therapy, designated IRD, consisted of eight cycles, during which rituximab was started in cycle three. Those who achieved at least a minor response continued with rituximab maintenance for two years. A total of 59 patients participated. After eight cycles, the overall response rate was 71%, improving to 85% at month 12. Median duration of response was 36 months. Median progression-free survival and overall survival at 24 months were 56% and 88%, respectively. Patients who were MYD88 mutated/CXCR4 wild-type or were MYD88 wild-type/CXCR4 wild-type had the highest rates of very good partial responses and partial responses, while no patient who was MYD88 mutated/CXCR4 mutated achieved a very good partial response. Toxicities included cytopenias (low blood counts), neuropathy, and infections.

**Rory Morrison Registry Publishes Second Report on WM Patients in the United Kingdom** – The Rory Morrison Registry, developed by WMUK to collect real world data from WM patients in the United Kingdom, has published its second report, which can be viewed at *https://wmuk.org.uk/wp-content/uploads/2021/11/Rory-Morrison-Report-2021-2-11-21-Final-Version.pdf*. The Report provides updated data and further insights into the diagnosis, treatments, and outcomes for WM patients. At data cut-off on September 1, 2020, the Registry held information from 926 patients, including 802 with confirmed WM and the remainder with other IgM-related conditions.

*The [Rory Morrison] Report provides updated **data** and further **insights** into the **diagnosis, treatments,** and **outcomes** for WM patients.*

**Venetoclax and Rituximab Combination to Be Compared with DRC in Phase 2 Trial for Treatment Naïve WM Patients in Germany and France** – A clinical trial in 30 sites in Germany and France was to open for recruitment in December 2021 to study the efficacy of venetoclax (Venclexta) in combination with rituximab (Rituxan) in treatment naïve WM patients. This Phase 2 randomized trial will compare the combination of venetoclax and intravenous rituximab for 12 cycles to the combination of dexamethasone, intravenous rituximab, and cyclophosphamide (DRC) for six cycles, followed by six cycles of intravenous rituximab only. The primary outcome measure will be the rates of complete and very good partial responses in the two groups. On *www.clinicaltrials.gov*, the trial identifier is NCT05099471.

**Phase 3 Trial Recruiting WM Patients for Carfilzomib and Ibrutinib Combination Therapy Compared to Ibrutinib Alone** – A Phase 3 study out of Germany is recruiting treatment naïve and relapsed/refractory WM patients to randomized therapy with carfilzomib (Kyprolis) and ibrutinib (Imbruvica) in Arm A or with ibrutinib alone in Arm B. The investigators hope that the addition of carfilzomib will increase the complete and very good partial response rates in patients with CXCR4 mutations, as well as show high activity in patients with MYD88 wild-type disease. According to *www.clinicaltrials.gov*, trial sites will be international, and the trial identifier is NCT04263480.

**DFCI Plans to Open Trial of Acalabrutinib Combination for Treatment of IgM-Related Neuropathies** – Dana-Farber Cancer Institute (DFCI) is planning to open a Phase 2 clinical trial of acalabrutinib (Calquence) combined with either rituximab (Rituxan) or a biosimilar anti-CD20 antibody as treatment for IgM MGUS or WM patients with

*Medical News Roundup, cont. on page 13*

IgM-related neuropathies. The trial anticipates enrollment of approximately 30 participants; study treatment will be up to four years, with two years of follow-up. Acalabrutinib will be administered twice daily in 28-day cycles, and rituximab or a biosimilar will be administered on days 1, 8, 15, and 22 of treatment cycles one and four. The identifier on *www.clinicaltrials.gov* is NCT05065554.

**US FDA Approves Zanubrutinib for Relapsed or Refractory Marginal Zone Lymphoma** – The US Food and Drug Administration (FDA) has granted accelerated approval to zanubrutinib (Brukinsa) for the treatment of patients with relapsed or refractory marginal zone lymphoma who have had at least one prior treatment with an anti-CD20-based therapy. Marginal zone lymphoma is closely related to, and is included in the differential diagnostic workup of, WM.

**Pooled Safety Analysis Evaluates Zanubrutinib Treatment in Patients with B Cell Malignancies** – A pooled safety analysis of zanubrutinib (Brukinsa) has been completed by an international group of researchers to better understand treatment toxicities in patients with B cell malignancies. Data were pooled from 779 participants in six clinical trials and published in the journal *Blood Advances*. Most patients had WM (33%), chronic lymphocytic leukemia/small lymphocytic lymphoma (29%), or mantle cell lymphoma (19%). Median treatment duration was 26 months, with 16% of patients treated for three years or more. The most common non-hematologic toxicities were upper respiratory tract infection, rash, bruising, musculoskeletal pain, diarrhea, cough, pneumonia, urinary tract infection, and fatigue. Atrial fibrillation and major hemorrhage occurred in 3% and 4% of patients, respectively, and atrial fibrillation, hypertension (high blood pressure), and diarrhea occurred at lower rates than reported for ibrutinib. Treatment discontinuation and dose reduction for toxicities occurred in 10% and 8%, respectively. Fatal toxicities occurred in 4% and included pneumonia, sepsis, unspecified cause, and multiple organ dysfunction.

**French Researchers Discuss Safety Profile of Ibrutinib in Large-Scale Analysis of Case Reports from WHO Database** – French researchers have evaluated the safety profile of ibrutinib (Imbruvica) therapy in a large-scale analysis of individual case safety reports extracted during November 13, 2013-December 31, 2020, from VigiBase, the World Health Organization (WHO) global safety database. A total of 16,196 case safety reports on ibrutinib were identified, with more than half resulting in hospitalization. While a complete discussion of the study analysis is beyond the scope of this *Torch* summary, several potential safety signals emerged. With some differences noted between patients less than 75 years old and those 75 and older, those potential safety signals included: cardiovascular disorders (including ischemic heart disease, pericarditis, bradyarrhythmia, and aortic aneurysm), deafness, hypothyroidism, eye disorders (including cataract, uveitis, glaucoma, and retinal disorders), fractures, hyponatremia, depression, and pleurisy. The full analysis, including limitations of the study, was published in the journal *Frontiers in Pharmacology* and can be viewed at *https://www.frontiersin.org/articles/10.3389/fphar.2021.769315/full*.

