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INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION

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CLINICAL TRIALS – THE CORNERSTONE FOR BETTER TREATMENTS

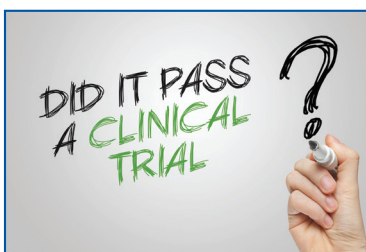
BY TOM HOFFMANN, MD
IWMF VICE CHAIR FOR RESEARCH

How do drugs come to market?

In 1812 tomato ketchup was invented and sold as a medicinal treatment for diarrhea, indigestion, rheumatism, and jaundice in the pre-Civil War era. Of course, there was no testing or truth to the promises. Many people were harmed by believing empty hoaxes about drugs, and something had to be done. In 1906 the US government developed the Food and Drug Administration (FDA), but it wasn't until 1938 that the Food, Drug, and Cosmetic Act increased regulatory authority by mandating a pre-market review of the safety of all new drugs and banning false therapeutic claims. Now, no reputable drug can come to market in the US without clinical trials and subsequent FDA approval. All clinical trials, including those for new drug therapies, must also pass Institutional Review Board (IRB) approval at their respective institutions.

Clinical trials have become the backbone for testing all new drugs and are the cornerstone of progress in disease treatment. They determine safety profiles, appropriate dosing, and correct usage. In order to get a drug cleared to start a clinical trial, it must first be tested vigorously in basic science projects. These include everything from test tubes to animal testing to human tissue testing. This is the kind of research that the IWMF supports. Many drugs are dropped from production at the basic science level and never enter clinical trials.

What is a clinical trial?



The National Institutes of Health defines a clinical trial as “a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.” The term “prospectively assigned” refers to a pre-defined process, such as randomization, specified in an approved protocol

that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

The drugs that make it past pre-clinical research must then pass three sequential clinical phases to make it to the mainstream market. Some go through a fourth phase after FDA approval.

Phase 0

In this phase only a few people are given a very small amount of the drug to see how the body reacts. This phase can be done as part of a Phase 1 study.

Clinical Trials, cont. on page 3

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Phase 1 – Safety

This phase is to determine if patients can tolerate the dosage of the drug that was determined to be efficacious in the pre-clinical basic science testing. Participants are started off at a very low dosage, which is slowly increased in increments to a level that will work on the disease. This helps to identify a safety margin for the drug, sometimes referred to as the “maximum tolerated dose (MTD).” The participants are usually healthy volunteers or people with the targeted disease. This phase usually takes around three months.

Phase 2 – Efficacy

Now that we know the drug is fairly safe, we want to see if it works on the targeted disease. This takes many more people diagnosed with the disease, and some may get more or less of the drug than others in the study. Combinations with other drugs that are known to work may be added. This usually takes several months to a couple of years. If you want to be sure you receive the drug being tested, rather than another drug as in a Phase 3 trial, a Phase 2 trial may be the best option for you.

Phase 3 – Comparison

This is the final phase before the drug is given FDA approval. The trial must have enough participants to be sure that it can scientifically prove it will work, compared to current drugs used for the disease. This typically requires a head-to-head testing between two drugs. Participants will know which drugs are being used in the trial. Phase 3 trials take one to four years, and the patient requirements are very stringent. The trial patients are randomly assigned either to the study group, which takes the new drug, or to the control group, which takes a drug that is normally used to treat the disease (referred to as the “standard of care” drug). These two groups must be as identical as possible. If the trial is “blinded,” each participant does not know which drug he or she is receiving in the trial, nor does the doctor (which is the optimal way to remove bias). There are some studies where patients are given a placebo (sugar pills or the like), but placebos are rarely used in trials of cancer drugs. The trial investigators must tell you if that is a possibility. No one is used as a guinea pig.

Phase 4 – Post-Marketing Surveillance

Phase 4 trials are done after the drug is approved. They may need hundreds to thousands of patients to reach statistical results. This is where drugs are tested in different diseases or in patients who weren’t appropriate in the other phases. Rarer side effects will be found, and long-term survival is determined. These can take five to ten years.

The time from discovery of a drug to an FDA approval is

ten to twenty years. Adding Phase 4 lengthens that time. The drug can then be tried by patients with other diseases that are similar to the disease tested in the clinical trial. That is called using the drug “off label.” It is best if that is done in a new trial. The number of patients needed for trials and the length of trials are hobbled by the number of patients with the disease. Waldenstrom trials take longer to perform because there aren’t enough of us to enroll in the process to obtain statistically relevant results. We tend to use things that work for our “cousin” diseases such as chronic lymphocytic leukemia or multiple myeloma, but this is not always in our best interest. We must also understand that FDA approval does not mean that all of the side effects have been found, or that the drug won’t be unapproved in the future because of some unforeseen safety issue.

...FDA approval does not mean that all of the side effects have been found...

Why would you want to enter a clinical trial?

- You want to contribute to science.
- Current drugs don’t work for you.
- You are afraid of the side effects of current approved drugs.
- Drug companies cover the cost of trial drugs and a lot (but not all) of the other trial expenses.
- Your disease is genetic, and you want to help your family.
- You want access to new treatments.
- Your doctor thinks a trial would be best for you.
- The new drug is a better fit for you.

As you can see, there are many reasons that could make clinical trials appropriate for you as a WM patient. The drug(s) in any given trial may be the best fit if available therapies have not been successful, or if you are unable to tolerate conventional drugs because of your past treatments or other health conditions. Also, the financial aspects of some conventional drug regimens may be a burden that you cannot handle, while trial drugs are gratis. There are many more prospective drugs in the pipeline than ever before. As we learn more about the mutations occurring in Waldenstrom, we are finding that newer drug regimens are able to target the mutation(s) you may have with fewer side effects. Newer trial drugs may be focused more on your particular mutation, disease location, or physical situation than current proven drugs.

