IWMF TORCH

April 2021

Issue 22.2 International Waldenstrom's Macroglobulinemia Foundation

INSIDE THIS ISSUE

A GUIDE TO CXCR4 MUTATIONS AND THEIR IMPORTANCE IN WALDENSTROM'S MACROGLOBULINEMIA

By Steven Treon, MD, PhD, FACP, FRCP

Dr. Steven Treon

Editor's note: Dr. Steven Treon is a professor of medicine at Harvard Medical School and a senior attending physician at the Dana-Farber Cancer Institute. He was elected a faculty member of the American College of Physicians and the Royal College of Physicians (London). His laboratory first identified the MYD88 and CXCR4 mutations and their importance for BTK signaling in Waldenstrom's macroglobulinemia (WM). Dr. Treon was also the principal investigator of the pivotal trial for the BTK inhibitor ibrutinib (Imbruvica) that resulted in the first breakthrough designation by the US Food and Drug Administration (FDA) in oncology, and the first drug approval for WM by the FDA and the European Medicines Agency (EMA). His ongoing interests include development of novel, targeted agents for WM, such as inhibitors for mutated MYD88 and CXCR4 signaling.

Genomic Insights into CXCR4 Mutations in WM

After MYD88 mutations, which occur in 95-97% of Waldenstrom's macroglobulinemia (WM) patients, mutations in CXCR4 are the next most common, occurring in 30-40% of patients. Mutations in CXCR4 almost always occur in those with mutated MYD88, although some WM patients without mutated MYD88 can also have CXCR4 mutations. CXCR4 mutations are essentially unique to WM, with only a few cases reported in patients with marginal zone lymphoma and a subtype of aggressive lymphoma known as ABC diffuse large B cell lymphoma (ABC DLBCL).

In WM patients, CXCR4 mutations are present only in the malignant cells. However, there are patients with a condition known as WHIM (Warts, Hypogammaglobulinemia, Infection and Myelokathexis) syndrome, who are born with mutations in CXCR4 in the same part of this molecule as patients with WM. This area is the C-terminal domain, and patients with WHIM syndrome have the mutation in every cell in their body. CXCR4 is a receptor (a sort of antenna) found on the surface of cells (see Figure 1) that binds to a signaling molecule called CXCL12, a molecule released by cells in the bone marrow known as stromal cells. As a result of CXCL12 binding to mutated CXCR4 in WHIM syndrome, white blood cells go to the bone marrow and become sequestered there, a process known as myelokathexis. This leads to recurring infections and also impacts development of lymphocytes which fight infections, leading to low antibody levels (hypogammaglobulinemia) and viral infections that cause warts in WHIM syndrome patients. WHIM syndrome is very rare, with an estimated annual prevalence of 300 cases/year in the United States. Despite its rarity, the mechanisms surrounding mutated CXCR4 signaling in WHIM syndrome have been

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The *IWMF Torch* is a publication of IWMF. This publication is designed to provide information about the disease Waldenstrom's macroglobulinemia. It is distributed as a member service by the International Waldenstrom's Macroglobulinemia Foundation, Inc., to those who seek information on Waldenstrom's macroglobulinemia with the understanding that the Foundation is not engaged in rendering medical advice or other professional medical services.

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IWMF is a 501(c)(3) tax exempt non-profit organization Fed ID #54-1784426. Waldenstrom's macroglobulinemia is coded 273.3 in the International Classification of Diseases (ICD) of the World Health Organization.

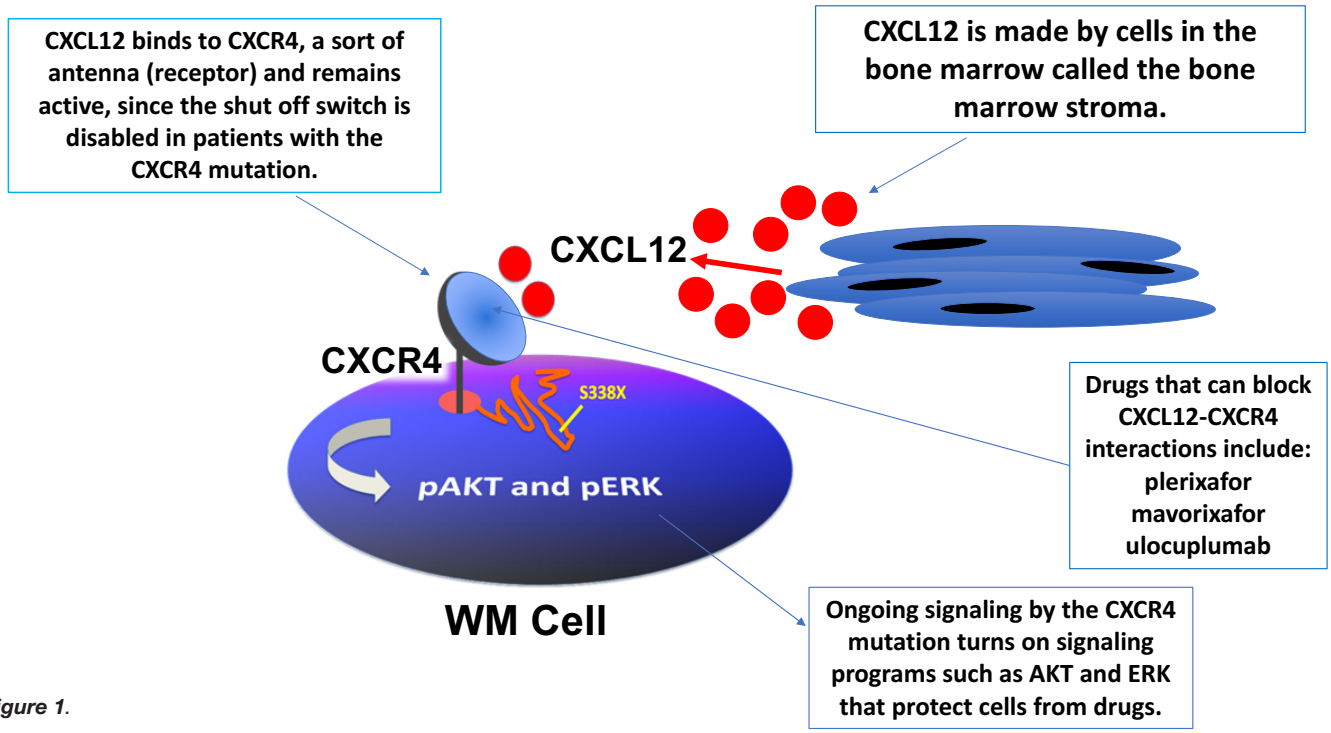

Figure 1.

extensively studied, and they have provided much valuable background information on CXCR4 signaling in WM.

In WM, over 40 different types of mutations in CXCR4 have been discovered. These occur in the C-terminal domain, the same region where mutations occur in WHIM syndrome patients. Mutations in this region come in two general groupings: "nonsense" and "frameshift," with approximately 50% of WM patients who carry CXCR4 mutations falling into each category. "Nonsense" mutations, the most common variant of which is S338X, involve a change in the DNA genetic code that introduces a "stop" signal in the protein that is coded by the CXCR4 gene, leading to part of the CXCR4 protein being cleaved off. Hence the part of the protein that follows a "nonsense" mutation is missing altogether (see Figure 2). Among WM patients with "frameshift" mutations, random DNA is either added or deleted, resulting in a scrambled protein being coded. While the entire CXCR4 protein may be there, the part with the "frameshift" mutation is garbled. There are potential consequences to whether a patient has "nonsense" or "frameshift" mutations, which are discussed later.

These mutations in the C-terminal domain of CXCR4 affect amino acids known as serines, which have important regulatory function. These serines undergo a process known as phosphorylation, where a phosphate group is added and distorts the protein shape in a way that affects binding of other proteins. When CXCL12 binds to CXCR4, the regulatory serines become phosphorylated, changing the conformation of the CXCR4 protein and attracting molecules known as arrestins to shut down CXCR4 signaling. If the serines are missing due to "nonsense" or "frameshift" mutations, the arrestins cannot bind, leading to prolonged signaling by CXCR4. Modeling has shown that this process helps promote WM cell survival and causes drug resistance.

Unlike mutated MYD88, which is present in all WM cells (for those patients that carry this mutation), mutations in CXCR4 are "subclonal," meaning that a fraction of all malignant cells typically have the mutation. On average, about 35% of a WM patient's WM cells actually carry a CXCR4 mutation, but there can be a considerable range from patient to patient. Multiple CXCR4 mutations can also exist within individual patients, and they can occur in separate clones or occur within the same clone. The "subclonal" nature of CXCR4 mutations relative to MYD88 suggests that CXCR4 mutations occur after MYD88 becomes mutated, hence the primary event that induced the malignant state in WM was likely a mutation in MYD88.

There is evidence now based on genetically engineered (transgenic) mice to suggest that having a mutation in MYD88 by itself is unlikely to cause WM or other lymphomas. A second genomic event is likely needed. Current evidence suggests that such "second hits" may involve having a second genomic event such as mutations in CXCR4; deletions involving part of the long arm of chromosome 6 (6q); and mutations in CD79. The latter may be associated with aggressive lymphomas such as ABC DLBCL. In WM, about 30-40% of patients have CXCR4 mutations, and 50% have deletions in chromosome 6q. These tend to be mutually exclusive events, as recently

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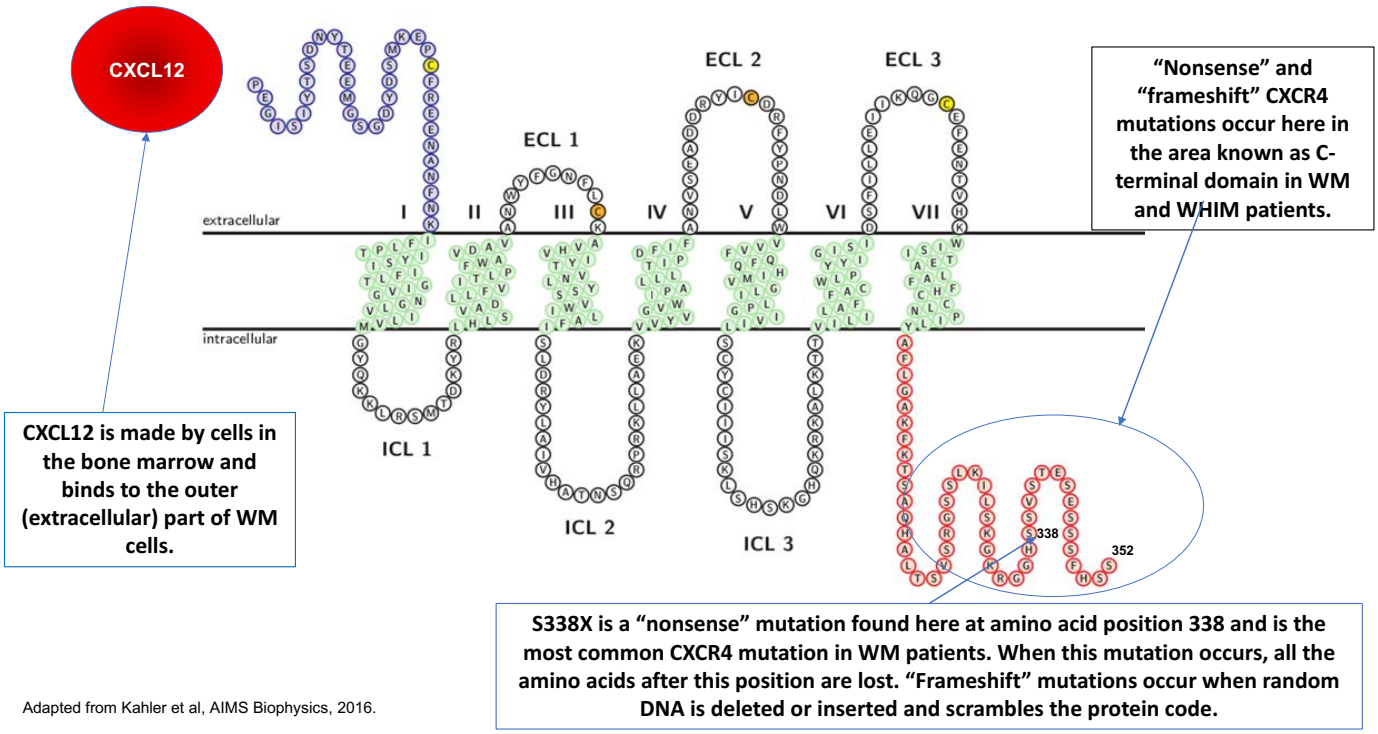

Adapted from Kahler et al, AIMS Biophysics, 2016.

Figure 2.

reported by our laboratory, and may involve triggering similar downstream molecular signaling. Indeed, our laboratory recently described dysregulation of 16 overlapping genes that occurred in patients with either CXCR4 mutations or chromosome 6q deletions. Some of these genes are particularly interesting, since they regulate key pro-survival pathways in WM.

Like MYD88, CXCR4 mutations can impact WM disease presentation. Patients with CXCR4 mutations less commonly have enlarged lymph nodes, and those with "nonsense" CXCR4 mutations have increased bone marrow disease involvement, high serum IgM levels, and/or symptomatic hyperviscosity at diagnosis. "Nonsense" CXCR4 mutations are also associated with acquired von Willebrand factor deficiency, a condition predisposing to bleeding. Despite differences in clinical presentation, CXCR4 mutations do not appear to adversely impact overall survival but do appear to impact time to when treatment is needed. Patients with CXCR4 mutations, particularly those with "nonsense" type, are more likely to need treatment sooner.

Like MYD88, ***CXCR4 mutations*** *can impact WM disease presentation.*

WM cells genetically engineered to express mutated CXCR4 show increased drug resistance in the presence of CXCL12 to multiple therapeutics including ibrutinib. These studies also showed that drug resistance mediated by mutated CXCR4 could be reversed by use of drugs blocking CXCR4 signaling in both cell-based and animal studies.

Impact of Genomic Alterations on WM Treatment Outcome

The impact of MYD88 and CXCR4 mutations on treatment outcome has been evaluated in several clinical trials. Patients with MYD88 mutations who do not have mutated CXCR4 have better outcomes associated with ibrutinib single agent therapy, including time to achieve a major response (i.e. 50% or more reduction in IgM), depth of response, as well as progression-free survival (time the disease shows response to treatment). For those patients with both MYD88 and CXCR4 mutations, a delay by 3-5 months may occur for attaining a major response to single agent ibrutinib when compared to patients with only the MYD88 mutation.