**Study Examines Adverse Cardiovascular Events and Hypertension in CLL Patients on Acalabrutinib** – A study published in the journal *Haematologica* has examined adverse cardiovascular events in chronic lymphocytic leukemia (CLL) patients receiving acalabrutinib (Calquence) as single-agent therapy. Acalabrutinib was given orally at total daily doses of 100-400 mg, later switched to 100 mg twice daily, and was continued until disease progression or toxicity in 762 CLL patients participating in four clinical trials of the drug. Median follow-up was 25.9 months. Cardiac adverse events were reported in 17% and led to treatment discontinuation in 1%. The most common cardiac adverse events noted were atrial fibrillation/flutter in 5%, palpitations in 3%, and tachycardia (rapid heartbeat) in 2%. Overall, 91% of patients with cardiac adverse events had risk factors for these conditions before acalabrutinib treatment. Hypertension (high blood pressure) adverse events were reported in 9% of patients, close to half of whom had a preexisting history of the condition, but no patients discontinued acalabrutinib treatment because of hypertension. No sudden cardiac deaths were reported.

*French researchers have evaluated the safety profile of* ***ibrutinib (Imbruvica) therapy*** *in a large-scale analysis of individual case safety reports...*

**Preliminary Data Presented at ASCO for Phase 1 Part of Clinical Trial of Novel BCL-2 Inhibitor Lisaftoclax** – Preliminary Phase 1 data from a trial of the novel BCL-2 inhibitor lisaftoclax (APG-2575) in relapsed/refractory chronic lymphocytic leukemia (CLL) and other hematologic malignancies were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2021. Lisaftoclax is a second-generation BCL-2 inhibitor, developed to bind reversibly to BCL-2 as a way to reduce toxicity, in contrast to venetoclax that binds irreversibly. The overall response rate for the CLL participants was greater than 80%, and no incidents of tumor lysis syndrome (a potentially serious event caused by massive tumor cell die-off and the release of large amounts of potassium,

*Medical News Roundup, cont. on page 14*

phosphate, and nucleic acids into the blood) were reported. Adverse events included diarrhea, neutropenia (low neutrophil count), thrombocytopenia (low platelet count), and nausea. Data from other hematologic malignancies in Phase 1, including WM, were not presented; however, a Phase 1b/2 portion of the study, called MAPLE-1, is accruing only WM patients; its identifier on *www.clinicaltrials.gov* is NCT04260217.

**Nurix Therapeutics Offering Phase 1a/b Trials of Novel Drugs That Degrade BTK to Patients with Relapsed/Refractory B Cell Malignancies** – Nurix Therapeutics, Inc. is offering Phase 1a/b trials to patients with relapsed/refractory B cell malignancies, including WM, for its novel drugs NX-2127 and NX-5948. Both drugs lead to the degradation of BTK, in contrast to BTK inhibitors such as ibrutinib that block expression of BTK. Both purportedly work equally well against unmutated and mutated BTK and could potentially be used in patients who become resistant to BTK inhibitors because of BTK mutations such as C481S. The trial for NX-2127 is currently enrolling patients, and its identifier on *www.clinicaltrials.gov* is NCT04830137, while the trial for NX-5948 is not yet recruiting.

**European Trial Publishes Results of Bispecific Antibody Treatment in Relapsed/Refractory B Cell NHL** – European researchers have reported results in *The Lancet* journal from a Phase 1/2 clinical trial of epcoritamab, a bispecific antibody that targets CD3 and CD20, in relapsed or refractory B cell non-Hodgkin's lymphoma (NHL). Of 73 patients enrolled in Denmark, the Netherlands, the United Kingdom, and Spain, 68 received escalating doses of subcutaneous epcoritamab. No dose-limiting toxic effects were observed in Phase 1, and a dose of 48 mg was recommended for the Phase 2 part of the study. The overall response rate in indolent lymphoma patients was 90%, with 50% achieving a complete response. Common adverse events were fever and injection site reactions. The CD3 portion of the antibody is intended to induce the body's own T cells to better target and destroy malignant B cells that are CD20+.

**Interim Results Reported for Another Bispecific Antibody Used in Phase 1/2 Study of Relapsed/Refractory NHL** – Meanwhile, another bispecific antibody targeting both CD3 and CD20 has been used in a Phase 1/2 study of relapsed/refractory non-Hodgkin's lymphoma (NHL), with interim results reported at the Annual Meeting of the Society of Hematologic Oncology. This study incorporated the intravenous antibody glofitamab, which was administered in step-up dosing fashion following initial treatment seven days prior with 1000 mg of the intravenous antibody obinutuzumab (Gazyva). After step-up dosing to the target dose, glofitamab was subsequently administered every 21 days for up to 12 cycles. Most patients were refractory to their most recent and any prior anti-CD20 therapy. At data cut-off, 52 patients had completed step-up dosing. With a median follow-up of 6.3 months, the best overall response rate for indolent lymphoma patients was 79.2%. Treatment-related adverse events included cytokine release syndrome (systemic inflammatory response caused by the release of signaling molecules called cytokines), neutropenia (low neutrophil count), and fever.

*...the US FDA granted* ***emergency use*** *authorization to oral medications from* ***Pfizer*** *and* ***Merck*** *to treat early COVID-19 infection...*

**US FDA Grants Emergency Use Authorization for Oral Medications to Treat Early COVID-19 Infection in Those at High Risk of Serious Disease** – At press time, the US Food and Drug Administration (FDA) granted emergency use authorization to oral medications from Pfizer and Merck to treat early COVID-19 infection in those who are a high risk of developing serious disease. Pfizer's treatment, called Paxlovid, consists of three tablets (two tablets of nirmatrelvir and one of ritonavir) taken twice a day over the course of five days; it must be started within five days of first developing symptoms. Clinical trial data provided by Pfizer indicated that Paxlovid reduced the chances of hospitalization or death by 88% in adults at high risk of severe COVID-19, compared to placebo. Merck's pill, called Lagevrio (molnupiravir), cut the risk of hospitalization or death by 30% among high-risk adults, when compared to placebo. Lagevrio should also be taken within five days of symptom onset, with four capsules taken every 12 hours for five days. Early data suggest that Paxlovid and Lagevrio are effective against the omicron variant. The federal government will control distribution to the states; both will be available by prescription only. Neither treatment is authorized to prevent COVID infection or as a substitute for vaccination.

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

# IWMF-FUNDED RESEARCH: PROGRESS REPORT

By Glenn Cantor, Science Editor and IWMF Trustee

**Zachary Hunter and Steven Treon, Dana-Farber Cancer Institute, Harvard University, Boston, MA, USA**

***Multiomic analysis of DNA, RNA, and epigenomic networks for prognostication and novel target identification in WM***

Life is complicated.