What are the problems of entering a clinical trial?

- Clinical trials are tightly controlled and you must fit into their inclusion and exclusion criteria.
- You will usually have to travel for each course of the drug and for lab testing. Some protocols allow your local MD to administer the drugs. Your lab testing must be done in the same lab as the institution conducting the trial, but blood samples can be mailed from your local MD to the institution.
- You will have more tests and lab work required for a trial than using an approved drug.
- You must stay on their protocol if possible.

How do I get into a clinical trial?

Before participating in a study, talk to your health care provider and learn about the risks and potential benefits. The easiest way to get into a trial is to have your oncologist

do the legwork. If you have access to the trial phone number, you can call the trial administrator. You can find current trials for WM here: <https://clinicaltrials.gov/>. Just type “Waldenstrom” in the “Condition or disease” line and “United States” or the desired country in the “Country” line.

PATIENT PERSPECTIVE ON CLINICAL TRIALS

BY RON TERNOWAY, CONTRIBUTING WRITER



Let's start with a patient survey. Tick the box that fits:

- ☐ I have participated in one or more clinical trials.
- ☐ I applied for a clinical trial but was not accepted.
- ☐ I have never considered a clinical trial.
- ☐ What's a clinical trial?

Let's work backwards through this list:

A clinical trial is a scientifically controlled study of the safety and effectiveness of a therapeutic agent using consenting human subjects. In other words, a clinical trial is an experiment using the scientific method, like you did in high-school chemistry, and patients are part of the apparatus and materials. The trial is NOT ABOUT YOU—it is about proving or disproving a hypothesis.

The decision to participate in a clinical trial should be a thoughtful process in which patients carefully evaluate the many aspects of the clinical trial option. Among the personal considerations:

Why am I doing this trial?

- Desperation – out of options
- Altruism – advance research for others
- Blind Optimism – this drug will cure me!
- Considered Optimism – my research says GO FOR IT!

Eligibility: What types of eligibility issues could be barriers for me entering a specific clinical trial?

Requirement for Medical Tests: Am I willing to undergo extra testing that may be required, such as bone marrow biopsies, scans, and frequent blood tests?

Requirement for Travel: Am I willing and able to travel for treatment and testing?

Insurance Coverage: If my health insurance will not pay for additional testing, does the trial sponsor cover the cost? Does my health insurance pay for routine tests and drugs for side effects caused by the trial regimen?

Unknown Risks of Treatment: Am I able to cope with the uncertainty of unknown risks of the trial drugs?

Protection of Patient Rights: How are my rights protected during a clinical trial?

Continuation of Treatment Beyond Clinical Trial: If the drug is working for me, can I continue treatment after the end of the trial?

Patient Perspective on Clinical Trials, cont. on page 5

Pros and Cons of Clinical Trial vs. Standard Care: How do I make the right treatment decision?

That's an awful lot of considerations, so where can you turn for help? Before you decide, here are some questions to ask your doctor:

- What is the scientific rationale for using this therapy for my cancer?
- What is the trial phase, and what are the goals or endpoints?
- Has this drug been used on humans before? If so, what are the side effects?
- How is the treatment administered and for how long?
- What are the number and frequency of medical tests and clinic visits?
- How many extra tests are specifically for trial purposes?
- What is the likelihood that this therapy will help me?
- Are there approved or standard therapies we should try first?

For non-American WM patients, the choice of a clinical trial as first treatment may affect subsequent availability of standard treatments. As a case in point, in Australia the bendamustine/rituximab combination is only available free from the National Pharmaceutical Benefits Scheme to “previously untreated” WM patients. Relapsed patients prescribed bendamustine must pay full price for it from the manufacturer. The Canadian and United Kingdom health systems have similar hurdles of free access to certain drugs, dependent on the patient's treatment status.

I would like to share my own experience with clinical trials, and the experiences of some fellow travellers. The first clinical trial I applied for was open to non-Hodgkin lymphoma (NHL) patients who were refractory to rituximab. Because most NHL types include lymph node involvement, one of the criteria for admission was a CT scan showing that rituximab had not reduced lymph node size. Like many of us, I had no lymph node involvement, no CT scan, and no way to be part of the trial.

I didn't give up, and in December 2014, I was accepted into a clinical trial for ibrutinib. I have gone from bedridden and transfusion-dependent to feeling healed—not cured yet, but healed. My Story of Hope is here: <https://www.iwmf.com/get-support/patient-stories/canada-ron-ternoway-how-clinical-trial-changed-my-life>.

But ours is a perplexing malady, with a wide variety of symptoms and of responses to treatment, so outcomes may vary, including on clinical trials.

WM patients on the IWMF Facebook page benefit daily from the clarity, compassion, and competence of group administrator Meg Mangin. Meg was one of the early participants in the first ibrutinib trial, much to her ultimate

chagrin: “I joined a clinical trial because it offered a new treatment that wasn't chemotherapy and that was very attractive to me. Also, this medication is very expensive, and it was provided free during the trial. As a nurse, I'm aware of the importance of clinical trials to develop new treatments, and I wanted to do my part.

“Unfortunately, after taking this drug for two months my liver enzymes rose dramatically. Lab tests ruled out other causes, and when my liver enzymes failed to return to normal within

*I joined a clinical trial because it offered a **new treatment** that wasn't chemotherapy and that was very attractive to me.*

a month, I had to be dropped from the trial. This very rare side effect is serious, but I'm glad it happened while I was in a clinical trial because it was discovered quickly with routine monthly lab tests. The clinical trial didn't have the outcome I was hoping for, but I don't regret participating.”

Marcia Klepac, IWMF support group leader in Ohio, Pennsylvania, and West Virginia, may hold the record for most WM clinical trials—eight. You can read her Story of Hope here:

<https://www.iwmf.com/get-support/patient-stories/marcia-klepac-different-path%E2%80%A6my-world-clinical-trials>.