In a recent update of the pivotal trial that supported FDA and EMA approval, patients who carried only the MYD88 mutation achieved five times the number of very good partial responses (i.e., 90% or more reduction in IgM) than did patients with both MYD88 and CXCR4 mutations. Lastly, patients who carried only the MYD88 mutation were far more likely to stay in remission at five years compared to those with both mutations (70% vs. 38%). By comparison, for those without a MYD88 mutation, none achieved a major response, and all progressed much sooner (less than two years) in this study. Earlier disease

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progression has also been observed among patients with both MYD88 and CXCR4 mutations who received ibrutinib plus rituximab in the INNOVATE study, a large randomized trial that compared ibrutinib plus rituximab versus placebo plus rituximab. Depth of response was also impacted in this study, while the time to get to a major response was similar for MYD88-mutated patients with and without a CXCR4 mutation.

In the ASPEN trial that randomized MYD88-mutated patients to receive single agent ibrutinib or zanubrutinib, more very good partial responses were observed among those who received zanubrutinib (28% vs. 19%). While the implications of achieving more very good partial responses in this trial remain to be clarified, it was notable that fewer of these deep responses occurred in CXCR4-mutated patients treated with either ibrutinib or zanubrutinib, signifying the impact of CXCR4 mutation status for both ibrutinib and zanubrutinib response. Deeper responses could potentially impact how long an individual responds and may also be important to those patients for whom IgM is causing symptoms such as neuropathy, cold agglutinins that destroy red blood cells and lead to anemia, and cryoglobulins, where the IgM causes blood vessel blockage during cold exposure.

*...fewer of these **deep responses** occurred in CXCR4-mutated patients treated with either **ibrutinib** or **zanubrutinib**...*

The presence of CXCR4 mutations has also impacted clinical outcomes with other agents. Time to achieving a major (>50% reduction in IgM levels) response was also reported to be longer in those WM patients with CXCR4 mutations receiving the proteasome inhibitor ixazomib-based therapy in a prospective Phase 2 study. Conversely, CXCR4-mutated WM patients treated with carfilzomib-based therapy showed no impact on clinical outcome. In another study, bortezomib-based therapy was shown to overcome the negative impact of CXCR4 mutations on progression-free and overall survival. Hence, the type of proteasome inhibitor may result in different outcomes for those carrying mutated CXCR4. In a retrospective study by the French Innovative Leukemia Organization (FILO) research group, the use of bendamustine plus rituximab resulted in similar progression-free survival among MYD88-mutated patients with and without CXCR4 mutations. Conversely, those without MYD88 mutations showed earlier progression.

While the above studies show that CXCR4 represents an important modulator of drug activity in WM, differences in response outcome may occur based on the type of CXCR4 mutation present, as well as what percentage of cells carry the mutated CXCR4 (i.e., clonality). In one study, patients on ibrutinib with "nonsense" mutations showed fewer major responses as well as shorter progression-free survival compared to those with "frameshift" CXCR4 mutations or those without mutated CXCR4. Since "nonsense" CXCR4-mutated patients are particularly at risk of presenting with symptomatic hyperviscosity and are more likely to require immediate disease control, knowledge of the type of CXCR4 mutation may be helpful in deciding treatment choice.

*The clonality of CXCR4 may also be an **important determinant** of ibrutinib response.*

The clonality of CXCR4 may also be an important determinant of ibrutinib response. A Dana-Farber study investigated the impact of CXCR4 "nonsense" variants on ibrutinib response outcome in WM patients. When patients had greater than 25% of their WM cells carrying the CXCR4 mutation, they were more likely to have greater bone marrow disease involvement and serum IgM levels, fewer very good partial responses, and shorter progression-free survival to ibrutinib.

Given the importance of CXCR4 mutation status in WM, there is great interest in targeting CXCR4 itself. A clinical trial (designated on *www.clinicaltrials.gov* as NCT03225716) assessing the impact of the CXCR4 inhibitor ulocuplumab with ibrutinib in CXCR4-mutated WM patients has completed enrollment, and the results are awaited. Mavorixafor, an orally administered CXCR4 antagonist, is being combined with ibrutinib in an international clinical trial (designated on *www.clinicaltrials.gov* as NCT04274738). Other CXCR4 inhibitors are also being evaluated in preclinical studies.

Molecular Diagnostic Approaches and Limitations

Access for CXCR4 mutation testing continues to evolve, as more medical centers are now including CXCR4 in their molecular diagnostic panels. At present, targeted next generation sequencing (NGS) represents the most widely used approach for evaluating mutations in CXCR4, since over 40 different "nonsense" and "frameshift" mutation types have been reported in WM. This stands in contrast to MYD88 where one single type of mutation variant (i.e., L265P) occurs in 93-95% of WM patients. Much more rarely, 1-2% of WM patients may also express other non-L265P mutations. As such, more sensitive polymerase chain reaction (PCR) testing is frequently used to detect mutated MYD88.

Because CXCR4 mutations are subclonal with a median clonal distribution of 35%, false negatives often occur

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with next generation sequencing, particularly for patients with low bone marrow disease burden. In a study to be reported in the *British Journal of Hematology,* nearly two-thirds of WM patients with mutated CXCR4 had a false negative result by the NGS approach, and the sensitivity correlated with the extent of bone marrow involvement as well as low CXCR4 clonality. Malignant WM cell selection, not practical in clinical molecular diagnostics that use NGS, also played a role. Ultra-deep NGS may improve detection of CXCR4 mutations in patients with low tumor burden and clonality, and such assays are starting to find their way into hospital-based molecular diagnostic labs. Other testing platforms that prioritize "nonsense" CXCR4 mutations, such as digital PCR and cell free DNA, are also being developed, and may allow peripheral blood use for determining both MYD88 L265P and the more common "nonsense" CXCR4 mutations to be evaluated.

Summary

In summary, CXCR4 mutations are commonly found in WM patients and impact disease presentation and treatment outcome, particularly to BTK inhibitors. The subtype of CXCR4 mutations, i.e., "nonsense" or "frameshift," and clonality impact clinical manifestations and/or treatment response to BTK inhibitors. The recognition of CXCR4 mutations in WM has enabled targeted drug development and the potential for a precision-guided, individualized treatment approach to WM. Access and testing accuracy for mutated CXCR4 detection remain important concerns for the widespread use of CXCR4 mutation status for clinical decision-making.

RESULTS OF THE 2021 *IWMF TORCH* SURVEY

YOUR OPINION MATTERS

Thank you to everyone who took the time to respond to our survey about the *IWMF Torch* in February. It had been a long time since we took the pulse of our readership, and we are astounded that over 500 of you completed the survey and offered opinions and suggestions.

It will take a while to digest all this information and figure out what changes we might make to improve our quarterly magazine. Meanwhile, here is a snapshot of some of the findings.

The basic statistical questions showed that 87% of respondents were patients, and, not surprisingly, over 75% live in the US.

The majority of respondents "always read" the cover story, Medical News Roundup, IWMF research project summaries, and human-interest articles, while the majority "sometimes read" International Scene, US Support Group News, From IWMF Connect, and the CEO's article.

Also, the majority of respondents reported that both the technical level and the mix of articles are "very effective" or "effective." Article density had the most respondents report that they were "not effective" (24 people). For frequency of donor recognition, 53% of respondents indicated that the annual report is sufficient, compared to 44% of respondents who would like to see quarterly recognition.

As for usefulness to readers of two of the regular sections, the IWMF Connect summary is considered useful to 82% of its readers, while Support Group News is useful to 68%.

We greatly appreciate all the comments submitted about the *Torch:* what readers like, don't like, would like to see covered, and in what way. We will be referencing these two hundred thoughtful comments constantly in the future, as we make decisions on how to improve the *Torch*. Thank you again for a very successful and useful survey!

TODAY, TOMORROW, AND BEYOND

IWMF Launches the Carl Harrington Accelerate the Cure Campaign

By Newton Guerin, IWMF President and CEO

The IWMF has undertaken a special campaign to recognize and honor Chair Emeritus Carl Harrington for his incredible contributions to the IWMF's growth and success. We are well on our way in conducting the Carl Harrington Accelerate the Cure Campaign. It is modeled after a traditional capital campaign, with proceeds supporting all IWMF mission programs.

Newton Guerin

Like a capital campaign, we have completed the quiet phase of securing lead gifts. Our primary audience for the quiet phase included our major gift donors, our existing pharma partners, and the broader corporate community. This campaign provides an opportunity to engage additional corporate partners where we may already have a relationship through a Board member, donor, patient, or caregiver. As IWMF Board Chair Pete DeNardis commented when reflecting on Carl's accomplishments, "What better way to honor Carl than for this campaign to begin opening doors to the broader corporate community!"

Carl Harrington served as IWMF Board chair from 2012 through 2020. During his eight years as our leader, the IWMF experienced tremendous growth in our mission programs as well as revenue generation. Carl was able to accomplish all that he did because he treated his non-paid, volunteer position as a full-time job and excelled at whatever he did on behalf of the IWMF. He placed an emphasis on generating an income stream that could support the ambitious mission of the IWMF by investing in building an effective, efficient, and sustainable fundraising infrastructure.

In 2019, Carl led the IWMF Board through a strategic planning process focusing on our organizational priorities and what we should do to have the greatest beneficial impact to the global WM community. From those discussions, the Board crafted six Compelling Intentions (see *https://iwmf.com/vision-and-mission/*), which provide guidance and direction and help tell our story to all IWMF stakeholders. This organization-wide plan will continue to drive the transformation of the IWMF for years to come and may be looked upon as one of Carl's greatest accomplishments.

Carl's contributions to the IWMF have influenced every aspect of what we do. Here are just a few:

Research – The IWMF partnered with the Leukemia & Lymphoma Society (LLS) in 2015 to begin a Strategic Research Roadmap Initiative for WM, creating a global plan for research that identifies priorities for improving our understanding of WM. Of the total $18 million in research grants funded by the IWMF since 1999, $10 million was funded as part of the Roadmap. Research funding by the IWMF is critical, as evidenced by the fact that IWMF-funded research has led to FDA approvals for new therapies that result in better outcomes for patients with WM. In fact, the number of treatments available since the IWMF was founded has increased from four to 40. Over this same period, life expectancy for those newly diagnosed with WM has increased from 3-5 years to 16-20 years, further proof that IWMF funding yields concrete results that benefit WM patients around the world.

Education – Each year, Carl encouraged the IWMF to further enhance the sessions offered at the IWMF's Educational Forum, and each year, attendance increased significantly (there were 350 people in 2019—a far cry from the handful of participants in 1999). He remained undaunted by the COVID pandemic and steered the course toward the first ever Virtual Ed Forum in 2020. It was our 25th and by far our largest ever. Participation exceeded 1,400 people, representing over 30 countries throughout the world, who joined to hear uplifting and encouraging updates from leading experts in the field of WM.

Information and Support – Our network of support groups throughout North America and the world, who do so much to keep their members connected and informed, has grown to over 80. Our global presence continues to expand through our 22 international affiliates.

Funding – None of this incredible growth could have happened without a significant increase in revenue. During Carl's eight years as chair, income increased from just over $1 million to over $4 million. He did this by:

- Creating an organizational culture that sought out and pursued all opportunities for revenue generation.
- Developing and fostering relationships with many of our major gift donors.
- Spearheading our outreach efforts and relationship building with our pharma partners from inception to now generating over $400K in annual revenue. These sponsorship dollars fund some of our most important programs, including: the Ed Forum, the *IWMF Torch*, support groups worldwide, publications and translations of publications into other languages, and

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the recent upgrade of our website (*www.iwmf.com*) to better meet the needs of the global WM community.

- Fostering the growth of the IWMF's signature fundraising event, Walk for Waldenstrom's, which provides participants a great way to raise money while creating awareness about WM and its impact on the lives of patients and caregivers.
- Creating a global effort to fund Research Roadmap projects with like-minded organizations, including the WM Foundation of Canada (WMFC) and the Leukaemia Foundation of Australia (LFA).
- As we move forward with this campaign, we will continue our strong commitment to good stewardship of our donor dollars, ensuring that we retain our top rating from Charity Navigator (the largest watchdog agency for nonprofits in the US). The IWMF achieved a Charity Navigator overall score of 95.59 on a scale of 100, and a 100 rating on accountability and transparency. This is the IWMF's third consecutive 4-star rating from Charity Navigator. Fewer than 25% of the organizations reviewed by Charity Navigator have received this ranking three years in a row.

*Our **hope** is that gifts to the Carl Harrington Accelerate the Cure Campaign will be **above and beyond** the amount that folks normally give...*

Carl's leadership can best be described through his own words, "I can see a world without WM, and it's a marvelous place. If we all work together, we can get there."

We welcome your thoughts, ideas, and advice about this campaign and encourage you to support this effort as generously as you can. Our hope is that gifts to the Carl Harrington Accelerate the Cure Campaign will be above and beyond the amount that folks normally give to the IWMF on an annual basis, to properly show our appreciation and acknowledgment of Carl's accomplishments on our behalf.

A special reply envelope is included in this edition of *Torch* or please visit *www.iwmf.com* and click on the donate button.

More details will follow. As always, we thank you for your support!

IWMF-FUNDED RESEARCH: NEW 2020 GRANTS

BY GLENN CANTOR, IWMF TRUSTEE AND SCIENCE EDITOR

Editor's Note: In 2020, the IWMF selected and funded two Strategic Research Roadmap grant proposals. The grant proposal from Dr. Zachary Hunter, "Multi-omic analysis of DNA, RNA, and epigenomic networks for prognostication and novel target identification of WM," was described in the January 2021 issue of the Torch*. This article describes the second grant proposal.*

Dr. Ruben Carrasco, Dana-Farber Cancer Institute, Harvard University, Boston, MA, USA

MYD88 L265P signaling-associated multiplex characterization of the bone marrow microenvironment in WM patients for clinical application

In this IWMF-funded project, Dr. Carrasco's lab at the Dana-Farber Cancer Institute at Harvard will harness new and powerful digital pathology and artificial intelligence technology for better diagnostics and understanding of WM.

More than 90% of WM patients have a mutation of the MYD88 gene, resulting in an altered protein called MYD88 L265P. The altered MYD88 protein drives abnormal signaling, which is key to survival and growth of WM cells. Detection of the MYD88 mutation in the DNA of WM patients' bone marrow samples using polymerase chain reaction (PCR) testing is one of the cornerstones for making the diagnosis of WM. Dr. Carrasco proposes a simpler, faster way to identify cells with mutated MYD88. As a pathologist who examines bone marrow cells under the microscope, he has detected an interesting feature of WM cells—the mutant MYD88 protein forms distinctive microscopic aggregates inside the cells.