I was diagnosed with Waldenstrom macroglobulinemia (WM) in 2017. After an initial gulp when I heard I had cancer, the scientific part of my brain kicked in. I quickly realized I was lucky to have a scientifically fascinating disease. Thanks to earlier work by Drs. Hunter and Treon, it was known that WM cells in most patients (including myself) had mutations of MYD88 which resulted in excessive signaling through known molecular pathways, causing too much activation and proliferation of the WM cells. Scientists down the hall from my lab worked on MYD88 and its signaling pathways, so I was somewhat familiar with the science. I considered WM the poster child of cancers whose biology was well-understood.

How little I knew! Now, scientists realize that the MYD88 mutation is only part of the story. The same MYD88 mutation, called L265P, is found in non-WM conditions, in which people do not have WM. These include other cancers, and mutated MYD88 is present even in many people with non-cancerous conditions such as monoclonal gammopathy of undetermined significance (MGUS), a finding that affects millions of people and generally causes no signs or symptoms. Meanwhile, researchers found the same story in mice. When they mutated the mouse MYD88 to make it act like the mutation in WM patients, they found that mutated MYD88 was insufficient to cause the mouse version of WM.

So, more than mutant MYD88 is needed. What other molecular changes, in addition to mutated MYD88, are necessary to cause WM? And are there different forms of WM, each with its own unique pattern of molecular changes? That would be good to know, because then perhaps targeted treatment could be devised for each specific form of WM.

Dr. Zachary Hunter and Dr. Steven Treon's research, funded by a IWMF-LLS Strategic Research Roadmap grant, is making good progress toward figuring out this complicated question, as reported in their recent progress report on the second six-month period of their grant. Using samples from 300 patients with untreated WM ("The 300 Project"), Drs. Hunter and Treon hypothesize that it is not enough to look at only one aspect of cellular biology, such as the sequence of DNA and its mutations. Instead, they are attempting to integrate many types of analysis, using techniques called multi-omics, which I described in a *Torch* article in January 2021 (see *https://iwmf.com/wp-content/uploads/2021/01/Torch-Jan-2021_final-web.pdf*, page 11).

In addition to looking at DNA and its mutations, they are analyzing RNA to see what sequence and quantity of RNAs are actually being transcribed from the DNA. Moreover, regardless of DNA sequence, only certain parts of a cell's DNA are available for reading and transcribing (see my article in the previous *Torch*, October 2021, *https://iwmf.com/wp-content/uploads/2021/10/Torch-Oct-2021_web.pdf*, page 18. Techniques to show what parts of the DNA are available include methods called ATACSeq and methylation analysis. (For those of you who want to know what ATACSeq stands for, it is "Assay for Transposase-Accessible Chromatin with high-throughput sequencing," but don't get hung up on that… the point is that it is a tool to reveal specific areas of cells' DNA that are open and available.)

In the recent six-month reporting period, Dr. Hunter has completed analysis of ATACSeq data from 41 WM patients. He will be presenting this data at the upcoming American Society of Hematology Annual Meeting in December and is preparing a full paper. The nice thing about completing the ATACSeq analysis is that those results can now be superimposed on other data that the group has already generated, including gene sequence and RNA data, to get a fuller picture of what is going on.

*The goal of coordinating all these different ways of* ***analyzing cells*** *is to build artificial intelligence computer models (called* ***"machine learning"****)...*

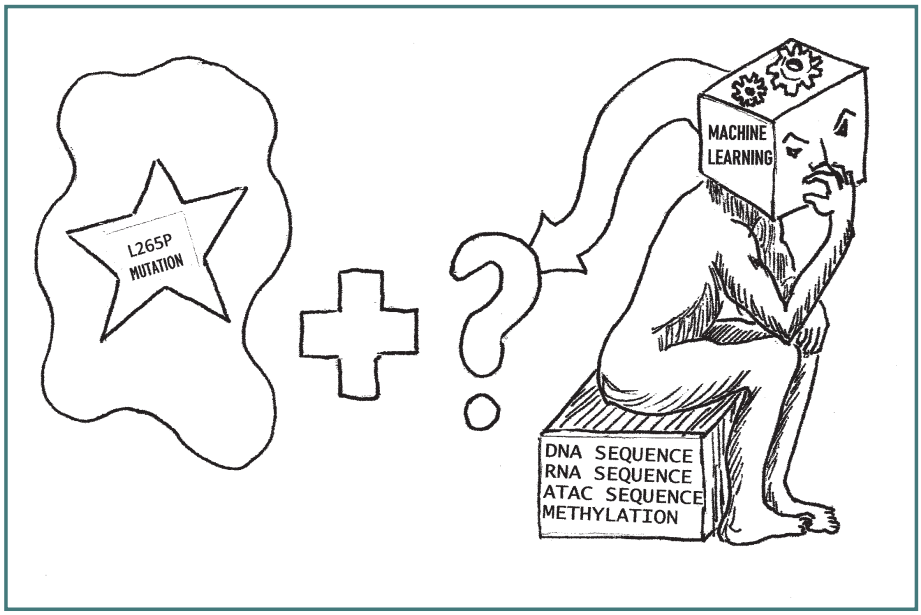
The goal of coordinating all these different ways of analyzing cells is to build artificial intelligence computer models (called "machine learning") to better understand the biology of WM. Often, new machine learning computer models can reveal insights that would be hard to discover otherwise. For example, high levels of gene x may predict for poor prognosis, but only if mutation y is present in another gene. [This is only a simple example with two genes....it is likely that the machine learning systems will find interacting involvement of many more than two genes.] The key to machine learning is to continue to teach and fine-tune the computer models with both improved data and newer computer technology.

*IWMF-Funded Research, cont. on page 16*

An important part of building reliable and predictive machine learning models is to incorporate good data on clinical outcomes. Which patients progressed to disease, how were they treated, and did they respond to treatment? In the recent six-month reporting period, the group has made good progress in collating and incorporating this type of information.

This project brings together expertise from a number of different scientific specialties. When I wrote to Dr. Hunter about his work, he said that he was "particularly proud of the way that collaborators from several institutions have come together to make this happen." Dr. Ruben Carrasco of Dana-Farber handles the WM biopsy staining and imaging, Dr. Ari Melnick at Memorial Sloan Kettering provides expertise on epigenetics, and Drs. Derrick DeConti and Brian Lawney from the Quantitative Biomedical Research Center at Harvard's T.H. Chan School of Public Health are handling the deep learning and message-passing neural networks (artificial intelligence). Dr. Hunter went on to say, "Everyone has really pulled together to make this happen. I also want WM patients to know that there are a lot more people than just me and Steve giving their all to find a cure."

This is only the mid-point of this collaborative IWMF-funded Roadmap grant. With another year of funding yet to come, it will be interesting to see how the work unfolds. Thanks to earlier work from Drs. Hunter and Treon, we already know about MYD88, BTK, CXCR4, and the power of BTK-inhibiting drugs such as ibrutinib, acalabrutinib, zanubrutinib, and others. Potentially, scientists could learn what other genes and proteins contribute to development of WM. This could identify new drugs for WM patients. Indeed, life is complicated, but this research looks like a good way forward.