Marcia's capsule summary: “When I started on my clinical trial adventure, my goal was to search for targeted therapies to avoid standard chemotherapy, which didn't work for me. Trials for WM were just beginning and very scarce, so I jumped at any opportunity. Because research with WM was very limited, it was basically a hit or miss situation.

“Today, due to the extraordinary research and abundance of clinical trials, the decision to enter a trial should be a much more selective process. Genetic mutation analysis can provide very important guidance in determining whether a clinical trial will be effective for an individual patient. With so many treatment options now available outside of a trial, it is important for the patient and physician to evaluate whether a trial is in the best interest of the patient in terms of risks and benefits. Ideally, the patient considering a trial will discuss the option with a trusted non-trial physician in collaboration with the clinical investigator.”

Thank you to all trial participants, and especially to you, Marcia, for being such a courageous clinical trial pathfinder and for sharing your experiences and wisdom with *Torch* readers.

TODAY, TOMORROW, AND BEYOND

BY NEWTON GUERIN, CEO OF THE IWMF

It has been a little over a year since the IWMF Board of Trustees took a hard look at our organizational priorities and what we should do to have the greatest impact going forward. It was clear that there was much more that could be done with additional resources and a renewed sense of focus and urgency.



Newton Guerin

From those discussions, they crafted these six **Compelling Intentions** to provide guidance and direction and help tell our story of where we want to go and how we plan to get there:

1. Assume leadership to significantly increase the number, scope, and coordination of WM research projects.
2. Become the global thought leader and authoritative source of information and resources in WM.
3. Every doctor and nurse worldwide who works in blood cancer knows about the IWMF and the resources we offer.
4. Every person diagnosed worldwide with WM knows about the IWMF and the resources we offer.
5. Expand worldwide awareness of WM and the IWMF.
6. Significantly increase and diversify our sources of funding to support our mission.

During its August meeting, the Board of Trustees took several key actions that will continue to move the IWMF forward. First, they reviewed the components of our strategic plan (IWMF Vision, Mission Statement, Values, and Compelling Intentions) and agreed that this plan continues to be relevant and reflects our most important organizational priorities. It enables us to tell our story to all IWMF stakeholders, using big ideas that are simple to understand. It's optimistic and focuses on the future. We cannot underestimate the importance of sharing a common vision that provides organization-wide focus and direction. Our vision of a "World Without WM" is simple and compelling and is shared by volunteer and staff leaders throughout the organization.

The Board also reviewed and approved funding an additional \$500,000 to renew Dr. Steven Treon's legacy research project. Since 1999, the IWMF has invested over \$18,000,000 in 50 research projects throughout the world.

Our ability and capacity to take on these important goals is dependent on how well we "significantly increase and

diversify our sources of funding to support our mission" (Our Compelling Intention #6). With that in mind, the Board approved the expansion of the "Imagine A Cure" campaign to raise an additional \$25 million over the next five years, bringing the overall campaign goal to \$50 million. Getting there will require focusing on several key sources of funding that could significantly increase our revenue:

- **Corporate/pharmaceutical partnerships:** Our outreach efforts and relationship-building with our corporate partners has resulted in over \$400,000 revenue in 2020. These sponsorship dollars fund some of our most important programs, including the Virtual Ed Forum, support groups, publications, and translations of publications into foreign languages. In addition, their support will fund the design and launch of our new website to better meet the needs of the WM community worldwide.
- **Traditional donor development:** We must implement relationship enhancement strategies and practices with donors at all giving levels. Encouraging more donors to participate in the Ben Rude Heritage Society by including the IWMF in estate planning will be critical to our success.
- **IWMF's Signature Event:** Our 2020 Virtual Walk for Waldenstrom's is already our most successful ever and will continue through the end of the year. If you haven't already signed up, there's still plenty of time. It's a great way to raise money while creating awareness about WM and its impact on the lives of patients and caregivers.

With each of these development strategies, we will continue our strong commitment to good stewardship of our donor dollars. Our reputation is one of our greatest assets, and we are extremely proud of 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.

We experienced our first virtual Ed Forum on August 27-28. This was our 25th Ed Forum and by far our largest ever. One of the biggest obstacles we all face during these very challenging times is staying connected with each other. This pandemic gave the IWMF an opportunity to engage a much larger global audience through this virtual Ed Forum. And that's what we did! The Ed Forum Committee did an incredible job in planning and producing an international

Today, Tomorrow, and Beyond, cont. on page 7

event with over 1,300 people from 30 countries throughout the world registering to hear uplifting and encouraging updates from leading experts in the field of WM. Hundreds more have since accessed this program on demand. If you were unable to join us, check with the IWMF website, where the links will be announced and posted soon. Also, because our time was limited during this two-day virtual Ed Forum, we supplemented our program with a Global Educational Webinar Series. Please visit the www.iwmf.com website events calendar for a complete schedule of speakers and topics. These programs would not have been possible without our speakers who volunteered their time to share their knowledge and expertise. Thank you to each of them!

We also would like to thank our sponsors for underwriting production costs and enabling the IWMF to offer this Ed Forum at no cost to our participants. A very special thank you to our 2020 Ed Forum Title Sponsors: BeiGene Pharmaceuticals, Pharmacyclics, and Janssen Biotech, along with other sponsors: Collectar Biosciences, The Treadway Foundation, and X4 Pharmaceuticals. None of our sponsors

influenced our program or its content in any way. They all recognize that the IWMF is a leading source of accurate and up-to-date information and fully support our commitment to providing independent information for patients and caregivers.

At the conclusion of the Ed Forum, we paid tribute to Carl Harrington as he plans to step down as IWMF Board chair at the end of 2020. Carl is truly a very special person and an inspiration to us all! Under his leadership, the IWMF has seen tremendous growth in revenue that has enabled us to expand outreach to patients and caregivers through our information, education, and support programs. We have significantly increased our investment in funding research projects that have resulted in better therapies and brought us closer to a cure.