*Dr. Carrasco proposes a **simpler, faster way** to identify cells with mutated MYD88.*

The aggregates appear to be composed of large complexes of multiple proteins, which include the mutant MYD88 protein, associated intracellular signaling proteins, and several cell surface proteins called TLR9 and BCR. Interestingly, Dr. Carrasco first detected these MYD88 aggregates in genetically-engineered mice, during an IWMF-funded project to create a clinically relevant mouse model of WM, in which the mice were altered so that they expressed human MYD88 L265P in their activated B cells. He then checked human WM cells and found that patients carrying the mutated MYD88 had similar MYD88 aggregates, while those patients

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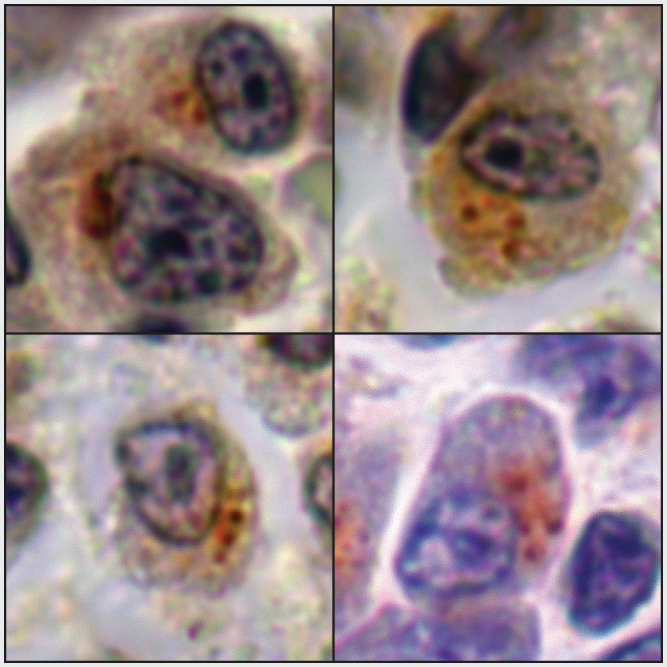

WM cells stained to show MYD88 L265P aggregates (golden-brown). Four separate photomicrographs are shown here. The cells are out of focus, because the photomicrograph images are taken at such a high magnification that only a tiny area of the three-dimensional cells is in focus at one time, while the rest of the image is unfocused. The aggregates inside the WM cells are composed of multiple proteins, all loosely attached to each other. The proteins include the mutated MYD88 protein (known as MYD88 L265P), together with intracellular and cell-surface signaling proteins. The large, dark, approximately circular structure inside each cell is the nucleus.

with unmutated or "wild type" MYD88 protein did not have the aggregates.

Using a technique called immunofluorescence, the microscopic aggregates of mutant MYD88 can be labeled in the lab with special antibodies that bind to mutant MYD88 and are linked to a bright, fluorescent dye. This bright dye makes the MYD88 aggregates stand out when a pathologist examines a slide under the microscope. This technique is called "immunostaining."

When a new technique is proposed, it must be validated to ensure it is accurate and reliable. A new technique must be shown to be sensitive (able to detect small numbers of abnormal cells) and specific (does not mistake a normal cell for an abnormal one). The new technique must work in a wide variety of patients, using the type of samples normally received in a pathology laboratory. In this project, Dr. Carrasco will attempt to validate this new method. He will also evaluate the presence of MYD88 aggregates in patients with the precursor disorder IgM-MGUS (monoclonal gammopathy of undetermined significance) and with different stages of WM—asymptomatic watch-and-wait, early disease, more severe disease, after treatment, and in patients who are relapsing or who have transformed to a more aggressive cancer, such as diffuse large B cell lymphoma (DLBCL).

One use of this new technique would be to assist in a more rapid and less expensive diagnosis of WM in clinical laboratories around the world. Additionally, the technique could be quantitative, that is, a pathologist could use cell counting techniques to determine how many cells in the bone marrow sample express the mutant MYD88 protein. This might help to better determine disease severity and stage of progression.

The technique might also be useful for identifying patients who still have residual disease after therapy and might help to distinguish WM from marginal zone lymphoma (MZL), another low-grade B cell lymphoma that resembles WM. The project will also investigate whether the presence of MYD88 aggregates correlates with changes in the bone marrow microenvironment.

[Immunostaining] also has ***potential to improve*** *our understanding of WM and how it works*

The technique also has potential to improve our understanding of WM and how it works. Presently, a sample is taken from a patient's blood or bone marrow, DNA is extracted from the sample, and the DNA is analyzed for the MYD88 mutation. If the mutation is present in the sample, it is not possible to figure out which cells have the mutation and which cells do not. Using Dr. Carrasco's new method, it might be possible to specifically pinpoint individual cells on a microscope slide that have the mutant MYD88.

A major IWMF Strategic Research Roadmap goal is to better understand the bone marrow microenvironment that sustains WM cells and allows them to survive and grow. Within the complex bone marrow microenvironment, different cell types interact with WM cells at close range. Some cells in the bone marrow enhance the survival or

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growth of WM; other cells in the bone marrow attack the WM cells and kill them.

An advantage of Dr. Carrasco's new technique is that WM cells with mutant MYD88 could be efficiently visualized in bone marrow biopsy samples, in the context of the other cells that surround them.

To identify these different cell types, Dr. Carrasco's lab will use many different stains at the same time, in a technique where each of the different stains produces a different color. This method, called multiplex immunofluorescence, allows the simultaneous detection of many cell markers on a single tissue section. This will enable Dr. Carrasco and his group to identify the cells that are interacting with the WM cells in the bone marrow. Differences in the cell numbers, subtypes of cells, and patterns of their distribution within the bone marrow will be correlated with clinical features and disease progression.

This type of analysis requires examination of a large number of cells and quantitative analysis. To avoid misleading results, it is not enough to observe a cell here and there that is located next to another one. Dr. Carrasco has set up a collaboration with a group at Harvard that can take images of the slides after they are stained and then use digital imaging technology to score the fluorescent markers on thousands of cells and their precise locations. Then, using artificial intelligence that has been developed for this type of analysis, the Harvard scientists can analyze interactions of the WM cells with other bone marrow cells, including cells of the immune system. Some of these immune cells are likely to attack the WM cells; others are likely to prevent an attack.

Several drugs are currently available to alter the bone marrow microenvironment and improve the body's immune response to attack cancer cells. Many more such drugs are in development. A better understanding of how WM cells manage to survive and proliferate in the bone marrow may enable WM physicians to use these drugs in a tailored way to more effectively treat WM.

IWMF-FUNDED RESEARCH: PROGRESS REPORT

By Glenn Cantor, IWMF Trustee and Science Editor

Editor's Note: In this ongoing series of articles, the Torch *will update the WM community on progress by IWMF-funded researchers. At the recent 2020 American Society of Hematology (ASH) Annual Meeting, Dr. Sara Rodríguez presented conclusions from the project described below. Key co-contributors to the project were Drs. Ibai Goicoechea and Jon Celay.*

Bruno Paiva and José Ángel Martínez Climent, Clinica Universidad de Navarra, Pamplona, Spain

Single-cell next-generation flow and sequencing to unravel the pathogenesis of WM and design genetically-driven human-like experimental models

In an IWMF-funded project, Drs. Sara Rodríguez, Ibai Goicoechea, and Jon Celay, working in the laboratory of Drs. Bruno Paiva and José Ángel Martínez Climent in Pamplona, Spain, studied the early development of WM in the body. Potentially, if WM could be identified at very early stages, early treatment and better control might be possible. A well-known hallmark of WM is a mutation of the MYD88 gene, resulting in a change in one amino acid (leucine) to another (proline). This is called MYD88 L265P. (L is the symbol for leucine, 265 is the position of the mutated amino acid, and P is the symbol for proline.) The MYD88 L265P mutation is so common in WM that molecular detection of MYD88 L265P is part of the diagnostic criteria.

However, the switch from normal (called "wild type") MYD88 to mutated MYD88 L265P is not unique to WM. MYD88 L265P is also seen in some other B cell cancers, including one type of diffuse large B cell lymphoma, marginal zone lymphoma, and others, and is also seen in a precursor condition, IgM-MGUS (monoclonal gammopathy of undetermined significance). So, MYD88 L265P alone is not enough to explain why a patient would develop WM and not some other B cell malignancy.

Normally, B cells and plasma cells develop in a well-orchestrated series of steps, starting with a parent cell called a hematopoietic stem cell, which then matures in stages from a pro-B cell to a pre-B cell to a mature B cell and, eventually, to a plasma cell. (For more information on these development

Research: Progress Report, cont. on page 11

stages, there is a great article in the January 2020 *Torch* by Dr. Irene Ghobrial at *https://iwmf.wpengine.com/wp-content/uploads/2020/10/Torch_January2020.pdf*).

Knowing this series of well-defined maturation stages, the group asked at which stage the mutated MYD88 L265P first appears. If MYD88 L265P is the sole cause of WM, then they expected to find MYD88 L265P only in the cancerous WM cells and not in the early-stage cells. On the other hand, if MYD88 L265P is found in early-stage cells that do not have the characteristics of WM cells, it implies that MYD88 L265P alone is insufficient to produce WM and something else is required.

The researchers took bone marrow cells from ten WM patients, isolated the B cells and their various precursor stages, and sequenced the genes at each stage. Surprisingly, they found one patient in which the very earliest stage, the hematopoietic stem cell, had the MYD88 L265P mutation. In addition, six of eight patients had MYD88 L265P in early-stage B cell precursors, while all the patients had MYD88 L265P in their mature B cell and plasma cell populations. This suggests that in some people, the MYD88 L265P mutation occurs at an early stage, but the MYD88 L265P mutation is not the event that pushes cells over the edge to form actual WM. Something else, some other genetic change, is likely required as well.

*...are there **gene changes** in addition to MYD88 L265P that could be driving **progression** to WM?*

The body normally makes B cells with a huge variety of different detector proteins called BCR (B cell receptor). Because of the large variety of these detectors, the body can recognize, respond to, and defend itself against the wide number of different pathogens and other foreign material in our environment. Although there is a large number of different BCRs, the population of B cells with any one specific BCR is normally small. But in WM, one cell initially multiples excessively, resulting in many daughter cells with the same BCR. The process starts slowly. At first, there is a barely detectable increase in abnormal B cells with the same BCR (called a "clonotype"). As time goes by, the abnormal B cells, all sharing the same BCR, become more and more numerous until full-fledged WM develops, sometimes years later.

The group wanted to find out how early this abnormal multiplication of clonotypes starts. To do this, they sequenced the DNA encoding the BCR of thousands of cells from WM patients. They found that in some patients, expanded clonotypes—large groups of cells with the identical BCR—were found in B cell progenitors, well before actual WM appeared. Then, they looked at gene changes in these abnormal clonotypes. Is MYD88 L265P the only abnormality? Or are there gene changes in addition to MYD88 L265P that could be driving progression to WM? In some patients, as expected, they found changes that are already known—mutations of a gene called CXCR4 or deletions of part of chromosome 6. Beyond that, they found approximately 100 other unique mutations. Some might be relevant to WM; others might be just coincidences and not actually causing WM. Clearly, there is more to learn from future research.

*The work with human patients suggests that the **MYD88 L265P mutation** alone is insufficient to cause WM.*

In a parallel project, Dr. Jon Celay, a post-doctoral researcher in close collaboration with Dr. Rodríguez and Dr. Goicoechea, wanted to make genetically-engineered mice with WM. Mice with WM could be useful tools for WM researchers around the world. New drugs could be tested in these mice, and they could be used to better understand the basic biology of the disease. To make mice with WM, they inserted a mouse version of the MYD88 L265P gene and further engineered the mice so that the MYD88 L265P would be expressed in each of the different stages of B cell development, respectively. Despite the presence of mutated MYD88, however, they found that none of the mice developed WM, even when the mice grew older.

The mice with MYD88 L265P had a moderate increase in some cell types, especially early and mature plasma cells, but none of the mice developed WM. They didn't even have subtle signs of early WM, such as expansion of clonotypes. This was frustrating news, but it reproduced very recent findings by Dr. Ruben Carrasco's laboratory at Dana-Farber Cancer Institute. The work with human patients suggests that the MYD88 L265P mutation alone is insufficient to cause WM. Similarly, in the mice, it was also insufficient to cause WM. The two lines of research—human patients and mice—come together to reinforce the conclusion.

What's next? The more we study WM, the more complicated it becomes. It is not enough to have mutated MYD88. Researchers around the world are trying to identify other gene mutations that act together with MYD88 L265P to cause WM. For example, Drs. Zachary Hunter and Steven Treon found that many patients have not only MYD88 L265P but also mutated CXCR4. This discovery led to several interesting clinical trials to see if these WM patients would benefit from combination treatment that includes a CXCR4 inhibitor. Hopefully soon, researchers will discover additional mutations that lead to optimal personalized treatment combinations.

ADVOCACY UPDATE ON US HEALTHCARE LEGISLATION

By Bonnie Beckett

Bonnie Beckett follows healthcare legislation informally for the IWMF. She retired from a 25+ year career at the US Government Accountability Office (GAO) where she researched and wrote reports and testimonies for Congress. She regularly attends a variety of meetings for the IWMF hosted by the Rare Disease Legislative Advocates (RDLA), National Organization for Rare Disorders (NORD), Rare Disease Congressional Caucus, and Community Congress of the EveryLife Foundation for Rare Diseases, as well as events such as Rare Disease Week on Capitol Hill, NORD Rare Diseases and Orphan Products Breakthrough Summit, and World Orphan Drug Congress.

As I write this article in February, Congressional focus remains on economic recovery and COVID-19 testing, contact tracing, and access to the vaccines. Many healthcare-related bills have not yet been introduced in the current legislative session and do not have Senate or House bill numbers. The information below focuses on legislation most likely to be introduced soon that is of interest to WM patients, as well as relevant issues that could emerge in legislation.

Legislation likely to be introduced soon

STAT Act (Speeding Therapy Access Today of 2021) is in the final stages of drafting.