## 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*

# FROM THE FACEBOOK WM SUPPORT GROUP: WINTER 2022

By Betty Ann Morton

The Facebook WM Support Group continues to be quite active. We're over 4,500 members now, with at least two-thirds having been recently active. This is an increase of approximately 300 members over the past three months. Our new group members are often quite active, asking about medical tests, symptoms, and treatments: Am I going to die soon? How do I find a good doctor? What is IgM? Those who have been around longer may provide some answers, encouragement, and helpful hints. Veteran WMers share their own experiences and guide the newcomers to IWMF resources and scientific papers with reliable information.

Group moderators work hard to ensure that any medical information posted is accurate. Questions are frequently answered both in easily understood language and with links to scientific studies or publications and recordings on the IWMF website. A lively recent discussion centered on the topic of early retirement. Some WMers are seriously impacted by WM and are unable to work and might qualify for disability, while others have been able to continue their jobs—even some physically demanding ones. Members urged meeting with a financial adviser to look at anticipated needs in comparison to savings, pension, Social Security, and investments. In planning for retirement, consider family longevity, since often WMers live a long time after diagnosis. A thorough investigation concerning available and affordable health insurance is also important.

*In **planning** for retirement, consider family longevity, since often WMers **live** a long time **after diagnosis**.*

Speaking of health insurance, it has been a frequent topic of conversation. Although some WMers have excellent medical coverage, others have found that the doctors they wanted to see were outside their insurance network, or that copays for prescription medicines were outside their budgets. Group members have helped others to find assistance from charitable foundations or the Leukemia & Lymphoma Society (LLS) to help with those copays.

COVID-19 has also been frequently discussed. Early in the pandemic, people stayed home and took many precautions. Discussions focused around how to sanitize mail or groceries (remember doing that?). Later conversations turned to vaccines: When would they be available? Were vaccines effective for WMers? Which type might be most effective for us? How many doses did we need? Many of the support group members signed up for the LLS vaccine study that tested antibody levels before and after vaccination. Discussions then moved on to questions about the meaning of test results, which WM treatments seemed to interfere most with developing immunities, and what activities might be safe to resume. As with so much about WM, in many cases the answer seems to be, "That depends. We are each unique."

*Despite **precautions** and sometimes even despite **vaccinations**, some group members have contracted COVID-19.*

Unfortunately, we learned that many of us did not develop much antibody protection from the initial series of one or two doses (depending on vaccine manufacturer). For some of us, an additional dose spurred the development of a much higher level of protection. Our shared experiences validate what the WM expert doctors said at IWMF Ed Forum presentations: immunocompromised people such as WMers have lower antibody responses to vaccinations, and Rituxan further lowers the response rate.

Despite precautions and sometimes even despite vaccinations, some group members have contracted COVID-19. One of our active support group members posted when she first suspected that she might have COVID-19. The group provided encouragement when **CC** tested positive. After contacting her doctor right away, she was immediately treated with Regeneron. CC returned home without requiring hospitalization and recovered with the additional help of lots of water and over-the-counter medicines, and she urged others who contract COVID-19 to request prompt treatment to decrease the likelihood of serious disease.

Unfortunately, not all cases of COVID-19 within our WM community have had good outcomes. The daughter of a French-speaking WMer posted a heartfelt tribute to her father who died after contracting a breakthrough case, "Hello, my dad passed in my arms last night. He had Waldenstrom, got vaccinated, and was about to receive

*From the Facebook WM Support Group, cont. on page 18*

his third dose. He protected himself in everyday life but succumbed to his passion for going dancing as soon as possible, and it was fatal for him. Without a mask, in a room with many people, and with a lot of gullibility, believing himself invincible because of his vaccination" *(translated from French)*.

Numerous posts have discussed decisions about choosing doctors. This community values our medical providers and frequently encourages seeing a WM expert. The consensus is that it is important to have a doctor who is well-informed about WM and who listens to the patient. Some of us prefer to see local oncologists, while others travel to the large medical centers. One wise WMer wrote that she likes to have her doctors get to know her when she's not in a medical crisis, so that they are familiar with her "normal" self.

WMers often ask about others' experiences with a specific treatment. Although they have talked with their doctors and may have even read the IWMF Fact Sheets, they still have questions that can best be answered by someone with personal experience. Here's a typical post. "About to start treatment with zanubrutinib. Was wondering what typical side affects people have experienced and whether the side effects show up right away or a couple weeks down the line." Responses guided the poster to journal articles and IWMF publications, but people also described their own experiences, both positive and negative.

A WMer who had been very concerned about her upcoming treatment later wrote, "I can't thank you all enough for easing my fears. I was OK until they handed you the paper with possible, not probable, side effects. Usually I get the bad ones, but today couldn't have gone more smoothly."

A significant percentage of the posts are from new members, many of them newly diagnosed. Here's the start of a typical post: "This may sound a little left field, but since I'm a newbie I was wondering…" This particular person was concerned about stomach and intestinal issues and whether they might be connected to WM. One responder described having had an enlarged spleen that pressed on stomach and intestines; others mentioned indigestion that cleared up after treatment for WM. Additional comments mentioned causes not related to WM, such as scarring from previous abdominal surgery. The original poster was reassured that her post was not "out in left field," but was instead a concern that others had encountered. In addition, she learned about possible explanations for her symptoms.

Some of our group members are not WMers, but rather their support people. Periodically, **Elaine H** posted about her husband's serious health challenges and received encouragement and practical suggestions. Having supported the two of them through very challenging months, group members rejoiced when she posted, "Wow! Such a good day today for Gary. First, he's had good news about his bloods and paraprotein in the last week, which has really picked us both up for the first time in the last ten months. And today, for the first time since he fell ill in January, I managed to help him out of bed (he's been bedridden since he came home from hospital last May) onto a slider board into his wheelchair. He sat in the lounge with our daughters and grandkids who were visiting. I also cut and washed his hair, which was so much easier for me to do rather than when he's in a bed. What a mental health boost it was for him! He said he feels like he's been out for the day. Well, as soon as the door ramp arrives, he WILL be going outside...just had to share some GOOD NEWS."

> *..."WM is **not** who **we are**. WM is just what **we have**."*

Positive posts are encouraging to the group, while posters who are struggling receive encouragement. As our Zoom Yoga instructor, Ann Grace McMillan, says, "WM is **not** who we are. WM is just what we have."