Carl's impact on the WM community and his leadership of the IWMF 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."

RESEARCH IS THE IWMF'S CONTINUING SUCCESS STORY

BY GLENN CANTOR, SCIENCE EDITOR

Editor's Note: In 2019, the IWMF awarded funds for three new research proposals. The July 2020 issue of the Torch described two of the proposals; this article describes the third.

Dr. Yong Li, Baylor College of Medicine, Houston, Texas

Direct targeting of the MYD88 L265P driver mutation in Waldenström's macroglobulinemia

Summary:

- More than 90% of WM patients have a specific abnormality (mutation) in the MYD88 protein, termed MYD88 L265P. The abnormal MYD88 L265P protein causes WM cells to grow and proliferate.
- This research aims to discover a drug that will specifically block the abnormal MYD88 L265P protein in WM cells but spare the body's normal MYD88.
- A new drug to block abnormal MYD88 L265P in WM cells would be useful to most WM patients.

Proteins are composed of long strings of amino acids. More than 90% of WM patients have an abnormal change (called a "mutation") in one particular amino acid in a protein known as MYD88. This mutation involves a change in the 265th amino acid, from an amino acid called leucine ("L") to a different amino acid called proline ("P") and is abbreviated as MYD88 L265P. The change causes the MYD88 protein to become abnormally active and send



*Dr. Yong Li's laboratory group at Baylor College of Medicine
Dr. Li is on the right in the light blue shirt.*

signals to the WM cell to grow and proliferate. This single mutation is the major driver of WM.

Considerable drug development effort has focused on blocking the excessive cell signals resulting from the MYD88 L265P mutant protein. For example, excessive activation of a protein called Bruton's tyrosine kinase (BTK) is one consequence of the MYD88 L265P mutation. A small molecule drug, ibrutinib, blocks the abnormal activation of BTK and has been approved to treat WM, and

Research, cont. on page 8

newer BTK inhibitors like acalabrutinib and zanubrutinib have been developed.

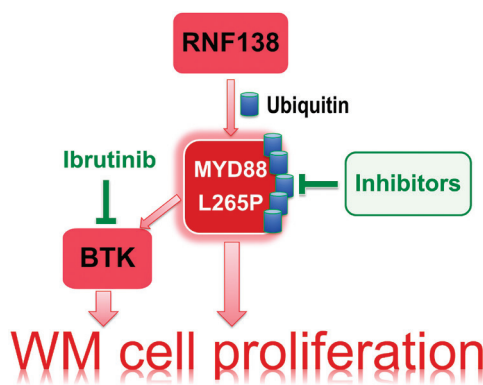
Dr. Li and his group at Baylor College of Medicine are instead focusing on the original source of the problem—the abnormal, mutated MYD88 protein itself. Their IWMF-funded proposal is to discover a new drug that will block the abnormal MYD88 L265P protein which drives WM, but not get in the way of the normal MYD88 protein in healthy cells, where it plays an important role in normal immune function.

Before submitting this proposal, Dr. Li's laboratory made an innovative observation, that the abnormal MYD88 L265P protein is modified in a unique way, unlike normal MYD88. This unique modification of MYD88 L265P may be the critical weakness that would allow investigators to target drugs to it. Specifically, his team observed that another protein, called RNF138, attaches small regulatory proteins called ubiquitins at specific places on the abnormal MYD88 L265P protein, but not on the normal MYD88 protein. Dr. Li's group found that once ubiquitins are attached to MYD88 L265P, additional changes ensue,

which then lead to abnormal signaling and growth of the WM cells.

Dr. Li and his group hypothesize that a drug which prevents RNF138 from interacting with MYD88 L265P would prevent ubiquitins from attaching to MYD88 L265P and would control the growth of WM. To discover a drug that does this, they will start with high-throughput screening. They will examine the effects of 110,000 different compounds in a rapid, automated way. Any compounds that show activity will be further tested, first in molecular and cellular (“in vitro”) assays in the laboratory, and then in a mouse model (“in vivo”) to test for anti-tumor activity against WM cells implanted under the skin of mice.

Successful completion of this innovative project may lead to development of a novel WM drug that complements existing WM therapies. Importantly, the molecular target of Dr. Li's group, MYD88 L265P, is found in more than 90% of WM patients, suggesting that a successful drug would be widely applicable, even with the diversity of clinical presentations seen among WM patients.



Key: Red arrows: Proliferative signals. Green T's: Drugs (or potential drugs) that inhibit. Blue cylinders: Ubiquitins

Most WM patients have a mutation called L265P in the key signaling protein MYD88. It is known that MYD88 L265P causes proliferation of WM cells by excessively activating a second signaling protein, BTK. Ibrutinib blocks BTK activation, which controls WM cell proliferation.

Dr. Li's group is working on another approach. They found that the RNF138 protein attaches small proteins called ubiquitins to the MYD88 L265P protein, but not to normal, wildtype MYD88 protein. Could this interesting finding be the Achilles heel that allows scientists to target drugs to the mutant MYD88 protein and avoid altering the normal MYD88? Dr. Li hypothesizes that the attachment of ubiquitins enables MYD88 L265P to stimulate WM cell proliferation. The lab is attempting to discover a drug to inhibit RNF138-mediated ubiquitin attachment to MYD88.

The IWMF recently announced the new 2020 research grant awards. Two scientists received grants, Dr. Zachary Hunter and Dr. Ruben Carrasco, both at Dana-Farber Cancer Institute in Boston, MA. Dr. Hunter's project is "Multiomic analysis of DNA, RNA, and epigenomic networks for prognostication and novel target identification of WM," and Dr. Carrasco's project is "MYD88 L265P signaling-associated multiplex characterization of the bone marrow microenvironment in WM patients for clinical application."