- Improves rare disease coordination, stakeholder engagement, and policy development within the Food and Drug Administration (FDA) by expanding existing authority to create a Rare Disease Center of Excellence.
- Informs rare disease policies and the development of innovative approaches to drug approval through a Rare Disease and Conditions Drug Advisory Committee.
- Funds the development of best practices and research to support development of therapies to treat very small populations.
- Strengthens rare disease patient access to FDA-approved therapies in both public and commercial plans through enhanced FDA-CMS (Centers for Medicare and Medicaid Services) coordination, proactive engagement of payers, and specific actions intended to strengthen Medicare and Medicaid beneficiary access to novel therapies.

PDUFA VII (Prescription Drug User Fee Act) originally passed in 1992, needs to be reauthorized every five years; it expires September 30, 2022.

- Authorizes FDA to collect fees from companies that produce certain human drug and biological products.
- Mandates patient/caregiver engagement in study and clinical trial design.

Bonnie Beckett at Rare Disease Week on Capitol Hill

- Incorporates real-world evidence (what matters to patients) in regulatory decision-making.
- Provides a dedicated process to improve use of biomarkers as surrogate endpoints in drug development.
- Works with the FDA on development and dissemination of new drugs.
- Provides needed resources, including staff funding, for the FDA to review new gene and cell therapy treatments.
- Encourages the FDA to increase diversity in drug trials and to increase the rare disease drug pipeline.

The reauthorization of PUDFA VII is an opportunity to improve the drug approval pipeline for rare diseases at the FDA.

Appropriations priorities

- National Institutes of Health (NIH) – Increase funding for rare disease research and rare disease clinical research network; end the diagnostic odyssey.

Advocacy Update, cont. on page 13

- FDA – Increase investment in infrastructure and research; add funding for natural history studies and small population studies.
- CDC (Centers for Disease Control and Prevention) – Encourage use of ICD codes (International Classification of Disease codes) for rare diseases for ease of research.

Cures 2.0

- Builds on the framework of the 21st Century Cures Act passed in 2016.
- Aims to further modernize the nation's healthcare pipeline in the hopes of avoiding some of the burdens the system has faced during the COVID-19 pandemic.

Proposed policy areas include public health and pandemic preparedness, healthcare delivery systems, patient engagement in healthcare decision-making, caregiver integration into the care team, modernizing CMS, and increasing diversity in clinical trials.

Issues with past or new legislation that may be introduced

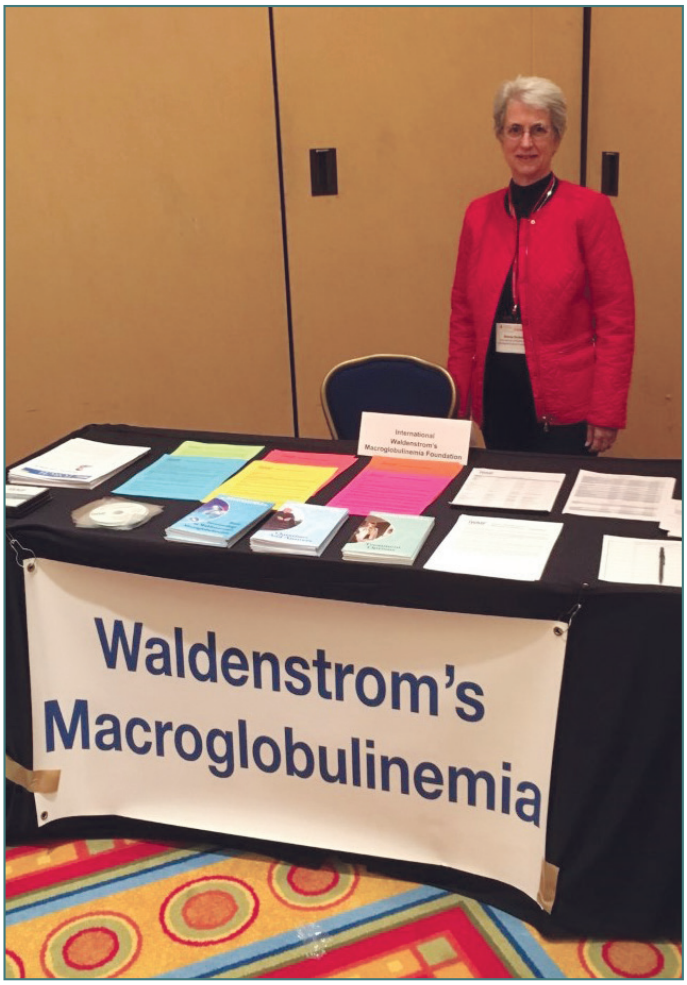
Several past bills were aimed at lowering prescription drug prices or total healthcare costs. Remaining issues include:

Medicare

- Limit out-of-pocket costs with a Part D redesign—all other forms of insurance have catastrophic caps.
- Modify legislation so that Medicare can negotiate prescription prices (the Veterans Administration has this authority).
- Lower eligibility age to 60.

Oral parity

- Lower the patient cost of oral cancer drugs by treating them the same way as infusions for billing and insurance purposes rather than as prescription drugs.



The IWMF table at the National Organization for Rare Disorders Summit

Telemedicine

- Allow for insurance charges for telemedicine visits and to permit doctors to practice telemedicine across state lines.

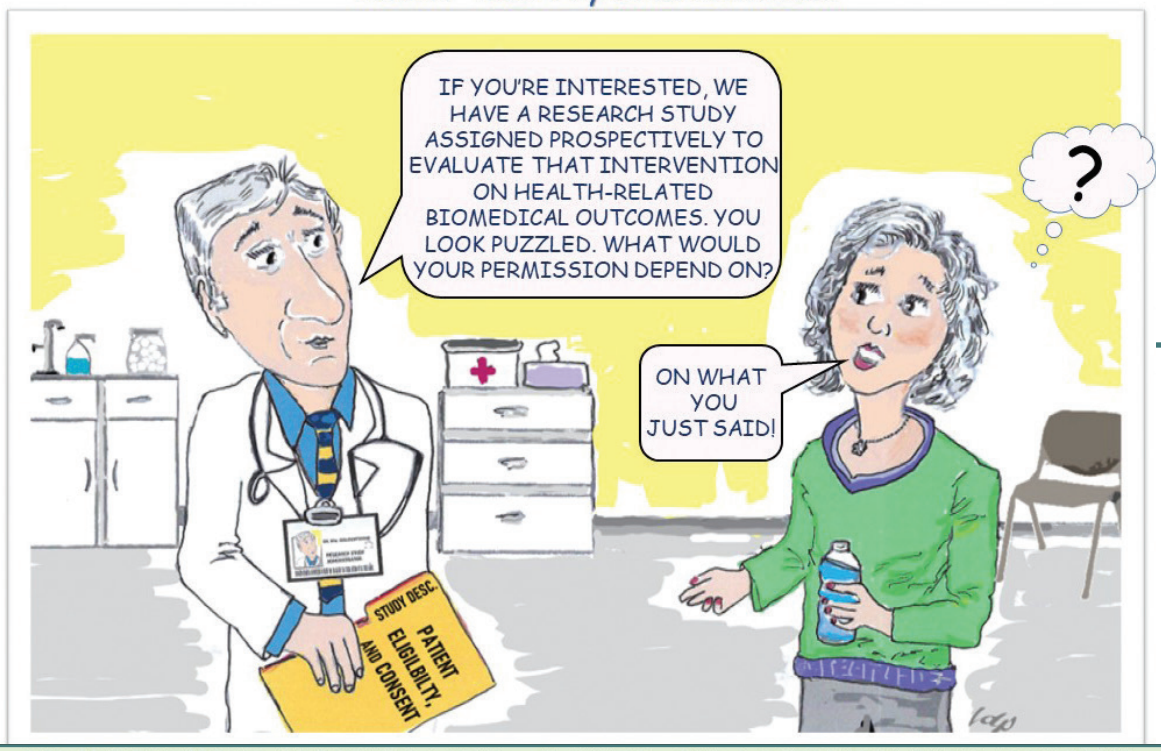
Have Your Say

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*

Linda (on right) enjoys a wine tasting in the Seattle area with (left to right) Torch *Editor Shirley Ganse, former IWMF Trustee Marlyn Friedlander, and staff member Sara McKinnie in the summer of 2019.*

It is with great sadness that we report the passing on March 1 of Linda Pochmerski, our fun-loving, self-described "Jersey girl" cartoonist, from WM complications. Linda was born in New Jersey and in 1980 moved with her husband Bill to the Seattle area, where she worked first at Lockheed Shipbuilding and then at Boeing as a spare parts analyst, the job from which she retired. Her WM was diagnosed after retirement, and in 2007 she connected with the IWMF. Alice Riginos, the second editor of the *Torch*, asked her to draw WM-relevant cartoons, and Linda eagerly took up the challenge. Her first cartoon appeared in the 10th anniversary issue of the *Torch* in October of 2008, and we've been enjoying her wit and sense of humor ever since. The staff and readers of the *Torch* will miss her regular artistic offerings, including the antics of Wally and Winnie, the model mice, who debuted in the 15th anniversary issue in October 2013.

TORCH TOON by Linda Pochmerski



BEFORE ENTERING A RESEARCH STUDY, TALK TO YOUR DOCTOR TO LEARN ABOUT THE RISKS AND POTENTIAL BENEFITS.

SELECTED HIGHLIGHTS FROM THE 2020 AMERICAN SOCIETY OF HEMATOLOGY (ASH) ANNUAL MEETING

By Glenn Cantor, IWMF Trustee and Science Editor

This article reviews some of the more interesting research with potential application to WM that was presented during the 2020 American Society of Hematology (ASH) Annual Meeting held virtually last December.

LOXO-305: A Next-Generation, Highly Selective Non-Covalent BTK Inhibitor in Previously-Treated Mantle Cell Lymphoma, WM, and Other Non-Hodgkin Lymphomas: Results from the Phase 1/2 BRUIN Study – Presented by Michael Wang, MD Anderson Cancer Center, Houston TX, USA

Ibrutinib inhibits a protein inside cells called BTK, which is part of a chain of signals to the WM cells to grow and proliferate. Unfortunately, BTK is not the only signal disrupted by ibrutinib. Unintended inhibition of signaling proteins other than BTK can lead to some side effects seen in WM patients on ibrutinib therapy.

In an effort to improve the safety of BTK inhibitors, second-generation drugs were developed. These second-generation drugs, including acalabrutinib and zanubrutinib, are more specific, in that they inhibit their intended target, BTK, but have less effect on other signaling proteins. This increase in specificity has been shown to reduce some of the ibrutinib side effects such as atrial fibrillation and hemorrhage. But, a problem with all three of these BTK inhibitors—ibrutinib, zanubrutinib, and acalabrutinib—is that patients' WM cells eventually begin to grow again. While the reasons for this regrowth are not entirely understood in WM, pharmaceutical companies are trying to discover and develop next generation BTK inhibitors to address this challenge. One of these next generation BTK inhibitors is LOXO-305. While still in early clinical trials, its results are interesting. LOXO-305 is a specific BTK inhibitor, and is additionally differentiated from the first and second generation BTK inhibitors by its ability to inhibit the BTK target all day long.

A Phase 1/2 clinical study of LOXO-305 included 323 patients, with the Phase 1 portion determining the best dose and the Phase 2 portion using this dose to evaluate safety and efficacy. Patients had a variety of B cell lymphomas, including 26 patients with WM. The WM patients had all been treated with other drugs previously, with 69% receiving prior BTK inhibitor treatment.

The safety results showed that the typical side effects seen in the other BTK inhibitors (called adverse events of special interest) were markedly reduced. These included bruising, rash, sore joints, hemorrhage, hypertension, and atrial fibrillation or flutter. Of all the 323 patients in the study, none had grade 3 or 4 treatment-related adverse events of special interest, and less than 1% had grade 3 or 4 treatment-related fatigue. Even the incidence of less severe adverse events looked promising—less than 1% had grade 2 atrial fibrillation/flutter; 4% had grade 2 or 3 hypertension; 1% had grade 2 hemorrhage (plus one patient who had a non-drug-related bicycle accident and developed grade 3 hemorrhage); and 2% had grade 2 bruising. Altogether, only 1.5% of patients discontinued the trial due to treatment-related adverse events.

*It is **worth paying attention** to the progress of LOXO-305 and other next-generation BTK inhibitors...*

In the WM group, of 19 patients evaluated for efficacy, the overall response rate (ORR) was 68%, which included 47% with a partial response and 21% with a minor response. None of the patients had complete responses (CR) or very good partial responses (VGPR). The response rate was similar in the subset of patients who had been pre-treated with other BTK inhibitors.

One note of caution is that this is a small, early study. As more patients are treated and followed for a longer period of time, the safety and efficacy results may change. The study only examined efficacy in 19 WM patients. Also, the study was designed to evaluate monotherapy (only LOXO-305). Results might be different when LOXO-305 is given in combination with other drugs. Nonetheless, this is an interesting new drug. Even if it ultimately proves to be not as effective as the more established BTK inhibitors, it may play a role in treating patients with resistance to other BTK inhibitors or for patients who are more prone to side effects. It is worth paying attention to the progress of LOXO-305 and other next-generation BTK inhibitors during their future clinical development.

Monoclonal Gammopathies of Determined Significance: Management of Waldenström Macroglobulinemia in 2020 – Educational program presented by Jorge Castillo, Dana-Farber Cancer Institute, Boston, MA, USA

In a special continuing education session for hematology and oncology physicians worldwide, Dr. Jorge Castillo reviewed WM, including recent advances in treatment, assessment of the risk of progression for asymptomatic, watch-and-wait patients, and how to personalize treatment options based on patients' clinical features and genomic profiles.

2020 ASH Annual Meeting, cont. on page 16

Dr. Castillo drew particular attention to two clinical trials that are on-going and still recruiting WM patients:

- A Phase 2 trial of venetoclax (a BCL-2 inhibitor) at multiple medical centers for patients who have relapsed or are refractory to previous treatment with other drugs.
- A Phase 2 trial at Dana-Farber Cancer Institute of ibrutinib plus venetoclax in previously untreated patients (called "first-line therapy"). In this trial, ibrutinib and venetoclax therapy will not be given indefinitely. Instead, investigators will try to determine if limited duration treatment for two years, using these two drugs together, will provide adequate disease control.