As I was working on this column, I learned that a dear member of my extended family is dealing with a recurrence of a cancer that is rare like WM. In searching for resources, I found several Facebook groups, with combined membership less than ours and much lower activity. Again, I am grateful for the amazing support and strength of our WM community. Thank you, friends.

This Facebook WM Support Group is active with almost 250 posts a month. To join, you need a Facebook account. There are two simple membership questions to answer; the screening questions help with privacy. Go to *https://www.facebook.com/groups/wmsupportgroup*.

*[Group members' initials, rather than complete names, are used in this column, since the Facebook group is private.]*

# 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/*

NEW SUPPORT GROUP

## JUST A PHONE CALL AWAY

BY PAT GREENLEAF JAMES
PEOPLE OF COLOR SUPPORT GROUP MEMBER

In response to an 80+ year old African American female diagnosed with WM, the People of Color (POC) Support Group was launched in the spring 2021. Her request was in the form of a simple question, "Are there any other African American people like me with Waldenstrom's?"

*Pat James*
*People of Color SG member*

This has been the question for an undetermined number of people of color diagnosed with WM. On a personal note, it would be 25 years before I would find another person of color with my diagnosis, which was in spring 1992. I was 40 years of age. This was a scary time for my husband Larry and me. Because of the complexity and rarity of this disease, we did not share it with our family or friends because we could not explain it. Not only had we never heard of WM, for the next 25 years we were unaware of any other persons (of any race or ethnicity) with this disease. Needless to say, it was exciting for us to discover the International Waldenstrom's Macroglobulinemia Foundation (IWMF) in 2016.

*Today, the IWMF continues its efforts in* ***closing the gap*** *of disparities and resources for POC with WM.*

Spring 2022 marks my 30-year anniversary with WM. My personal journey is chronicled in my book, *The Air I Breathe*. This book is an authentic-humorous-real life-no holds barred account of my experiences with WM.

Today, the IWMF continues its efforts in closing the gap of disparities and resources for POC with WM. The POC Support Group meets virtually on Zoom every other month, the first Friday of the month, from 1:00 to 2:00pm EST. Presently, there are 12 identified members; however, attendance ranges from five to seven persons. Meetings are casual, but highly informative, as we attempt to unravel information about our particular circumstances. Each member has an opportunity to share their experiences and challenges while trying to manage this disease. Several members have issues in addition to or as part of their WM, particularly chronic leukemia lymphoma, lymphoproliferative disorder, and Bing Neel syndrome.

Recently, the POC group had the privilege of an invited guest, Meg Cyr Mangin. Meg is quite familiar with WM, both as a health practitioner and WM patient. She is also an IWMF Trustee and moderator of the WM Support Group on Facebook. Her vast and invaluable input was highly regarded during our Zoom meeting as she answered questions.

We invite you to encourage other POC you personally know or may be familiar with to join our meetings by contacting Michelle Postek, manager of Information and Support at the IWMF.

Thank you, Michelle, for responding to the call which gave birth to this much needed support group. We salute the IWMF in its continuing effort to provide resources to enhance our daily lives as we manage our health needs.

*Spotlight on Support Groups, cont. on page 20*

NEW SUPPORT GROUP

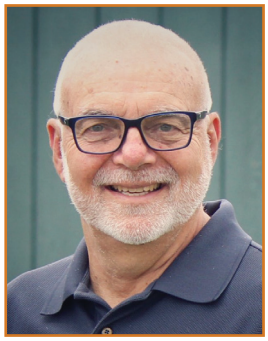
# THE IWMF PLANS CONTINUED SUPPORT FOR WMERS SUFFERING FROM PERIPHERAL NEUROPATHY

The Peripheral Neuropathy (PN) Support Group is getting off to a good start and planning a next session for early 2022. Following a webinar featuring Dr. Todd Levine last April 21, we held four international support session pilot meetings on July 21 and 31. These groups were co-led by seasoned Support Group Leaders Jane Loud, Steve Pine, Joel Rosenblit, Eileen Sullivan, and Bob Ulkus.

Out of 270 people on the PN mailing list, the combined attendance was 54 for the pilot sessions. A follow up survey was sent to attendees, with very positive feedback and requests to have a speaker at the next meeting. Attendees experienced PN as a symptom of WM, PN resulting from treatment, and PN from other and unknown sources. These sessions resulted in the creation of a chart listing various medications, therapies, products, exercises, and treatments patients have used to help manage their PN symptoms. Stay tuned for 2022 details; group leaders are exploring speakers from the fields of neurology, physical therapy, and complementary medicine, while also incorporating time in the sessions for caring and sharing.

To join the PN Support Group mailing list, contact *office@iwmf.com* or call 941-927-4963.

## CO-LEADERS OF THE PERIPHERAL NEUROPATHY SUPPORT GROUP



*Bob Ulkus*

*Eileen Sullivan*

*Joel Rosenblit*

*Steve Pine*

*Jane Loud*

# SURVIVAL TO THRIVING IN A COMMUNITY OF WMERS

By Don Brown

In March of 2002, I was sitting in my office when my newly found hematologist-oncologist called me. "Don, you appear to have multiple myeloma (MM); we need to do more tests." I immediately turned to my computer and looked up MM on the internet—it did not sound good. That Sunday at church a lawyer friend said, "It sounds like you have Waldenstrom's." Ya sure, what is Waldenstrom's? He made a diagnosis based on his personal experience. How could a lawyer know more about cancer than a medical doctor? After further tests, a second opinion at Northwestern Memorial Hospital in Chicago, discussions with my doctor, and the Mayo Clinic's review of my pathology tests, the lawyer had it right. Living in community at our church and having an open-minded physician may have saved my life. It took at least six months to sort things out after 18 plasmapheresis sessions to reduce my dangerously high serum viscosity and five rounds of Rituxan, Fludara, and Cytoxan added later to bring my IgM of 7,500 mg/dL down to the 4,000 level.

The story continued as the IWMF became my centerpiece for living with WM. I was and still am a tennis player and love snow skiing. I had been treated for low hemoglobin and low iron with a vitamin supplement for the two years prior to diagnosis. My family doctor said I was getting old at 59. In early 2002 after sitting down during a tennis game and again while skiing through powder snow in Steamboat, Colorado, I knew something was wrong. It took about six

*Spotlight on Support Groups, cont. on page 21*

*Chicago Area Support Group picnic in 2019*

months to a year and more drugs before I found out about the IWMF and our local support group, which was then led by John Hynes. John had undergone several treatments and, after years of support group leadership, needed help. The late Ron Draftz and I tried to fill his shoes. After John passed away in 2007, Ron convinced me to take on the leadership, but only with his support. My wife, Mary, and I became close friends with Ron and his wife, Germaine. We attended many IWMF Educational Forums and became very active. I was a trustee of the IWMF for six years, and after five grandchildren and a hearing issue, I decided to step down from the Board but kept leading my Chicago Area Support Group, including SE Wisconsin and all of Illinois. We liked our focus on having speakers but felt something was missing—fellowship!