Funding for these new projects includes support from the Waldenström's Macroglobulinemia Foundation of Canada (WMFC), the Leukaemia Foundation of Australia, and Waldenström France.

Dr. Tom Hoffmann, Vice Chair for Research of the

IWMF, said "Each year the IWMF solicits requests for proposals from the research community, and each year, we receive many high-quality proposals from researchers around the world. The quality of the proposals and the potential for impact on the lives of those affected by WM is astounding, making it a difficult process to choose among them. In a way, this is a good position to be in for the IWMF—with many top-quality proposals to select from—but naturally, we wish we could fund them all!" The two winning projects were selected from ten global proposals.

These two projects will be discussed in more detail in upcoming Torch articles in this series on IWMF-funded research.

THE 2020 ED FORUM: A VIRTUAL SUCCESS

BY SECRET WALLIE

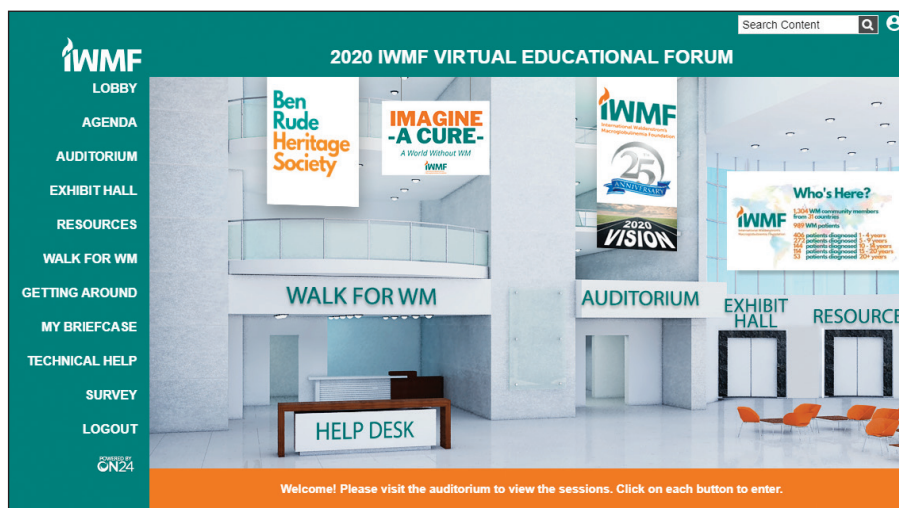
As many of you know and experienced, the 2020 IWMF Educational Forum was held virtually, out of an abundance of caution for everyone involved. In June, the coronavirus pandemic was still of great concern in Seattle (where the “live” forum would have taken place), in the United States, and in the world. As a result, staff and volunteers of the IWMF worked many, many hours behind the scenes to provide an abbreviated virtual version of the Ed Forum for the global WM community on August 27-28.

One cannot thank the participating speakers enough for the time they took to record their presentations and to be available for the live question and answer sessions! They are truly amazing, caring doctors who are deserving of our undying gratitude—undying because, due in part to their efforts, we ARE all living longer lives with WM!

The virtual Forum this year captured sentiments, activities, and reactions remotely. Hopefully, at some point in the future, the in-person experience will be available once again, where patients and caregivers can share compassionate hugs and handshakes and stories of their experiences, while also having the opportunity to talk one-on-one with the amazing clinicians and researchers who are on hand to present the latest information regarding WM symptoms, treatments, and research.

Harrington, welcoming everyone to the Virtual Ed Forum and providing some interesting facts and statistics regarding what the IWMF has accomplished over the years, the age ranges and longevity of WM community members and Ed Forum attendees, and the vision for the future for the WM community. Carl provided some tips on how to get to a world without WM: keep giving of your time, money, and expertise to the IWMF, keep participating in clinical trials, and keep sharing experiences with fellow WMers, utilizing the many mechanisms available via the IWMF (LIFELINE, support groups, affiliates, Connect, and Facebook). The added bonus, of course, was that we got to see one of the youngest WM “cheerleaders”—Carl’s 3-month-old grandson—cheering us on and looking forward to a world without WM for his grandfather. By the way, the professional-sounding “voice behind the activities” was that of Jeremy Dictor, the IWMF’s director of development and communications.

The formal presentations for the day began with Dr. Jorge Castillo, associate professor of medicine at Dana-Farber Cancer Institute, first taking us through the “Current Treatment Options for WM,” and then, in the second presentation, giving us a look into the future by discussing “Treatments on the Horizon for WM.” Dr. Castillo always provides a concise and informative review of both current and upcoming treatment



Virtual meeting “hotel” lobby with activity choices

Thursday morning, there was a heightened sense of anxiety on the part of the Ed Forum volunteers—all were going through worst case scenarios of what could potentially go wrong during each of the sessions. Would internet outages occur, would phone lines go down, would weather impact the ability of speakers to participate, would everything still work as tested and planned once the “live” switch was flipped? And how many people would actually attend? Initial registrants totaled over 1,300, hailing from over 30 countries!

Day 1 began with an introduction by IWMF Board Chair Carl

options, along with the pros and cons of each. Secret Wallie encourages those new to WM, as well as long-time veterans, to view the video recordings, as there is much to be learned from both presentations. Both of Dr. Castillo’s sessions were followed by live interactive Q&A sessions, with IWMF Board Member (and 17-year WM survivor) Peter DeNardis posing questions that attendees submitted when they first registered for the event, along with questions posed by participants of the online discussion group, IWMF Connect, and by IWMF

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Facebook followers. The Ed Forum Committee reviewed hundreds of questions that were submitted in advance and narrowed them down to 20 or so questions about topics that were submitted more often. Even so, there just wasn't enough time to address them all!