Monoclonal Gammopathies of Determined Significance: Monoclonal Gammopathies of Clinical Significance – Educational program presented by Angela Dispenzieri, Mayo Clinic, Rochester, MN, USA

There has been considerable interest in monoclonal gammopathy of undetermined significance, called MGUS. IgM-MGUS is a common disorder in which monoclonal IgM is present but without clinical disease. Recently, medical attention has been drawn to clinical conditions with monoclonal IgM that are not WM. There is a broad spectrum of syndromes in this category, often associated with kidney or neurological involvement. Collectively these diseases are now called monoclonal gammopathy of clinical significance (MGCS), which distinguishes them from disorders of "undetermined significance." Dr. Dispenzieri discussed how difficult it is to diagnose these conditions and reviewed for physicians some of the ways they can be diagnosed.

From a WM patient's point of view, the existence of many diseases that have monoclonal IgM but are not WM further emphasizes the importance of an accurate WM diagnosis. The diagnosis of WM cannot be made from elevated or monoclonal IgM alone. Additional tests, including bone marrow aspiration and biopsy, are necessary.

A Retrospective Study of 67 Inflammatory Waldenström's Macroglobulinemia – Presented by Dikélélé Elessa, Hôpital Saint-Louis, Paris, France

In a series of 234 WM cases at the Hôpital Saint-Louis in Paris between 2007 and 2019, physicians noticed that many of the patients presented with signs of inflammation as well as the classic signs of WM. These patients had fever, night sweats, and decreased appetite. Their blood tests showed an increase in C-reactive protein (CRP), a marker of inflammation. They termed these cases "inflammatory WM."

To be diagnosed as inflammatory WM, CRP levels had to be elevated to at least 20 mg/L (normal is less than 10 mg/L). The mean CRP level in these patients was 40.5 mg/L. Other causes of inflammation (another cancer, infection, autoimmune disease, other inflammatory diseases) were ruled-out. Altogether, 67 patients (28% of the total) had inflammatory WM, compared with 167 patients (68%) with classic, non-inflammatory WM.

*The **diagnosis of WM** cannot be made from elevated or monoclonal IgM alone.*

Of the 67 patients with inflammatory WM, 93% required treatment. Over the course of their disease, patients received an average of three different types of treatment. The first treatment varied: 60% were treated with rituximab combinations (including 47% with rituximab and an alkylating agent) and 39% with monotherapy, principally chlorambucil. The mean overall response rate was 84%, and progression-free survival, which is the length of time after treatment before the disease worsens again, was 32 months. The mean follow-up period was 12.6 years.

The investigators assessed two types of responses to treatment. A successful inflammatory response was defined as a decrease in CRP of at least 50%, with resolution of fever and night sweats, and a successful hematological response was defined as improved IgM and other blood parameters. A successful hematological response and a successful inflammatory response were highly correlated. That is, for most patients, if they responded with a decrease in IgM, the inflammation also resolved. The opposite was also largely true—if they did not respond with a decrease in IgM, the inflammation did not resolve.

The investigators asked the key question: Is inflammatory WM a different disease, or is it another manifestation of WM? The patients with inflammatory WM did not require earlier treatment, compared to non-inflammatory WM patients. There was no significant difference in overall survival (inflammatory at 14 years vs. non-inflammatory at 16.4 years).

This led the investigators to conclude that inflammatory WM is not different from classical WM. The two presentations have the same clinical features (other than fever and inflammation) and the hematological response is strongly correlated with the inflammatory response. Patients with inflammatory WM do not progress faster to symptomatic disease requiring treatment. Their response to treatment is similar to that of classic WM patients, as measured by overall survival and progression-free survival.

They did point out that for patients with inflammatory WM, blood CRP levels could be used to monitor the success of treatment. If CRP does not decrease during treatment or if it goes up after treatment, then there should be concern that the patient is not responding or is relapsing.

MEDICAL NEWS ROUNDUP

BY SUE HERMS, IWMF RESEARCH COMMITTEE MEMBER

Zanubrutinib Approved by Health Canada for WM Patients – BeiGene, Ltd. announced that zanubrutinib (Brukinsa) has been approved by Health Canada for the treatment of WM patients. Following a priority review in September 2020, the approval was based on efficacy and safety results from the Phase 3 ASPEN trial of the drug that compared it to ibrutinib. The recommended total daily dose of zanubrutinib is 320 mg, and the drug is expected to be available in Canada in the coming weeks.

BeiGene Announces US FDA Acceptance of Supplemental New Drug Application for Zanubrutinib in WM Patients – BeiGene, Ltd. also announced that the US Food and Drug Administration (FDA) has accepted its supplemental new drug application for zanubrutinib (Brukinsa) for the treatment of WM. The application is based on results from the Phase 3 ASPEN trial of WM patients comparing zanubrutinib to ibrutinib and from two previous Phase 2 trials. The target date for action by the FDA is October 18, 2021. Zanubrutinib has already received accelerated approval in the US for mantle cell lymphoma patients who have received at least one prior therapy.

Six-Month Ibrutinib Response Predicts Progression-Free Survival in WM – A multicenter study published in the *British Journal of Haematology* found that a partial response or better at six months of ibrutinib (Imbruvica) treatment is prognostic for superior progression-free survival in WM patients. The study evaluated two groups, a learning group of 93 participants from two clinical trials and a validation group of 190 consecutive patients not treated on a clinical trial. Rates of partial response (PR) or better at six months were 64% and 71%, respectively, in the learning and validation groups. In the learning group, three-year progression-free survival for patients who attained PR or better at six months was 81% vs 57% for patients who did not attain PR in that time; in the validation group, similar results were seen, with three-year progression-free survival at 83% vs 54%, respectively, for those who attained PR and those who did not.

Phase 2 Study in Japan Reports Tirabrutinib Results in WM – Japanese researchers have reported results from a multicenter Phase 2 study of the second generation BTK inhibitor tirabrutinib (Velexbru) in WM patients. The trial included two arms, cohort A with 18 treatment naïve and cohort B with 9 relapsed/refractory participants. The major response rate in both cohorts was 88.9%; the overall response rate was 94.4% in cohort A and 100% in cohort B. Approximately half of patients had lymphadenopathy (enlarged lymph nodes), and all experienced immediate reduction in size or complete resolution. The most common adverse advents were rash, neutropenia (low neutrophil count), leukopenia (low WBC count), and stomatitis (mouth sores). Bleeding events were mild, and there were no events of drug-related atrial fibrillation or hypertension.

Expansion Begins for Phase 2 Trial of CLR 131 in WM – Cellectar Biosciences has initiated an expansion of its currently ongoing Phase 2 CLOVER-1 trial of the novel agent CLR 131 in WM. The study will enroll 50 WM patients who have failed first-line therapy and have failed to respond to, or have progressed while on, treatment with a BTK inhibitor. Participants will receive up to four doses of CLR 131. CLR 131 is a small-molecule drug conjugate designed to provided targeted delivery of the radioisotope iodine-131 directly to cancer cells, while limiting exposure to healthy cells. On *www.clinicaltrials.gov*, the expansion is designated CLOVER-WaM, and the identifier number is NCT02952508. CLR 131 has received Orphan Drug Designation from the US Food and Drug Administration and from the European Medicines Agency for the treatment of WM.

BeiGene, Ltd. announced that zanubrutinib (Brukinsa) has been ***approved by Health Canada*** *for the treatment of WM patients.*

Chinese Trial Recruiting Previously Untreated WM Patients to Study Zanubrutinib Combined with Ixazomib – A Phase 2 clinical trial in China is recruiting previously untreated WM patients to study the combination of the BTK inhibitor zanubrutinib (Brukinsa) with ixazomib (Ninlaro) and dexamethasone. The completely oral regimen will be given up to 24 months and then stopped for observation; it is being proposed to deepen responses and result in a time-limited therapy. The trial anticipates enrollment of 55 participants, and its identifier number on *www.clinicaltrials.gov* is NCT04463953.

Canada to Begin Phase 2 Study of Bendamustine, Rituximab, and Acalabrutinib in Treatment Naïve WM – A multi-center Phase 2 Canadian trial is expected to begin recruiting treatment naïve WM patients to test the combination of bendamustine, rituximab (Rituxan), and acalabrutinib (Calquence). Participants will receive a bone marrow aspiration and biopsy to confirm the diagnosis and amount of disease present and to have molecular testing for MYD88, CXCR4, and P53 mutations. Bendamustine and rituximab will be given for six cycles, with rituximab dosing to be intravenous for the first cycle and then either subcutaneous or intravenous for the remaining cycles.

Medical News Roundup, cont. on page 18

Concurrently, participants will receive acalabrutinib for one year and then followed up for six years. The identifier number for this designated BRAWM study on *www.clinicaltrials.gov* is NCT04624906.

United Kingdom Recruiting Patients for Phase 2/3 Trial to Compare Rituximab and Ibrutinib Combination to DRC Therapy in Previously Untreated WM – In the United Kingdom, a Phase 2/3 study is recruiting 148 previously untreated WM patients for a comparison of the combination of rituximab (Rituxan) and ibrutinib (Imbruvica), called the experimental RI arm, to the combination of dexamethasone, cyclophosphamide, and rituximab, called the control DRC arm. Treatment will consist of a maximum of six therapy cycles, with ibrutinib in the RI arm given for up to five years afterward. The trial, designated RAINBOW, is identified on *www.clinicaltrials.gov* as NCT04061512.

A multicenter trial in Europe is ***recruiting*** ***IgM-MGUS patients*** *with anti-MAG neuropathy to study a* ***new drug*** *called PPSGG*

New Prognostic Scoring System Proposed for Transformed WM – Transformation into a more aggressive B-cell lymphoma, such as diffuse large B-cell lymphoma (DLBCL), is a rare complication of WM, usually associated with a poorer prognosis. A multicenter, international effort to develop a prognostic scoring system model for survival in transformed WM patients has been published in the journal *Haematologica*. The scoring system was developed from data collected on 133 patients with transformed WM who were evaluated between 1995-2016. For validation, a group of 67 transformed patients was used to evaluate the performance of the model. Three adverse factors at the time of transformation diagnosis were identified as independent predictors of two-year survival after transformation and assigned point values: elevated serum LDH (lactate dehydrogenase) – 2 points; platelet count less than 100 x 109/L – 1 point; and any previous treatment for WM – 1 point. Based on this point system, three risk groups were defined. The low-risk group scored 0-1 points, with a two-year survival rate of 81%; the study's authors indicated that this group could benefit from the R-CHOP regimen typically used in transformed patients. The intermediate-risk group scored 2-3 points, with a two-year survival rate of 47%, and high-dose therapy with stem cell transplantation or targeted therapies were suggested as appropriate. The high-risk group scored 4 points, with a two-year survival rate of 21%, and the researchers indicated that these patients should be directed to clinical trials with new agents, including CAR T-cell therapy. The authors pointed out that this study had limitations, including 1) that a majority of patients had been treated with older therapies such as fludarabine and chlorambucil and 2) that they were not able to assess the clonal relationship between WM and DLBCL in the study participants, which could affect some aspect of the model's validity because DLBCL can also arise as an independent cancer not related to the original WM clone.

Updated Phase 1 Trial Results Presented for IRAK4 Inhibitor in NHL – Updated results from a Phase 1 trial of oral CA-4948, an IRAK4 inhibitor developed by Curis Inc., were presented during the 2020 American Society of Hematology (ASH) Annual Meeting. IRAK4 is a part of the Myddosome signaling pathway downstream from BTK and is dysregulated in certain lymphomas, including WM. The trial included 30 patients with relapsed or refractory non-Hodgkin's lymphoma (NHL), five of whom were diagnosed with WM or LPL (lymphoplasmacytic lymphoma). Eight of 28 evaluated patients experienced overall tumor burden decreases of 20% or more from baseline; a WM patient with six prior lines of treatment achieved a partial response. The most common non-hematologic side effects were mild or moderate and manageable and included diarrhea, vomiting, fatigue, dyspnea (shortness of breath), and myalgia (muscle pain). Hematologic side effects included mild to moderate neutropenia (low neutrophil count), anemia, and thrombocytopenia (low platelet count). Meanwhile, Curis just recently announced that it has dosed the first patient in an expansion of this Phase 1 trial that combines CA-4948 with ibrutinib. The trial identifier on *www.clinicaltrials.gov* is NCT03328078. Dosing for an anticipated Phase 2 trial will be 300 mg twice daily.

Multicenter European Trial to Test New Treatment for Anti-MAG Neuropathy in IgM-MGUS Patients – A multicenter trial in Europe is recruiting IgM-MGUS patients with anti-MAG neuropathy to study a new drug called PPSGG, which binds to anti-MAG IgM antibodies and removes them from the blood circulation. Anti-MAG antibodies attach to a part of the myelin sheath covering the nerves called myelin-associated glycoprotein, thereby damaging the nerves. By selectively targeting these antibodies, PPSGG does not cause the immune suppression associated with current treatment strategies, such as rituximab (Rituxan), for this type of neuropathy. The Phase 1/2a trial, identified as NCT04568174 on *www.clinicaltrials.gov*, anticipates enrollment of 48 participants.

Acalabrutinib Fails to Meet Endpoint for Treatment of Serious COVID-19 Infection – The Phase 2 CALAVI trial to evaluate the efficacy and safety of acalabrutinib (Calquence) along with best supportive care in patients hospitalized with respiratory complications from COVID-19 failed to meet its endpoint. AstraZeneca stated that the addition of

Medical News Roundup, cont. on page 19

acalabrutinib did not increase the number of patients who remained alive and free of respiratory failure. The rationale for the study had been to reduce the hyperinflammatory response known as cytokine storm, which causes the body's reaction to infection with COVID-19 to go into overdrive and damage organ systems, including the lungs.

AstraZeneca Announces Results from Phase 3 Trial Comparison of Acalabrutinib and Ibrutinib in CLL – AstraZeneca announced that acalabrutinib (Calquence) passed the head-to-head Phase 3 trial ELEVATE-RR comparison against ibrutinib (Imbruvica) in 533 chronic lymphocytic leukemia (CLL) patients. After more than 40 months of follow-up, its efficacy matched that of ibrutinib, while its safety was superior, triggering fewer cases of atrial fibrillation. According to AstraZeneca, there was a trend toward a numerically favorable overall survival for acalabrutinib. More details are expected to be released about this first head-to-head trial of the two drugs.

Anti-CD20 Therapies Tied to More Severe COVID-19 Infections in Lymphoma Patients – Data presented at the American Association for Cancer Research (ACCR) Virtual Meeting on COVID-19 and cancer suggested that anti-CD20 monoclonal antibody therapies such as rituximab (Rituxan) are tied to severe COVID-19 infections in lymphoma patients. A study of 111 lymphoma patients in France who were hospitalized for COVID-19 from March-April 2020 found that those treated with anti-CD20 monoclonal antibodies over the previous year were at increased risk for longer hospital stays and death. Additionally, 29% of these patients experienced persistent COVID-19, with a median symptom duration of 83 days.