*Don Brown and John Gebhard on a 1904 Oldsmobile at the 2017 picnic*

Meetings and Educational Forums are so important for bringing people together to learn about this rare disease. I attended my first support group meeting in the fall of 2002 and the Reston, Virginia, Educational Forum in 2003. My post-2002 high quality-of-life is the result of learning about treatment options and collaborating with doctors and patients. I've had four major treatments in my 19 years as a patient. Maybe more importantly, getting to know others in our same situation has been the highlight of my journey. The time for fellowship at our meetings seemed so limited. I especially felt that I could not devote enough time to talk with 30 to 50 people during each meeting, so we agreed to experiment with a summer picnic. The first one in 2009 was attended by 20 people, including our two grown children, their spouses, and two new grandchildren. The picnic has since become a popular event each year. The first was held at a local park gazebo and later moved to multiple backyards of members, including a variety of beautiful venues (see photos). One family for several years provided a tent, another had a backyard swimming pool, and our own side patio overlooking a golf course has been used. It became very personal and always involved a time for sharing stories but without speakers. Don's "famous" beer-simmered brats became a featured meal, with many options brought by other members. I will never forget my first oncologist who attended one picnic with a friend of hers. She was so special to me and became a good friend, who still lives as a retired physician in our local neighborhood. Mary spotted her at this year's Fourth of July parade. Hugs were in order!

Things have changed in the last two years with the pandemic, and we all miss getting together in person. Just maybe, the most missed events are the picnics where we share food and stories and enjoy fellowship. I hope and pray 2022 will bring us all back to normal with our fellow patients, caregivers, and families. Thank you, IWMF family, for making Mary's and my Waldenstrom's journey an unexpected blessing.

# A THANK YOU TO DR. VERONIQUE LEBLOND OF FRANCE FROM THE IWMF

By Peter DeNardis, Chair of the IWMF Board of Trustees

On behalf of the global community of Waldenstrom's macroglobulinemia (WM) patients and caregivers who are part of the IWMF, I'd like to extend a message of extreme gratitude to you upon your retirement for everything you've done during your illustrious career to pursue better understanding and better treatments for our disease.

Your commitment to devote precious time and energy to our very rare form of lymphoma is commendable, and over and above what others in your field have done. One could easily gravitate to other, more "populous" or more "popular" diseases, but fate and fortune determined that we (WMers) would be the beneficiaries of your intellect and attention.

The publications that have arisen because of your efforts in focusing on WM since 1995 are too numerous to mention and span the history of WM treatments, from the harsher chemotherapies like fludarabine, to the emergence of inhibitors and antibodies like bortezomib and rituximab, to the more recent and efficacious targeted treatments such as ibrutinib and obinutuzumab.

Through the years, the WM global community has benefited greatly from your leadership role in determining prognostic indices for WM, being a key member of the Scientific Advisory Committee for the IWMF and for the International Workshops on WM, leading the French Cooperative Group on Chronic Lymphocytic Leukemia and Waldenstrom's Macroglobulinemia (FCG CLL-WM), and being responsible for the rare tumor network (K-VIROGREF).

Your efforts and accomplishments have greatly improved what is known about the disease and have set the bar high for the next generation of WM researchers and clinicians. While any new researchers would be hard-pressed to match your achievements, they have the benefit of your work to propel them toward the goal of rendering WM as either a curable or manageable chronic illness, rather than a serious, fatal form of cancer.

The IWMF global community is deeply grateful for everything you've done on our behalf and wish you good health and good fortune as you embark on the next chapter in your life.

*Bonne chance, meilleurs vœux, et profitez de votre retraite.*

*Nous sommes extrêmement privilégiés de vous avoir fait travailler si dur en notre nom, et vous considérerons toujours comme une sommité dans le domaine de la recherche sur la MW.*

# INTERNATIONAL SCENE

EDITED BY ANNETTE ABURDENE

## CANADA

### WMFC News
### By Betty McPhee

The WMFC is excited to report new support group start-ups. The new Manitoba and Friends Support Group launched on September 22, led by Vivian Kachanoski and Elsebeth Hansen-Kriening. The new Oakville/Niagara Falls Support Group launched on October 20, led by Lisa Dickie and Margaret Seliskar.

A national Zoom was held on October 14, 2021. The speaker was Megan Morrison, registered dietitian at the Princess Margaret Cancer Centre Malignant Hematology Program in Toronto. The link to this presentation, "The Role of Nutrition and Hydration," can be found on our website *www.wmfc.ca*.

### A Coincidence and a Friendship Led to a New WM Support Group
### By Stu Boland, Alberta Support Group Co-Leader

It was 1999 when a group of 12 skiers made their first trip to Chatter Creek, British Columbia, for three days of back-country downhill skiing—a snowcat-skiing experience like no other. Living conditions were very rustic. Ski conditions were nothing short of exceptional! The trip was organized by Cam Fraser and some of his friends; Stu Boland was invited to join the group.

Stu and Cam knew each other through a mutual friend. Stu, and Cam and his wife, Jane, lived a few blocks apart in Southwest Calgary. The annual ski "adventure" to Chatter Creek continued for at least three years. Stu's friendship with the Frasers grew.

Fast forward to the fall of 2004.

Stu was still living a few blocks from the Frasers. One day in early September Stu was out for a walk with his "best friends"—two Springer spaniels—on a walking path behind the Fraser home. Jane was working in the yard. She said, "How are you doing, Stu?" Stu's response was, "Not so good, I've just learned that I've got cancer, something called Waldenstrom's macroglobulinemia." Jane's response was, "That is terrible news, Stu. Let me go get Cam and our dog, and you guys can go for a walk together."Within a few minutes Cam and Stu and the three dogs were on a walk, Stu sharing his story of symptoms and the diagnosis. And Cam, much to Stu's dismay, shared that he had recently been diagnosed with the very same rare disease—WM. The friendship became even stronger.

It was in the spring of 2005 that Stu began his first treatment. Cam was on a watch-and-wait program.

*WMFC Chair Cam Fraser and WMFC Trustee Stu Boland*

Over the next few years Cam and Jane and Stu and his wife, Nancy, attended IWMF Ed Forums, initially in Seattle and then Las Vegas, San Diego, and Tampa. Cam and Stu learned, amongst many other things, that there are real benefits to being part of a group whose members face similar situations. By meeting and talking with support group leaders from around the world, it became clear that something needed to be started in Calgary. After numerous discussions, including with the Toronto WM Support Group Leader and Chair of the WM Canada Foundation (WMFC) Arlene Hinchcliffe, Cam and Stu invited a few patients and caregivers to a meeting in the basement of the Fraser home. That was in 2012.