Dr. Steven Treon

The last presentation of the day was the much-anticipated one by Dr. Steven Treon, director of the Bing Center for WM at Dana-Farber. Dr. Treon is a professor of medicine at Harvard Medical School and chair of the WM Clinical Trials Group. He presented details of past and ongoing research and discoveries (many of which occurred at the Bing Center) with regard to WM treatments and pointed toward what lies ahead as we look to the future for WM. Without any prodding from the IWmf, Dr. Treon also made it a point to raise awareness that many of these discoveries were because of research funding provided by the IWmf and its community of patients and caregivers. His session also was followed by a live question and answer session, where Dr. Guy Sherwood, former IWmf Board Member and a 20-year WM survivor himself, posed questions to Dr. Treon. Again—as earlier—there were many, many more very good questions than time available for this part of the session.

The formal part of the first day of presentations concluded at that point, and the Ed Forum volunteers all breathed a huge sigh of relief. There were no major outages or issues, other than perhaps folks not having received the notification email with the link for the event, something which will be addressed and corrected in the future. Fortunately, staff were on hand in the IWmf office, responding to calls and emails for assistance and to postings on Connect and Facebook from folks experiencing technical issues. Overall, an amazing effort on the part of all involved.

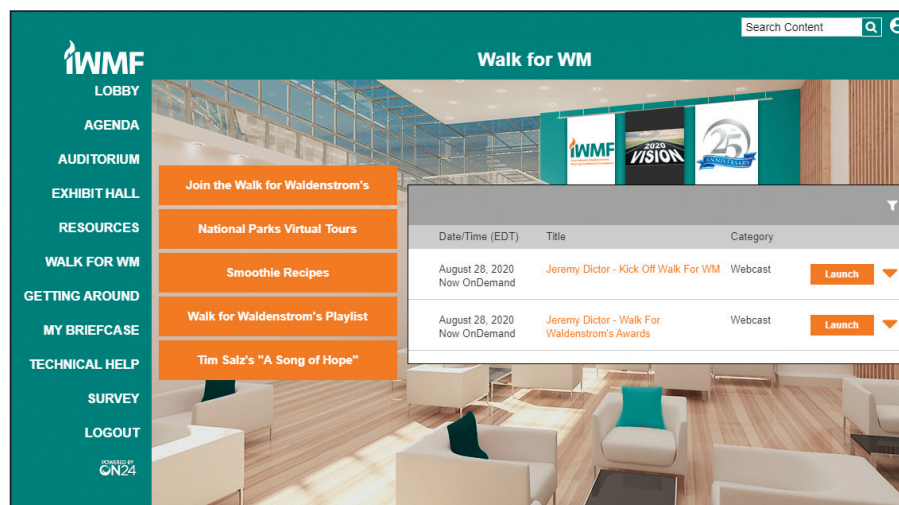
Of course, what was missing was the opportunity to sit together at breakfast, lunch, and dinner, or perhaps just to chat together throughout the day with fellow WMers from around the world. The compassion and support we provide each other at such events is always quite uplifting and invigorating. Hopefully, that was made possible even virtually via the presentations, question and answer sessions, and other information available on the virtual Ed Forum platform.

Secret Wallie had a few moments after Dr. Treon's presentation and before dinner at home, so he did take advantage of the opportunity to wander around the virtual Forum "rooms":

- The Exhibit Hall, which had information from each of the sponsors whose funding helped make the virtual Forum happen (free for participants, by the way!)
- The Resource area that contained various publications about the Ed Forum, the IWmf, and ways to interact with fellow WMers
- The Walk for WM (more on this later)
- The surveys (if you haven't done so yet, please take the time to complete the surveys of your opinions regarding the Ed Forum!)

The second day began at 9am with the kickoff for the 4th Annual Walk for WM, led virtually by Jeremy Dictor, who encouraged all of us to participate and to take a few minutes to move around and get some exercise before the presentations began. Incidentally, the IWmf, through the generosity of the many, many participants and their friends and family who gave on their behalf, received over \$60,000 to advance the search for better treatments and a cure for WM and to help the IWmf provide support, information, and education (like the Ed Forum) to WMers around the world.

The Walk was "officially" kicked off with a series of warm-up exercises led by Stacy Kennedy, registered dietician and licensed nutritionist with a specialty in oncology at Dana-Farber Cancer Institute. She is also a certified trainer and fitness expert, and has presented at past Ed Forums on the topic of health, exercise, and nutrition; it was exciting to be joining her on a morning workout. Even her dogs got into the act and wanted to participate with us that morning!



Entertainment possibilities for the Walk

Secret Wallie did participate in the Walk in his neighborhood with his wife, enjoying the morning air and taking steps in honor of and in support of the WM community around the world—we're all in this together! After the Walk concluded, Jeremy presented awards to the top fundraiser groups and individuals for the event and encouraged folks to continue giving and encouraging others to give at <https://www.mightycause.com/event/Walkforwm2020>. You can also set up a fundraiser any time of the year; just contact Jeremy Dictor if you need help doing that.



The Walk for Waldenstrom's tee, back view



Don and Mary Brown with grandsons Jack and Charlie doing The Walk

The activities for the rest of the day included a presentation by Dr. Stephen Ansell and the always much-anticipated “Ask the Doctors” session.

Dr. Stephen Ansell is a professor of medicine at Mayo Clinic College of Medicine and Science and chair of the Mayo Clinic Lymphoma Disease-Oriented Group. The IWMF President and CEO Newton Guerin welcomed the participants to the second day of activities, thanked the sponsors for providing generous funding for this event, and stressed that none of the sponsors had any influence on the IWMF or on what was presented during the Ed Forum. Newton also notified everyone that additional webinars will be taking place in the coming months and to stay tuned for further details.