BTK Inhibitor TG-1701 Tested Alone and in Combination in Phase 1 Trial for B-Cell Malignancies – TG-1701 is a covalent BTK inhibitor, in the same drug class as ibrutinib (Imbruvica). Single agent TG-1701, as well as the combination therapy of TG-1701 with the anti-CD20 monoclonal antibody ublituximab and the PI3K inhibitor umbralisib, were tested in a Phase 1 clinical trial of 102 patients with both relapsed/refractory and treatment naïve B-cell malignancies. The trial included 17 WM patients, almost all of whom were in the single agent arm. Atrial fibrillation occurred in 4% of patients, serious hypertension occurred in 1%, and bleeding events such as bruising occurred in 22%. With a median follow-up of 4.6 months in the single agent TG-1701 arm, the preliminary overall response rate in WM patients was 86%. The most common serious adverse events were neutropenia (low neutrophil count) in the single agent arm and neutropenia and elevated liver enzyme levels in the combination arm. Only one WM patient was in the combination arm, and that patient had a response to therapy. Recruitment to this study is continuing, and its trial number on *www.clinicaltrials.gov* is NCT03671590. The results were presented during the 2020 American Society of Hematology (ASH) Annual Meeting.

... anti-CD20 monoclonal antibody therapies such as rituximab (Rituxan) are tied to ***severe COVID-19 infections*** *in lymphoma patients.*

Long-Term Results Reported for Phase 2 Trial of Idelalisib in Indolent NHL – A Phase 2 trial of single agent idelalisib (Zydelig) for indolent non-Hodgkin's lymphoma (NHL) was completed in 2018, and final results, with up to 6.7 years of long-term follow-up for some participants, were reported in the journal *Leukemia & Lymphoma*. In the multicenter trial, 125 patients refractory to both rituximab (Rituxan) and an alkylating agent were enrolled and received 150 mg of idelalisib twice daily. The study included WM patients. The overall response rate was 57.6%. The median progression-free survival and duration of response were 22.2 months and 20.4 months, respectively, for WM/LPL (lymphoplasmacytic lymphoma). Idelalisib is an inhibitor of PI3K, which is a family of enzymes whose over-activity has been implicated in cancer proliferation, and it is approved for use in several blood cancers.

US FDA Approves Daratumumab Combination Therapy for AL Amyloidosis – The US Food and Drug Administration (FDA) has approved a subcutaneous formulation of daratumumab, called Darzalex FASPRO, in combination with bortezomib (Velcade), cyclophosphamide, and dexamethasone (VCd therapy) for the treatment of newly diagnosed light chain (AL) amyloidosis. AL amyloidosis is associated with abnormal protein production which leads to deterioration in vital organs such as the heart, kidneys, and/or liver. It can be a rare complication of WM. The FDA approval, which is the first ever for patients with AL amyloidosis, was based on Phase 3 findings from the ANDROMEDA study, in which the daratumumab/VCd combination yielded a complete response rate of 42% compared to 13% with VCd alone; however, the study did not include WM patients.

Phase 1 Study Results Reported for CAR T-Cell Therapy Targeting CD19 and CD20 – A Phase 1 study of CAR T-cell therapy targeting both CD19 and CD20 (called bispecific CAR T-cell therapy because it has two targets) reported results for 22 patients with relapsed/refractory non-Hodgkin's lymphoma and chronic lymphocytic leukemia. At day 28, 82% of patients achieved an overall response, including 64% with complete responses. Among patients with complete responses by day 28, the median duration of response was not reached at a follow-up time of 10.1 months. The median overall survival for

Medical News Roundup, cont. on page 20

all patients was 20.3 months. Serious events included cytokine release syndrome in 5% and neurotoxicity in 14% of patients. Cytokine release syndrome is the most common toxicity in this type of therapy and is a systemic inflammatory response caused by small signaling proteins released from the infused CAR T-cells. Neurotoxicity in CAR T-cell therapy can be mild to severe, ranging from headache and tremors to vision changes, speech problems, memory dysfunction, hallucinations, and even death. The loss of the CD19 antigen on patients' cancer cells, which has been a cause of relapse or treatment failure in other CAR T-cell therapies that target only CD19, was not seen in this study. At press time, a Phase 2 study was planned to begin in the first quarter of 2021.

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.*

IN MEMORIAM
W. THOMAS MYERS, JR.

Our WM community was saddened to hear of the recent loss of W. Thomas (Tom) Myers, Jr., a long-time IWMF member and Board Trustee who also served as the Foundation's second vice president for Research.

Tom was born and raised in Clarksburg, WV, and his lifelong career was in the pulp and paper industry. He graduated from Yale University with a BS degree and did post-graduate work at Lawrence University in Wisconsin, where he received MS and PhD degrees from its Institute of Paper Chemistry. His career spanned several locations and paper corporations, from research in New York to running paper mills in Battle Creek, MI and Rhinelander, WI. He eventually chose the James River Company in Richmond, VA, because of his love for the Chesapeake Bay and the opportunities associated with a rapidly growing international company. At the James River Company, he coordinated the purchase of paper mills and fiber in Europe and South American for the company's growth before its acquisition by Georgia Pacific Corporation.

Tom's background in science was invaluable to the IWMF after he joined the Board in 2001. When Judith May became IWMF President in 2005 upon the death of President Ben Rude, Tom was able to step into her former position as vice president for Research. At that time, the Foundation's research program was still fairly young, and Tom's years of stewardship resulted in diversity and expansion of IWMF-funded projects.

IWMF Board Chair Peter DeNardis remembers sitting next to Tom at quarterly Board meetings. As Peter recalls, Tom "had very organized details about each research grant the IWMF was funding. He calmly discussed issues on whatever topic was brought up during the meetings and provided vital insights into what might or might not work. He made sure to pay proper attention to whatever committee report was being discussed. I was always intrigued by his shuffling a stack of papers to hone in on a particular point he wanted to make—he knew exactly what sheet of paper he wanted but just had to find it in the stack!"

Karen and Tom Myers

Former Trustee Sue Herms recalls Tom as a "true gentleman" and very conscientious about putting together his Research Committee reports, which grew progressively longer as more projects were added to the IWMF's research portfolio.

Tom was diagnosed 24 years ago with WM. Although he developed a series of issues as a result of the disease and the treatments he received for it, he did not let it interfere with outdoor activities or his enjoyment of life. Judith May and former IWMF Trustee Michael Luttrell shared several skiing, whitewater rafting, and biking adventures with Tom and his wife, Karen.

In 2013, vision problems forced Tom to relinquish his position on the Board and his vice presidency, but he remained an active participant on the Research Committee. Peter DeNardis notes that Tom "set a great example of how a WMer should approach serving on the Board—selfless, committed, and focused on the ultimate goal of helping everyone affected by the disease."

In addition to Karen, Tom is survived by a sister, four daughters, a stepdaughter, a stepson, and 15 grandchildren who knew him as "Grandcrab" and shared his love of the outdoors.

Tom Myers honors retired President Judith May at the 2013 Ed Forum in San Diego.

FROM IWMF CONNECT: SPRING 2021

BY JACOB WEINTRAUB, MD

Now that winter is past, it is time to look to warmer weather. We hope the worst of the pandemic is behind us and anticipate a more hopeful future, when we can gather again socially and enjoy events like the Educational Forum. Discussion has continued unabated in our forum. It has been wide-ranging, from the pandemic and its effect on our lives with WM, to more routine subjects like welcoming newly diagnosed members, Medicare plans and coverage of treatments, and treatments themselves. You are all invited to join IWMF Connect to participate or just "lurk" and absorb all the different experiences, observances, and opinions.

PERSONAL INTEREST

Chair of the IWMF Board and former IWMF Connect Manager Peter DeNardis continues to be active in the discussion. As he has done in the past, Peter has posted links to very relevant personal interest and informational articles. In a recent post, he provided links to stories about survivorship and coping.

The first is "The loneliness of fighting cancer in a pandemic." Peter noted how fortunate he and others are to have a care partner. However, the current pandemic has changed a lot of our outlooks on life and the way we manage our care in relation to our partners.

https://www.theglobeandmail.com/canada/article-the-loneliness-of-fighting-cancer-in-a-pandemic/

Another link is to an article titled "Could More Cancer Patients Benefit from Rehab?" This is a subject that comes up for discussion more in relation to the peripheral neuropathy that a number of us have, or to the fatigue that many of us experience, or perhaps to effects of the treatments we endure. This article suggests that, while treatment outcomes are improving with respect to our WM, the lingering side effects and weakness also should be treated in some fashion. A simple guide is to try to move one step more each day than the day before, and in time we will find we're able to walk around the block.

https://www.cancerhealth.com/article/cancer-patients-benefit-rehab

A third link is to an article titled "I was always terrified of wasting time. Cancer diagnosis made me reconsider." This is a well written affirmation of sorts for all of us—a reflection from a person diagnosed with an incurable blood cancer and how it has affected her outlook on life. Sometimes it helps to see how others deal with situations similar to ours. The observations in this article mirror discussions that we have had in this group on a number of occasions.

https://www.vox.com/the-highlight/22090499/cancer-martha-crawford-psychotherapist

Finally, Peter also came across this posting on the "Mass Appeal" website; they give commonsense advice to care partners, and there's also a link to a lecture on the topic in the article. This is a five-minute video clip with a clinical psychologist, and it has potential to be very helpful. The link to a full lecture on this topic is included.

https://www.wwlp.com/massappeal/helpful-advice-for-those-who-support-cancer-patients/

Michelle Postek, IWMF manager of Information and Support, posted a link to a new video series on living with cancer produced by Michael Knowlton, a fellow WMer. You can subscribe to his YouTube channel and follow along, as he has about 15 short videos that he will be releasing. Michael said that after living with a terminal diagnosis for the last 14 years, he felt called on to create this series to inspire others to live their best life, even when the reality of life circumstances may feel really tough. He hopes to open up the conversation about living life with an illness and invites us along for the ride:

"Who Will Remember Me?"
https://www.youtube.com/watch?v=S1UXoibE--Q

Michelle posted later with links to the second and third videos in the series:

"How to Find a Voice Through a Life-Changing Diagnosis"
https://www.youtube.com/watch?v=0NNvY2MEcwU&feature=youtu.be

"How Will I Manage Without You?"
https://www.youtube.com/watch?v=Br94SMIKkR4&feature=youtu.be

Julianne Flora-Tostado, IWMF Connect manager, also posted that she has been enjoying these tender, funny, and wise moments that Michael and his family have shared. It touched her when, in the third post, Michael's wife Lynn stepped up and said what was in her heart. It's so kind of them to share these talks. Hopefully others of us may feel emboldened to be just as kind and open with our own dear heart.

ZANUBRUTINIB

This is a new treatment in clinical trials but shows much promise.

Armand T posted "Zanubrutinib, here I come!" He had been treated with Imbruvica for 45 months, but it was losing effectiveness. He also has experienced another episode of extramedullary (outside the bone marrow) disease, this time as palpable tumors in the region of his elbow. He is hoping the Bruton's tyrosine kinase inhibitor "zanu," aka Brukinsa, comes to his rescue and was looking for input on others'

From IWMF Connect, cont. on page 23

experiences and results. He also asked about availability. His oncologist's office has told him they have been unsuccessful in getting insurance to cover this med.

Brenda M posted that many of us have done extremely well on zanubrutinib, and it seems to be effective against extramedullary masses. She hopes Armand does well and asked him to keep us all informed on how he responds. She later posted that everyone she knows of on zanubrutinib in the US received it through a clinical trial.

Pete S responded that he has been taking zanubrutinib for one year and is doing very well. He previously had treatment with venetoclax. He had a chest tumor appear while on venetoclax, and zanubrutinib cleared that. However, Pete wondered whether zanubrutinib will be as good for Armand as others have reported, since Armand has been taking the BTK inhibitor Imbruvica.

Eileen S posted that she has been taking zanubrutinib for almost a year. She has been treated repeatedly with radiation for peripheral WM tumors. One of her oncologists said she needed an alternative to "spot welding with radiation." Based on her six-month PET scan in August, there was a great deal of improvement in the lesions. She has another PET scan coming that will give more information. She hopes for good results for Armand, given his history of multiple extramedullary lesions.

Kathy W suggested that Armand ask his doctor about acalabrutinib, since it is not too different from zanubrutinib. She knows of WM patients who take it, and it is not a trial drug.

Finally, **Paul L** posted that he switched from acalabrutinib to zanubrutinib in October. He was not in a clinical trial or study, just treated by his oncologist, and his insurance covered the med. In terms of efficacy, so far it seems to be the same as acalabrutinib. In terms of side effects, zanubrutinib is much less harsh on his GI tract than acalabrutinib or, especially, ibrutinib.

*[Fatigue] seems to **manifest** in different ways in different people and at different points in their **diagnostic** and **treatment journeys**.*

FATIGUE

This subject is discussed frequently. It seems to manifest in different ways in different people and at different points in their diagnostic and treatment journeys.

Don G posted that he was diagnosed with WM in 2012. He had remained completely asymptomatic, even though his IgM had steadily risen. However, in the prior few weeks, he has grown increasingly fatigued. He has been sleeping well, usually for eight plus hours a night and still wakes up feeling exhausted. He manages to continue working, but it takes all his effort to do so. He asked those who have had fatigue if they have complete exhaustion, and if it is ever connected with a brain fog? Does it get better only with treatment, or does it cycle day-to-day or week-to-week?

Hally D answered that she had complete exhaustion accompanied by brain fog. She was diagnosed in 2005 with MGUS (monoclonal gammopathy of uncertain significance), followed a year later by diagnosis of Lyme disease and chronic fatigue. The fatigue increased in 2016 when she started going to a hematologist. There was difficulty climbing stairs and functioning during the day. Treatment started with ibrutinib and improvement was noted. Hally still gets tired if she overdoes things, but not as bad as before. The brain fog has lifted. She hopes Don can get some answers to his fatigue and find improvement.

Charles W was diagnosed with WM in 2011 after many years of symptoms that included chronic fatigue at the time. He has not had any treatment, but he has some days when he is exhausted and other days when he is fine. When he wakes up exhausted, he usually is that way for the rest of the day, no matter what he does. He tries to exercise when he can. Some days he "fights" the fatigue, other days he just gives in and spends most of the day in bed. He has brain fog that he associates with depression. He likes to swim because of the feeling of weightlessness.