Fast forward to October 2021. Cam has been treated with bendamustine and rituximab and is doing very well. Stu has been treated a few times, and it is six years since a very successful, so far, stem cell transplant. All is good. The small handful of folks who first met in the Fraser basement grew to approximately two dozen Calgary area people. Because of COVID, a group from throughout the province meets on Zoom, about 40 people. Cam and Stu, along with Sari Martin, are the support group leaders. Cam, as of May 2021, is also the chair of the WM Foundation of Canada.

Stu is a trustee of the WMFC. The Alberta group will host its second Ed Forum, COVID be willing, on April 23, 2022, in Calgary. There is absolutely no doubt that being part of a supportive group is extremely rewarding. It is very interesting and co-incidental that two friends, living in the same neighbourhood, were diagnosed with the same rare disease. Cam and Stu are pleased and proud of the fact that

*International Scene, cont. on page 24*

they have been able to grow the Alberta group, that they actively participate in the WMFC, and that they have been able to find comfort for themselves and numerous others.

**Lymphoma Canada - National Patient Conference**
**By Raffaela Mercurio, WMFC Board Member and Toronto/Southwestern Ontario Support Group Co-Leader**

On Thursday, October 14, and Friday, October 15, Lymphoma Canada hosted the 5th Annual Patient Conference. This event was held virtually and included presentations by expert faculty and specialists across Canada. Topics ranged from disease and treatment-specific information, the importance of knowing your lymphoma subtype, how to speak with friends and family about the disease, and COVID-19 updates for patients.

Dr. Sasan Hosseini, from the University Health Network in Toronto, gave a 30-minute presentation entitled "COVID-19 Update for Patients with Lymphoma and CLL." He discussed the variants of concern and their transmissibility and presented a comparison of incidence in the provinces and territories. Some interesting points made regarding vaccination in patients with lymphoma or CLL include:

- Antibody testing not recommended. (Some studies show that these tests are not accurate in patients with hematologic cancers)
- Not necessarily at a higher risk of side effects
- Third dose recommended (Moderna or Pfizer) at least 28 days after second dose
- Fully vaccinated does not mean fully protected (continue practicing preventative measures)

On Friday afternoon there were several breakout sessions in which different lymphoma subtypes were discussed; it was important that WM was chosen as one of them. Dr. Christine Chen from the Princess Margaret Hospital in Toronto presented her 45-minute talk covering the following WM topics:

- Clinical features of WM
- How to diagnose WM
- When to start treatment
- First-line treatment options
- Second-line treatments and beyond
- Special situations

Dr. Chen discussed the importance of careful diagnostic tests to distinguish WM from other lymphomas that clinically look similar. She felt that testing for the presence of the MYD88 mutation was critical because it is important to know this information for the selection of effective treatment. Although not tested routinely (but they are working in this area), it is also valuable to know if the CXCR4 mutation is present. She next listed some clinical and laboratory factors that are used to determine when to start treatment. She mentioned that there is an online predictor where a few laboratory numbers can be entered and the risk of progression from asymptomatic to symptomatic WM can be estimated. This patient risk calculator tool is available at *www.awmrisk.com*.

Dr. Chen's presentation continued with a discussion of treatments: traditional, novel targeted therapies, and new therapies on the horizon. Based on clinical studies, the combination of bendamustine and rituximab (BR) has emerged as the first-line treatment of care in Canada for WM. She also told the audience that maintenance rituximab is no longer routinely used but may be helpful for patients who did not respond well to BR.

She next discussed the BTK inhibitors and noted that ibrutinib is being used more often. The newer BTK inhibitors such as acalabrutinib and zanubrutinib are "tighter" in what they target. Researchers anticipate equal potency and less toxicity with these newer treatments.

The newer therapies that are on the horizon include pirtobrutinib (LOXO-305) and venetoclax. Pirtobrutinib is an interesting BTK inhibitor that does not bind to the same site as ibrutinib, zanubrutinib, and acalabrutinib. It seems effective in patients who have failed ibrutinib, and it is very well tolerated. Venetoclax is a BCL2 inhibitor.

In the last few minutes of the presentation, she gave excellent explanations of hyperviscosity, peripheral neuropathy, Bing Neel syndrome, and WM-associated amyloidosis, plus some treatment options, helpful supportive therapy, and management options.

She concluded her very informative session with three major points. First, WM is now recognized as a unique disease, genetically and clinically. Second, there have been many recent advances in the understanding and management of WM. Lastly, there are exciting new treatments available.

The Lymphoma Canada two-day Patient Conference was filled with many great presentations by excellent speakers who imparted important information for patients and caregivers. To watch and listen to all the sessions go to the Lymphoma Canada website: *https://www.lymphoma.ca/news-events/national-conference-2021*.

**INDIA**
**By Saurabh Seroo, Waldenstrom India**

Waldenstrom India held its second national support group meeting on November 21. We welcomed a diverse group of members, from newly diagnosed patients undergoing treatment to those in remission for many years. As our members shared their stories of overcoming

International Scene, cont. on page 25

Waldenstrom, it was truly heartwarming to see the positivity and determination on display.

Many members spoke about how, after the initial shock of diagnosis, they were determined to stay positive and not let WM affect their mental health. They spoke about how their attitude helped them stay calm and think clearly about their treatment options and not spiral into a negative loop. One of our members, who at the time was one of the youngest patients to be diagnosed with WM in India, spoke about how, in his experience, the process of prevailing over WM began in the mind with an optimistic spirit and hopeful frame of mind. It is deeply inspiring to listen to our members as they talk about their journeys, and we are awestruck by their will and determination to overcome, no matter what.

Since our last update, which featured our member Jaya Mani's heartfelt article, we are in a much better place as a nation. Coronavirus lockdown and restrictions in most parts of India were gradually phased out by June, and our focus shifted toward vaccinating the eligible population. To date, we have fully vaccinated 404 million citizens while a further 364 million have received one dose and are in line to get their second. After a tough second wave in April and May, this is a happy and commendable turnaround for all of us.

As this year comes to an end, we hope that all of us can echo this spirit of determination and hope, which Waldenstrom patients display every day, and that 2022 will be a much better year for all of us. Happy New Year!

## AUSTRALIA

**By Michael van Ewijk, WMOZZIES**

**New treatment for Waldenström's macroglobulinemia now available**

A new treatment for WM has been approved by the Therapeutic Goods Administration for adult patients who have received at least one prior therapy, or in first line treatment for patients unsuitable for chemoimmunotherapy.