Dr. Stephen Ansell

Dr. Ansell, who also is a Board member of the IWMF, presented details about the IWMF/LLS Strategic Research Roadmap and the exciting discoveries with regard to WM

that are taking place due to the Roadmap research efforts, and encouraged everyone to participate and be engaged with what the IWMF is doing on their behalf. While great progress has been made, Dr. Ansell did want to point out that we still have a lot left to learn and to research if we want to find a cure for WM. He stressed that we need to get to a world without WM, and that funding by the IWMF has made a dramatic impact on the understanding of the disease and the development of new therapies for it. Anyone listening to his presentations quickly realizes that, while he is very knowledgeable about how WM behaves and what type of research is needed, he is also able to explain complex hematologic processes and issues in a manner that anyone can grasp and understand. In fact, each of the presenters had an amazing ability to distill complex topics into terms and examples that lay patients and caregivers could understand, as they seek to get a better understanding of their disease and how best to live with it. Peter DeNardis led the Q&A session at the end of Dr. Ansell's talk and presented additional insightful questions from fellow WM patients and caregivers around the world.

The Ed Forum activities concluded with the ever-popular “Ask the Doctors” session, in keeping with the time-honored tradition of the Ed Forum. This session is always the most anticipated one, and for good reason, as it's an opportunity to get specific questions answered that pertain to issues and concerns impacting the larger community of patients. Dr. Ansell, Dr. Castillo, and Dr. Treon participated in the session, with Dr. Tom Hoffman, himself a WM patient and Board member of the IWMF, presenting questions to the doctors. Questions covered a wide variety of topics—including symptoms, treatments, diagnosis, and research, and, of course, COVID-19. This session was fully live, and one could see the virtual nature of the session, with Dr. Hoffman presenting questions from his home office chair, Dr. Ansell participating from his office, Dr. Treon from his home office, and Dr. Castillo from his car (he was at a park with his wife and children and confined himself to his car while they were enjoying their time there). The care and commitment on behalf of these amazing doctors was fully evident by their taking time out of their busy work and home schedules to speak to us and answer our questions.



Dr. Jorge Castillo

The Ed Forum was almost over at that point... but a special, unexpected activity occurred. It was announced that Carl Harrington, chair of the Board of Trustees of the IWMF would be stepping down from that role. Dr. Hoffman and Drs. Ansell, Castillo, and Treon gave strong testimonials to the amazing achievements that the IWMF has had under Carl's leadership for the past seven years and encouraged the members of the IWMF to work diligently to continue to strive towards a world without WM. It won't happen without the

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efforts of the IWmf. Thank you, Carl Harrington! We cannot thank you enough for everything you've done on behalf of WMers around the world!

Next year's "live" Ed Forum will be in St. Louis, Missouri, pending the coronavirus situation, of course, and the IWmf Board of Trustees is developing a succession plan to replace Carl later this year.

The IWmf office staff and volunteers spent many, many hours putting this event together. Special mention should be made for the hard work performed by staff members Sara McKinnie, Jeremy Dictor, Michelle Postek, and Donna Cutillo and by volunteers Rick Savoy, Lu Kleppinger, and Lisa Wise. One could tell it was a labor of love, as every detail was meticulously planned and well-executed. They

even were able to share a song penned by a fellow WMer to encourage everyone on the Walk: see Tim Solz's "A Song for WM" at <https://www.youtube.com/watch?v=svySGKdjE7Y>.

Secret Wallie did see postings on Facebook about the Ed Forum, as well as pictures folks took of themselves walking on each other's behalf, and heard that several patients were messaging and texting each other during the Ed Forum, discussing statements made by the presenters. Sure, it was a virtual event, but the commonality of purpose and the camaraderie were still quite evident as we look toward a "World Without WM!"

Editor's note: Please check www.iwmf.com for the video links to these Forum sessions. They were not yet available before the Torch went to press.

THE USE OF BTK INHIBITORS IN COVID-19 PATIENTS

BY GLENN CANTOR, SCIENCE EDITOR

There has been IWmf Connect discussion recently about the use of BTK inhibitors in COVID-19 patients, based on reports from two groups with preliminary but potentially positive findings about ibrutinib and acalabrutinib in COVID patients. They suggest that BTK inhibitors may be useful for treating (or even avoiding) the severe, life-threatening form of COVID disease.

Ibrutinib or acalabrutinib do not prevent COVID infection. It is still important to practice social distancing, wash hands frequently, and wear a mask. The papers suggest it may be possible for people who are infected to only experience the milder form of disease and avoid or recover from severe disease if they are receiving BTK therapy.

With COVID, there are different phases of disease. Many people who are infected with the SARS-CoV-2 coronavirus are completely asymptomatic. Others develop mild respiratory disease or have other symptoms. Some go on to hospitalization, but do not develop life-threatening respiratory disease. Others develop severe disease, with exaggerated inflammatory responses and cytokine storms, which requires mechanical ventilators and often results in death.

The first paper, published in the journal *Blood* online on April 16, was from the Dana-Farber Cancer Institute's WM group—Drs. Treon, Castillo, and Yang, among others. The second paper, published in *Science Immunology* on June 5, was from a group at the National Institutes of Health (NIH), working in collaboration with hospitals around the US.

Dr. Treon's group used ibrutinib (Imbruvica), a BTK inhibitor approved for WM, while the NIH group used acalabrutinib (Calquence), a second-generation BTK inhibitor approved for CLL and mantle cell lymphoma, but not yet for WM.

Dr. Treon's paper described six WM patients who had been on ibrutinib treatment for a number of years. Five of the patients, dosed at 420 mg/day, became infected with the SARS-CoV-2 virus but only developed mild COVID-19 disease, with cough and fever but no difficulty in breathing, and did not

require hospitalization.