Brad S posted that when he was suffering from fatigue a couple of years ago, he had asked the same question of the IWMF Connect group. He received several answers, and he repeated the most helpful advice he received. It was that cancer and chemo-related fatigue is unlike "normal" fatigue. It is difficult to understand if you have not experienced it. You want just to lie down and rest, or you don't get up if you are down already, and you think you'll feel better. However, if you lie down and rest, you find you don't feel any more rested, even if you sleep. If you do light exercise such as walking, you may find you have more energy. This has helped him. Brad also suggested Don plan and list the day before what he would like to do the next day. Then, when getting up in the morning, just look at one thing and do that. Rest if needed, and then look at one other thing. Celebrate each accomplishment. The fatigue led Brad to start treatment, and he did feel less fatigue after treatment.

Kathy H added that when she was diagnosed in 2008 at age 57, she had been living with extreme fatigue for two years. The brain fog was so severe that she came out of meetings at work and couldn't remember what was said. She once lost her way to work on a drive that she had navigated many times before. No amount of rest helped. She finally asked for help from her hematologist. After treatment, it took about a year for her to start really feeling better. She

From IWMF Connect, cont. on page 24

noted that while WM is different for all of us, the fatigue feels the same. She hopes Don can get to feeling better soon but doubts his fatigue will lessen without treatment of his WM.

Jan H posted that she can relate. One comment she gets from doctors is that she must be depressed. However, she feels the only thing she is depressed about is that she needs to sleep so much because she is tired.

Finally, **IWMF Board Trustee Dr. Tom Hoffmann** answered that fatigue and related symptoms are difficult to find an etiology for and difficult to treat. Chronic fatigue is a big problem with many cancer patients, but there are also many other reasons to have fatigue. Possibilities include sleep disorders, anemia, low thyroid levels, depression, anxiety, stress, and others. He recommended a good medical evaluation by a primary care physician, possibly including thyroid and cortisol levels and perhaps a sleep study.

FAREWELL

We also said good bye to two old friends.

In January, we noted the passing of **John Paasch**, a long-time friend and contributor to IWMF Connect. He was diagnosed in 2004 and was active in the IWMF and this discussion group. Others added to the notice that they had talked with John on many occasions and that he even would pick up arriving members and take them to the Bing Center at Dana-Farber in Boston. Trained as a "rocket scientist," he had a sharp analytical mind and was always ready to help with charting critical data points and responses for other members. He was among the first to note the incidences of atrial fibrillation occurring in people getting ibrutinib. He served on the IWMF Research Committee.

Tom Myers also passed away in January. He was a former IWMF Trustee and served as vice president for Research. He too was a long-time contributor to IWMF Connect. His postings to the group indicated he had complications from his WM, but he remained an optimistic person who enjoyed life. John and Tom will be missed by all of us.

So, again, this is just a small sample of what is posted online in IWMF Connect. Everyone is welcome to join and participate, or just read the posts and benefit from the support and information. If anyone has any questions or wishes to see more on a particular topic, please contact me at *jmw003@aol.com*, and I will try to include those discussions in a future column. I wish you all continued good health.

SUPPORT GROUP NEWS

EDITED BY CHRIS STAY

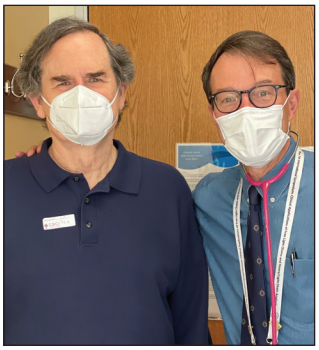
2020 Support Group Statistics
Support Groups: 38
Meetings: 72
People attending meetings: 1,345

PLEASE NOTE

Contact information for all support groups is available at *www.iwmf.com/get-support/us-and-international-support-groups*.

Details of support group meetings and other upcoming events are posted on *www.iwmf.com* under **NEWS & EVENTS**. Please check there to confirm details of future events.

ARIZONA; COLORADO & SOUTHERN WYOMING



Dr. Jeffrey Matous (right), who spoke in February to the combined Arizona and Colorado & Southern Wyoming Support Groups, is shown here with leader Bill Bass.

Dr. Jeffrey Matous of the Colorado Blood Cancer Institute spoke to the combined Arizona and Colorado & Southern Wyoming Support Groups in February, with over 40 WMers and caregivers in attendance. The WMers present included a broad cross-section, from the newly diagnosed to 20+ year longtimers.

Topics discussed included COVID-19 and the advisability of WMers being vaccinated. Also discussed were the basics of WM, why patients may get the disease, how MGUS/smoldering disease turns into symptomatic WM, what considerations go into deciding how and when to treat, and what treatments are available.

The two participating support groups are looking forward to their next meeting in the summer. They are hopeful that the October IWMF Educational Forum in St. Louis will be a hybrid virtual and in-person meeting.

Bill Bass reporting

CALIFORNIA

Los Angeles, Orange & San Diego Counties

Attendance at the January Zoom meeting included 23 members. Meeting attendees came from four widespread counties: Los Angeles, Orange, San Diego, and San Bernardino. One new member found out about the group through attending the IWMF Educational Forum. The group appreciates the IWMF for providing the Zoom platform for members to meet.

Discussion ranged from future guest speakers to share with a wider audience, to a newly diagnosed member's initial presenting symptoms, to a variety of symptoms shared by other members. One member recently applied to become a co-leader of the support group.

Nine members were able to join the February Zoom meeting. Detailed self-care topics of conversation included COVID-19 vaccine access, vaccine interactions with pain medications or IVIG infusions, and the treatment of deep fatigue with supplements and/or physical therapy.

Julianne Flora-Tostado reporting

CONNECTICUT

This group decided on a series of mini-meetings to stay in contact throughout the winter months. The condensed gatherings were used to share any significant health updates,

Los Angeles, Orange & San Diego Counties Support Group members smile their greetings.

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Support Group News, cont. from page 25

The Chicago Area/SE Wisconsin Support Group welcomed Dr. Janis Atkinson to their February meeting. She is shown in the upper left photograph of the Zoom session.

spend time to discuss the topic of COVID-19 vaccinations, and to chat socially (something that had been missing from the new virtual format).

In January, 23 members participated. Members shared personal updates, tips on managing during the COVID-19 pandemic, and a recent Zoom discussion by Dr. Jorge Castillo and Dr. Shayna Sarosiek of Dana-Farber Cancer Institute regarding their thoughts on the COVID-19 vaccines and their effectiveness for those with compromised immune systems.

In February, 12 members met. They reviewed a recent presentation by Dr. Stephen Ansell of Mayo Clinic and shared experiences with COVID-19 vaccinations to date. At the time of the gathering, Connecticut was ranked in the top five states for percent of vaccine distribution. The group also spent some time sharing favorite travel destinations. Most agreed that when the threat of COVID-19 spread has declined, traveling is high on the list of things to resume.

Bob Ulkus reporting

ILLINOIS

Chicago Area/SE Wisconsin

The Chicago Area/SE Wisconsin Support Group had a great meeting in February, with 20 families attending, including three first-time families. After introductions, Dr. Janis Atkinson, laboratory medical director, Saint Francis Hospital, and vice president of Medical Affairs, ALVERNO Laboratories for AMITA Health, presented a timely update on COVID-19 testing, vaccines, reactions and variant strains. Her presentation gave a concise response to previously submitted questions and were based on her in-depth practical experience, science, data, and current CDC guidelines, including concerns relating to WMers. Highlights included T cells acting as "generals" for the immune system, Pfizer and Moderna being good vaccines for WMers, and the probable greater protection for a person who receives the vaccine over people who have had COVID-19. A discussion of current travel options and risks included making sure target travel locations have low infection rates, avoiding crowds, and maintaining CDC guidelines wherever one travels.

The group is hopeful that they can meet in person for the annual summer picnic depending upon what level of herd immunity has been achieved and the health of attendees. Some patients expressed continued interest in using Zoom at in-person meetings, enabling more attendance from distant locations.

Don Brown reporting

MASSACHUSETTS

Eastern Massachusetts/Boston

The Eastern Massachusetts Support Group met virtually on a snowy Sunday afternoon in February. Fortunately, no one had to drive through the snow to get there, and the meeting didn't need to be cancelled due to the storm. Members had a chance to check in with one another and share their experiences with WM, COVID-19, and personal stories and questions. Toward the end of the meeting, they were joined by Dr. Shayna Sarosiek, the newest member of the WM team at Dana-Farber. Dr. Sarosiek introduced herself and fielded a few vaccination and treatment questions. Many members of the group are treated at Dana-Farber and will likely be meeting with her as she and Dr. Castillo share the practice. The group has been meeting bimonthly on Zoom and plans to continue doing so for the foreseeable future.

Eileen Sullivan reporting

MICHIGAN

Ten members and three spouses Zoomed from the comfort of their homes in January and shared updates on how everyone is doing during the pandemic. Co-leader Jenn Goldman showed the video of Dr. Stephen Ansell's education program on COVID-19 and the impact of vaccines on people with WM. Dr. Ansell is from the Mayo

Support Group News, cont. on page 27

Clinic in Rochester, MN, and he does a magnificent job of explaining a complicated topic with very engaging graphics and humorous characters.

The next Zoom meeting is scheduled for April 25. For information on meetings and to receive the link to the meeting, please contact Jenn Goldman (*goldmanjenng@gmail.com*) or Janice Wheeker (*dwheeker@comcast.net*).

Janice Wheeker reporting

MINNESOTA & WESTERN WISCONSIN

In January, this support group had an "Ask the Doctor" virtual presentation with Dr. Jonas Paludo. Dr. Paludo is an assistant professor of Medicine and Oncology at the Mayo Clinic in Rochester, MN. Members submitted questions in advance. Dr. Paludo included slides and answers to questions ranging from the PROMISE Study, WM mutations, and concerns regarding treatment responses, to overall survival and numerous COVID-19 and vaccine concerns.

Dr. Jonas Paludo answered questions in an "Ask the Doctor" presentation for the Minnesota & Western Wisconsin Support Group.

Dr. Paludo presented a very informative discussion, and members are always amazed at his ability to present dynamic and complex topics with ease. As one of the members indicated, "We always learn something and feel better about life and being connected."

The group's Zoom meetings (fondly called "Zoomies") on the first Thursday of each month allow members to connect and to chat face-to-face virtually. Attendance has been increasing monthly, while members share their medical experiences, welcome new members, and share IWMF news and upcoming webinars.

Eunice Quast reporting

NEW YORK

Western NY

Sixteen members of the Western New York Support Group met in January for a lively Zoom meeting. The group welcomed three newly diagnosed members. Veteran members briefly introduced themselves, and then the meeting was turned over to the new members for an informal question-and-answer session, which was both informative and well-received. The primary discussion centered around treatment options and doctor experiences. Both seemed quite varied. Veteran members emphasized the importance of getting a second opinion when clarifying diagnosis and deciding on treatment.

While group members all agree that meeting in person is the best, the group has become comfortable with the Zoom format, and conversation flowed with little need for muting!

Lynn and Tom Milliman reporting

OREGON & SOUTHWEST WASHINGTON

A grey, damp Oregon day brought 18 WMers together on Zoom. The meeting began with general chatting and catching up. A core group gathers on these Zoom calls, so a nice comfort level has developed over time among the participants. The main event of the meeting was watching the video of the December 9 support group leader webcast with Dr. Jorge Castillo. Several members of the group are his patients and most knew of him. All were interested in "meeting" his new colleague, Dr. Shayna Sarosiek, on Dana-Farber's WM team.

Oregon and SW Washington Support Group members attend their Zoom meeting.

Support Group News, cont. on page 28

COVID-19 vaccines are on everyone's mind, and there was a great deal of discussion following the video on the efficacy of the vaccines for WM patients. The topic of participating in clinical trials and finding the right one also arose.

Conversation shifted to a discussion about Dana-Farber's PCROWD and PROMISE research studies. Glenn Cantor is in the support group and is a participant in the PCROWD study. Among other WM topics, Glenn readily shared his personal and scientific knowledge on this research topic. Opinions varied regarding the impact to a first-degree relative of knowing that they have the markers for WM. Besides being the science editor for the *Torch*, Glenn is also on the IWMF Board of Trustees, and the group feels very fortunate to have him as a member.

Cindy Jordan reporting

PENNSYLVANIA

Eastern Pennsylvania, Southern New Jersey

Forty members attended the December meeting. Gratitude was expressed to Carl Harrington, past chair of the IWMF Board, for his inspiring vision, fearless leadership, and tireless efforts. Carl is a member of this support group, and all WMers are indebted to him for his passion and service!

Pete DeNardis joined the meeting and was warmly welcomed as the new chair of the IWMF Board. Pete is a 17-year WM veteran, long-time, invaluable volunteer, Board member, and past manager of IWMF Connect.

The group enjoyed a highly interactive and informative "Ask the Doctor" session with Dr. Edward Stadtmauer, section chief of Hematologic Malignancies at Penn Medicine's Perelman Center for Advanced Medicine. The group always enjoys his engaging teaching style, lively approach, and educational presentations.

Andrea Bensusan is the new co-leader of the Eastern Pennsylvania, Southern New Jersey Support Group.

Andrea Bensusan is the new support group co-leader for the Eastern Pennsylvania and Southern New Jersey group. Andrea lives in Berks County, PA, and has worked in the education field for more than 20 years as a teacher, higher education program coordinator, and student assistance specialist. Andrea has facilitated a range of support groups for students in grades K through 12. This will be her first venture into co-facilitating an adult group, and she is looking forward to her new role with the amazing Philly WM community she has come to know and love over the past four years.

Lisa Wise reporting

Dr. Edward Stadtmauer spoke with the Eastern Pennsylvania, Southern New Jersey Support Group.

SOUTH CAROLINA

This support group met by Zoom in January, with 15 attendees. The group welcomed several new members.

The co-leaders, Roger and Barbara Robinette and Jane Loud, opened the meeting with information obtained through monthly Zoom sessions with Lisa Wise (IWMF Member Services vice chair) and Michelle Postek (IWMF manager, Information & Support). Highlights were shared about the exciting increase in the use of Zoom and the possibility of creating specialty Zoom support on various topics. One group on Bing Neel has already started, and a new neuropathy group is in the planning process. Several members expressed interest in a neuropathy group.