Brukinsa (zanubrutinib) was developed by BeiGene, a global, science-driven biotechnology company focused on developing innovative and affordable medicines to improve treatment outcomes and access for patients worldwide.

WMozzies was proud to be invited by the Pharmaceutical Benefits Advisory Committee (PBAC) to take part in a pilot program as consumer advocates in the Brukinsa PBAC decision process.

WM patients will have immediate free of charge access to Brukinsa through a BeiGene sponsored Pre-Reimbursement Access Program, until such time that WM is listed for reimbursement on the Pharmaceutical Benefits Scheme.

**COVAX Lymphoma Study**

The COVAX Lymphoma Study began in May 2021. It had 85 participants—13 health controls, 35 with follicular lymphoma, and 37 with WM. Of the 37 WM patients, 9 were treatment naïve, 14 chemoimmunotherapy treated, 8 on zanubrutinib, 4 on ibrutinib, and 2 on venetoclax. All patients received two Pfizer vaccines two weeks apart. Blood samples were taken at both stabs and 28 days after the second dose. After six months, the WM treatment naïve subgroup showed an antibody response. Of the chemoimmunotherapy subgroup, 71% showed an antibody response. All the zanubrutinib-treated patients had some antibody response but no neutralising activity against the delta variant. Those on ibrutinib had even less antibody response and no neutralising activity to the alpha or the delta strains of COVID-19. The two participants on venetoclax had no response.

Prof Judith Trotman presented a webinar after the results were made known to the study participants. She explained that the BTK and BCL2 inhibitors affected the body's response to the Pfizer vaccine. WM participants on BTK inhibitors appear to have a markedly reduced immune response to two doses of the COVID-19 vaccine. New WM participants are invited to join either the current COVAX-Lymphoma Study or the new TRIBECA study to test their response to a third COVID-19 vaccination dose. For those WM patients using BTK inhibitors, the TRIBECA study is proposed to see whether the vaccination response is increased when there is a temporary (two to four weeks) pause in their inhibitor usage after getting a third vaccine. The third vaccine preferably recommended is Moderna. Participants will stop taking their BTK/BCL2 inhibitors four days prior to the vaccine and try to stay off their medication for four weeks. Blood samples will be taken each week.

## UNITED KINGDOM

**By Kat Tucker, WMUK, Fundraising and Communications Manager**

It has been an exceedingly busy quarter at WMUK, ending with our first virtual conference on 13 November. The day saw over 200 WMers come together to hear from experts and share personal stories online. We heard from clinicians on subjects as varied as COVID-19 vaccines, cryoglobulinaemia, and the importance of sharing data, as well as inspirational stories from long-term patients who shared their advice and learnings. A huge thank you to everyone who attended, especially our speakers who gave their time to help the WM community.

Reaching out to people who haven't found the amazing WM community is important to us. So, in September, we started an ambitious project of sending out leaflets to every haematology department in the UK. Over 500 leaflets have now been distributed, starting with centres we know have at least one WM patient. Working closely with clinical nurse specialists, we aim to get these leaflets into the hands of people living with WM, both newly diagnosed and longer term, so that they know where to turn if they have questions or need support.

*International Scene, cont. on page 26*

After talking with the community, we have learnt how difficult it is for a lot of people with WM to access expert care and support in the UK. We are delighted to announce that we will be launching the WMUK Support Line in 2022. The line will be open to anyone affected by WM, whether patients, families, or friends, who can call or email to speak directly to a health care professional. This vital service will ensure that no WMer is left in the dark about their disease.

To help us get the line up and running as soon as possible, we are asking the WM community to come together and Walk for Waldenstrom's. This virtual event is going to help us raise the £17,000 we need to launch the Support Line. You can join us here: *https://wmuk.org.uk/get-involved/walk-for-waldenstroms/*.

Our support groups continue to be popular. We now have 18 groups; 13 are regionally based, with another five specialist groups for mums, dads, Bing Neel Syndrome, peripheral neuropathy, and supporters of people with WM. Find out more: *https://wmuk.org.uk/support/finding-support/*.

As we enter the new year, we are starting to plan our next projects. As always, we want to ensure that everything we do helps people with WM and their families. If you have any ideas or would like to see us doing something, please reach out to us at *info@wmuk.org.uk*.

One piece of work we will be embarking on early in 2022 is putting together a submission for a National Institute of Health and Care Excellence (NICE) drug appraisal. If you are being treated with zanubrutinib in the UK and are happy to share your experience, please get in touch at *info@wmuk.org.uk*.

We cannot do any of this without the help of donors and fundraisers, and we are always in awe of these amazing individuals. This is just as true for Vicki, Jen, and Rach who ran the virtual Virgin Money London Marathon in October. The sisters decided to take on this monumental challenge when their dad was diagnosed with WM earlier in 2021. They did him, and us, proud, finishing all 26.2 miles and raising £2,441. Thank you so much, ladies!


*Vicky Towers supported the Walk for Waldenstrom's*

We were proud to launch the 2nd Rory Morrison WMUK Registry report last autumn. The report analyses the clinical and quality of life data of over 800 WM patients living in the UK. The findings are helping clinicians and researchers to better understand the disease and the experience of people living with it. Collecting and analysing data both play a crucial role in finding better treatments, improving outcomes, and caring for people living with WM; it is how WMers can make a real and powerful difference in the lives of others. If you live or are treated in the UK and want to ensure your data is a part of this important work, you can find out more on our website: *https://wmuk.org.uk/research/rory-morrison-wmuk-registry/*.

Remember, our Patient Support Manager Bob Perry is there for everyone affected by WM. As the nominated affiliate from the UK and Ireland, he is always open to chat and answer questions. A WM patient for six years, he takes enormous pleasure in bringing together the WM community in the UK and around the globe and to be there to help others. You can get hold of him at *bob.perry@wmuk.org.uk*.


*Vicki, Jen, and Rach raised £2,441 by running the virtual Virgin Money London Marathon in October for their father, who has WM.*

# 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 a 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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If you have discretionary giving power and would like to help move our research program forward in a special way, we invite you to join those listed above. For more information about Research Partners and Named Gift Fund opportunities and potential gifting options that might make that possible, please contact Director of Development and Communications Jeremy Dictor at JDictor@iwmf.com or 941-927-4963.

## BETWEEN OCTOBER 1, 2021, AND NOVEMBER 30, 2021, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN MEMORY OF:

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**Your 2022 IWMF Ed Forum Planning Committee is developing a superb program, with Ed Forum registration opening 1st quarter 2022.**

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