Highlights were shared about a presentation Dr. Stephen Ansell made to the support group leaders on the topic of the COVID-19 vaccines. An excellent presentation was made as to how the various vaccines work in the immune system. The group was encouraged to view his presentation on the IWMF website. His slide presentation was fun and easy to understand. He encouraged every WMer to "get the vaccine. It doesn't matter which company—just get the first one that becomes available to you."

The group then proceeded with introductions and brief histories of their experiences with WM. Specific discussion focused on reasons for watch-and-wait, as well as various treatments and symptoms. Additional talk focused on neuropathy. The group decided to meet again April 17.

Jane Loud reporting

WASHINGTON

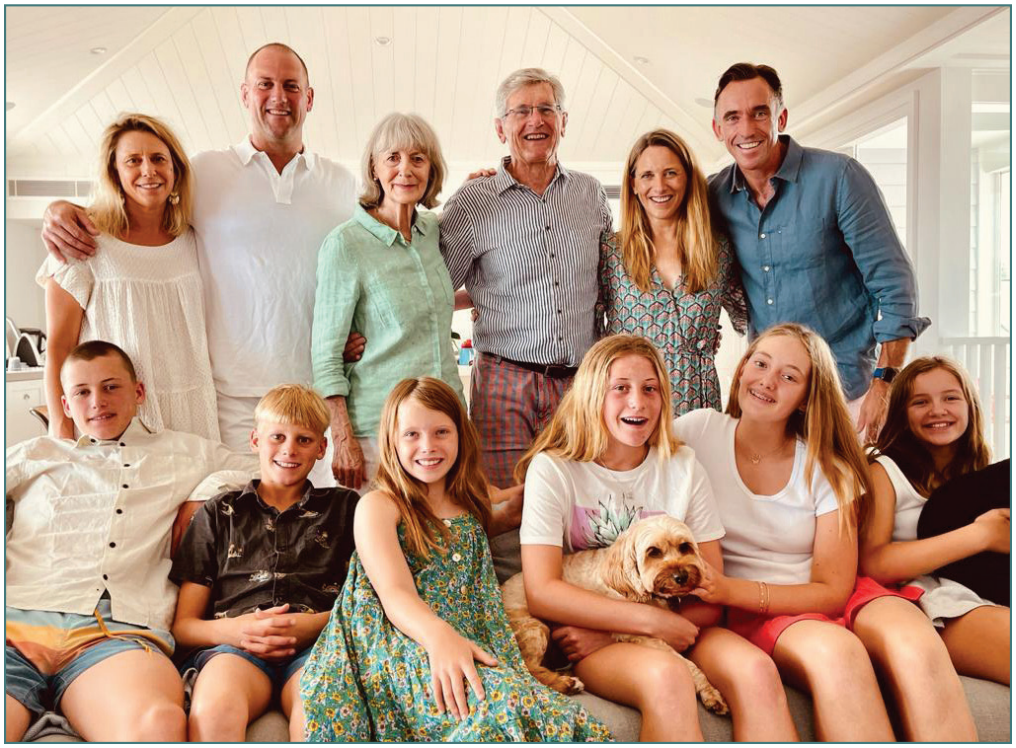
Northwest/Seattle Area

Sixteen members of the Northwest/Seattle Area Support Group met on Zoom on December 13, 2020. We don't normally meet in December, since our yearly big meeting with guest speakers takes place in November. But with the pandemic, that was cancelled, and by December, it was really time to talk with each other again. We did not have an outside speaker lined up, but we are always interested in hearing how others have been coping with the pandemic and with their WM, so we spent two hours catching up on our group's news.

Shirley Ganse reporting

INTERNATIONAL SCENE

EDITED BY ANNETTE ABURDENE



The Andrew Warden clan. Andrew (back row, center) has stepped down after leading the WMOzzies for seven years.

AUSTRALIA

WMozzies New Team Leader

After fourteen years of membership in WMozzies and seven years as its leader, Andrew Warden decided he needed to hand over the responsibility of leader. With that aim, a Zoom meeting was held on November 24, 2020, with Andrew, Kathy Fulham, Peter Carr, David Young, David Rabie, Neil Motyer, Michael van Ewijk, Paul Lenon, Peter Freese, Jacqui Merchant, and Lea Hullett (NZ WM). It became apparent very quickly how much work Andrew has been doing by himself for so long. It took a good hour for the group to go through all the different roles Andrew has done single-handedly. As each role was discussed, the meeting member who had some expertise in that area volunteered to take it over. David Young has agreed to be team leader.

Andrew has been outstanding with the advocacy work he has done, and he will be missed. Fortunately, he will stay involved with WMozzies, as he will keep his role liaising with the Cart-Wheel WhiMSICAL patient data base.

IWMF-LLS Strategic Research Roadmap Initiative

A$77,114 the joint fundraising goal of the IWMF, Leukaemia Foundation (of Australia), and WMozzies has passed the half-way mark toward its target of A$150,000. The funds raised will go to help further knowledge in five key areas:

- Genomics and epigenomics
- Signaling
- Immunology/immunotherapy
- Bone marrow/tumour microenvironment
- IgM monoclonal gammopathy of undetermined significance

WMozzies committee member Paul Lenon is planning to add to the target by doing a three-day fundraising walk in the Riverina of New South Wales.

Parliamentary Inquiry into Approval Processes for New Drugs and Novel Medical Technologies in Australia

Andrew Warden has written a comprehensive submission to the Federal Government to highlight the inequitable situation that patients with WM face in Australia. It seems that the high cost of PBAC (Pharmaceutical Benefits Advisory Committee) applications is making it not commercially viable for a company to seek reimbursement for a rare disease such as WM. Whatever the reason, the outcome for WM patients is not equitable. Other blood cancer patients receive funded access to ibrutinib, but WM patients do not. The approval process needs to evolve and have appropriate flexibility to handle current inequities being experienced by rare cancers.

Michael van Ewijk, WMozzies reporting

International Scene, cont. on page 30

International Scene, cont. from page 29

CANADA

The WMFC is very excited to announce the official launch of its new website, which happened at the end of January. We invite you to see what WMFC is all about at *www.wmfc.ca*. This was a major undertaking, and special thanks go to WMFC Board Member Cam Fraser, who organized this huge task. We are also grateful to Curtis Fraser and Tamara Brooks for their tremendous contribution to this project. Daniel Zlatin from the Ottawa Support Group has generously offered to be the web administrator for our new website. We already can see a difference in how he is adding more Canadian content, keeping our website interesting and user-friendly.

WMFC's fundraising campaign for research is being held during the month of May. We have encouraged everyone to consider how they can support WM research. Our own Paul Kitchen is setting the bar by walking for WM!

Support group meetings on Zoom continue to be going well. WMFC is thankful to the IWMF for their generous offer to provide Zoom subscriptions to our support group leaders. This will provide more independence and greater flexibility.

Chairman of the IWMF Board Peter DeNardis was the guest speaker on a Montreal Support Group Zoom meeting held on January 25. He spoke about his personal WM journey and about the services provided by the IWMF. He also gave a brief overview of the IWMF-LLS Strategic Research Roadmap and took time to answer questions.

Dr. Neil Berinstein from Sunnybrook Hospital in Toronto spoke at the national Zoom meeting on February 3. He gave a brief overview of WM and listed the preferred treatments in Canada. The most exciting announcement was a new clinical trial of which Dr. Berinstein is the principal investigator. This is a multi-center, open-label, single-arm Phase 2 trial of bendamustine, rituximab and the second generation BTK inhibitor acalabrutinib in previously untreated WM patients. More information about this trial can be found at *www.clinicaltrials.gov/ct2/show/NCT04624906*. This presentation can be found on our website at *www.wmfc.ca*.

Dr. Neil Berinstein spoke on Zoom at the national WMFC meeting in Canada.

Betty McPhee, WMFC, reporting

NEW ZEALAND

The situation for Waldenström Macroglobulinemia patients has improved over the past few years in New Zealand with the funding of bendamustine, after studies found the combination of bendamustine with rituximab improved the impact of rituximab. The newer treatments, such as BTK inhibitors, are not funded, though a few people have been able to go on trials or have paid for it themselves. For most people, the cost is prohibitive. Generally, New Zealand lags well behind other countries in funding for health.

A report by PharmaDispatch, dated June 2020 and commissioned by Medicine New Zealand, ranked us last in the list of twenty countries for publicly funded access to new medicines. Australia performed better, but still ranked only 17th.

Lea Hullett, reporting for WMozzies New Zealand

UNITED KINGDOM

COVID-19 in the UK

COVID-19 restrictions in the UK were tightened even further over the Christmas period, and a country-wide lockdown remains in place at the time of writing. WM patients, most of whom are deemed "clinically extremely vulnerable" have been advised to shield.

Meanwhile, in December the UK became the first country in the world to make a COVID-19 vaccine available. The vaccination programme has been rolled out throughout the UK, although the speed has varied from region to region. By February, most people in the WM community are reporting that they have either had, or have been contacted about, the vaccine. There are mixed reports of side effects caused by the vaccines, but overall, it is really providing hope for WM patients, their friends and families. Rebecca, a WM patient, shared her story about getting the vaccine to reassure other patients who were worried: *https://www.wmuk.org.uk/support/patient-stories/my-experience-covid-19-vaccine*.

We at WMUK continue to keep our COVID-19 pages up to date, giving people a reliable source of information during this difficult time, for example working with Dr. Dima el-Sharkawi, consultant haematologist at the Royal Marsden,

International Scene, cont. on page 31

and Dr. Shirley D'Sa, lead WM clinician at University College London, to produce a vaccine FAQ covering the most common vaccine-related questions.

Virtual Support Groups Launched

WM patients often report the loneliness or sense of isolation that comes with living with a rare disease. Before the lockdown, patient volunteer Bob Perry organised the UK's first regional face-to-face support group for WM patients. Unfortunately, the group has not been able to meet in over a year.

Although WMUK offers other online support, such as our Facebook group and email forum, we heard from patients that they missed chatting face-to-face. Working alongside Bob, we created the virtual support groups. These small sessions are held on Zoom for up to an hour, and allow people affected by WM to share concerns and exchange experiences in an informal environment. The groups have been a great success. With feedback such as "[attending the group] makes you feel less alone," every respondent to the charity's survey said they would recommend attending the groups to others affected by WM. The groups will continue to run on a weekly basis. More information can be found on WMUK's website: *https://www.wmuk.org.uk/get-involved/whats-on*

Zanubrutinib Appraisal

WMUK worked alongside Lymphoma Action and our WM clinician experts to put together a response to the National Institute for Health and Care Excellence (NICE) technology appraisal for assessing the licensing of zanubrutinib in the UK (except Scotland). Patient perspective took front and centre stage of the response, helping us to build a robust case for using the treatment, and we are hugely grateful to all the patients who submitted their experiences. The first appraisal committee meeting has been postponed and will now take place in September 2021.

Kat Tucker, Fundraising and Communications manager, WMUK, reporting

RESEARCH PARTNERS

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

The David and Janet Bingham Research Fund of the IWMF supports the following current research project:
Targeting MYD88 Signaling in WM

The Elting Family Research Fund of the IWMF supports the following current research projects:
Towards a Rational Targeted Therapy for WM by Kinome-Centered Loss-of-Adhesion and Synthetic Lethality Screens
Direct Targeting the MYD88 L265P Driver Mutation in WM
Targeting MYD88 Signaling in WM
Multiomic Analysis of DNA, RNA and Epigenomic Networks for Prognostication and Novel Target Identification in WM
MYD88L265P Signaling-Associated Multiplex Characterization of the Bone Marrow Microenvironment in WM Patients for Clinical Application

The Lynn M. Fischer Research Fund of the IWMF supports the following current research projects:
Factors Regulating Immunoglobulin-Producing B-Cells in Patients with WM
Multiomic Analysis of DNA, RNA and Epigenomic Networks for Prognostication and Novel Target Identification in WM
MYD88L265P Signaling-Associated Multiplex Characterization of the Bone Marrow Microenvironment in WM Patients for Clinical Application

The K. Edward Jacobi Research Fund of the IWMF supports current IWMF research

The Carolyn Morris Research Fund of the IWMF supports current IWMF research

The Ed and Toni Saboe Research Fund of the IWMF supports current IWMF research

The Paul and Ronnie Siegel Family Research Fund of the IWMF supports the following current research project:
CRISPR-Based Functional Characterization of WM Cells: Insights into Therapeutic Vulnerabilities and Strategies to Overcome Resistance

The Robert and Nadeline White Family Research Fund of the IWMF supports the following current research project:
Targeting MYD88 Signaling in WM

The Marcia Wierda Memorial Fund of the IWMF supports current IWMF research

The Yang Family Research Fund of the IWMF supports the following current research project:
Targeting MYD88 Signaling in WM

NAMED GIFT FUNDS

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

Baker Family Research Fund of the IWMF	Gary Green Research Fund of the IWMF	Gail Murdough Mission Support and Research Fund of the IWMF
Yoshiko Button Mission Support Fund of the IWMF	Dr. Robert Kyle Research Fund of the IWMF	Sesnowitz Family Research Fund of the IWMF
Friedlander-Scherer Family Research Fund of the IWMF	Lynn Martin and Carrie Wells Research Fund of the IWMF	Donald and Alison Weiss and Family Research Fund of the IWMF
Dr. Morie A. Gertz Research Fund of the IWMF	Dennis and Gail Mathisen Research Fund of the IWMF	Donald and Kathryn Wolgemuth Research Fund of the IWMF

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.

Ben Rude Heritage Society Roster

* Deceased ◊ Founding Member

ANONYMOUS (4)

JEAN-MARC AUDIBERT*

MARTIN BAER*

C. EDWIN BAKER*

JACK BAKER

JANET BAUSSER*

DAVID M. BENSON

BEVERLY J. BLOSS

VIVIAN AND ROBERT BOAS ◊

ELSA AND GARY BRADLEY

ARLOU BRAHM*

WILLIAM O. AND ELLEN KANER BRESNICK ◊

RUTH L. BROWN*

L. DON AND MARY BROWN

PETER CARR

GERALD PRESTON CLANCEY*

CHRISTINA CONLEY*

MRS. IVY COOPER*◊

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TONY DYE*

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NANCY KERR*

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Angie Meyer
Valerie Thompson
Melanie Thompson

Kenneth Miller
Brent, Theresa, Erin and Ben

Mary Ellen Mohr
Anonymous
Connie Mohr

My Parents
Bernard Robert Tyrrell

In Memory List, cont. on page 35

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IWMF is a 501(c)(3) tax exempt non-profit organization
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This issue of the IWMF Torch *was made possible by Pharmacyclics LLC and Janssen Biotech, Inc.*