The sixth patient, who had significantly worse disease, was described in more detail. He had been on a reduced ibrutinib dose of 140 mg/day, developed difficulty breathing, low blood oxygen (hypoxia), and was hospitalized. In the hospital, this patient received supplemental oxygen, but did not require a ventilator. At first, his ibrutinib was discontinued, and he was treated with other drugs. He had adverse cardiac events and became more hypoxic, so the other drugs, including hydroxychloroquine, were withdrawn, and ibrutinib (140 mg/day) resumed, along with other treatments. At that time, his oxygenation and blood values improved, but five days later, his condition worsened and he required a mechanical ventilator. Then, his dose of ibrutinib was increased to 420 mg/day, and he improved rapidly. Two days after the ibrutinib dose was increased, he no longer required a ventilator and within a few days was discharged home.

*...it was important to **further validate** these observations by doing clinical trials.*

Dr. Treon's paper was deliberately published as a preliminary, "hypothesis generating" observation to alert the medical community rapidly. Dr. Treon pointed out that it was important to further validate these observations by doing clinical trials.

Interestingly, a similar observation was published afterward from a group at Mt. Sinai Hospital in New York, with CLL patients who were being treated with ibrutinib and then became infected with SARS-CoV-2. Again, the small numbers of cases precluded drawing conclusions, but two patients who continued ibrutinib recovered quickly, while two of eight patients for whom ibrutinib or acalabrutinib treatment was discontinued developed severe respiratory failure and died.

The Use of BTK Inhibitors, cont. on page 13

In mid-June, I listened to the NIH-FDA Mini-Symposium on the role of cytokines in COVID-19 disease. One of the speakers, Dr. Mihalis Lionakis, was from the NIH group that did the acalabrutinib study, published a short time after Dr. Treon's paper. It was a fascinating presentation.

In that paper, NIH selected COVID patients who did not have WM and who were severely sick, either hospitalized with supplemental oxygen (11 patients) or on ventilators (8 patients). These patients had never previously received a BTK inhibitor. Dr. Lionakis explained that they chose the second generation BTK inhibitor acalabrutinib instead of ibrutinib because one of the off-target, undesirable effects of ibrutinib is that it inhibits a protein called ITK, which results in decreased T-cell function. Since T-cells are involved in killing viruses, they wanted to preserve T-cell activity.

Acalabrutinib was given at the approved dosage used in CLL patients, 100 mg/twice daily, and was given for 10 or 14 days. Since treatment of COVID was an off-label use, the doctors had to be careful to explain the treatment and its possible adverse effects and obtain informed consent from the patients or their legally authorized representatives. About half of the patients received concurrent steroids and/or hydroxychloroquine, and none of them received the anti-IL-6 receptor antibody or remdesivir.

These patients were initially quite sick. Most responded rapidly when treated with acalabrutinib, as measured by improved oxygenation—often within 1-3 days—and improved blood values. Twelve of 19 recovered well enough to be discharged on room air, without supplemental oxygen, two were still hospitalized or at a rehabilitation center, and five died. None of the patients had drug-related toxicities, such as cardiac arrhythmias, significant bleeding, diarrhea, or opportunistic infections.

BTK is a signaling molecule, which links signals from MYD88 to the rest of the cell. In WM, most patients have mutated MYD88, which is stuck in the activated form and drives excessive BTK activation. This results in excessive activity of the WM cells and much of the disease that we experience as WM patients. The goal of ibrutinib or acalabrutinib treatment in WM patients is to decrease excessive BTK activity in the WM cells.

However, BTK is found not only in B-cells and WM cells. It is also found in another cell type, monocytes and macrophages. These are the cells that are activated and/or recruited to the lungs and drive much of the injury in COVID patients. In COVID, unlike in WM, MYD88 is generally not mutated but becomes excessively activated due to the virus. This happens because of increased signaling from proteins called TLRs, which activate MYD88. A result of excessive MYD88 activation is activation of BTK, which then sends a signal to the inside of the monocyte or macrophage and causes exaggerated immune responses. The goal of acalabrutinib treatment in the COVID patients was to decrease excessive activation of monocytes and macrophages. By doing so, the drug appeared to prevent the huge secretion of cytokines such as IL-6 that drive the severe, hyperinflammatory form of COVID disease.

Dr. Lionakis also briefly reported a few COVID patients with a naturally occurring mutation that inactivates BTK.

Patients with genetic mutations of BTK have a disease called XLA (X-linked agammaglobulinemia). Interestingly, when the XLA patients presented with the coronavirus infection, they did not develop high levels of the cytokine IL-6 and seemed resistant to severe manifestations of COVID disease. However, the numbers of XLA patients were quite small, so it was not possible to draw definitive conclusions.

*Based on Dr. Treon's and the NIH papers, three companies have now initiated randomized, **controlled trials** to investigate whether BTK inhibitors are worthwhile in the treatment of severe **COVID disease**.*

It is amazing how fast science and medicine are progressing in the fight against COVID. Based on Dr. Treon's and the NIH papers, three companies have now initiated randomized, controlled trials to investigate whether BTK inhibitors are worthwhile in the treatment of severe COVID disease. These are AstraZeneca, which makes acalabrutinib; Johnson & Johnson, which makes ibrutinib; and Beigene, which makes zanubrutinib. In these trials, patients who consent to enroll will be treated with either the best supportive care or the best supportive care plus the BTK inhibitor.

We will see how BTK inhibitors such as ibrutinib, acalabrutinib, or zanubrutinib work out for WM patients. Will WM patients who are already taking BTK inhibitors and who happen to become infected with the SARS-CoV-2 coronavirus develop severe disease, or will they only develop mild disease? Will BTK inhibitors be useful in treating people with severe COVID disease, whether they are WM patients or not?

Dr. Lionakis emphasized that his NIH group initiated acalabrutinib treatment for the severely ill patients who had exaggerated inflammatory responses and excessive cytokine release, which they hypothesized was driven by excessive BTK activation. It was only a small study, though, and it is possible that the patients would have recovered even if they had not received acalabrutinib.

Dr. Treon reported that five of six WM patients who were already taking ibrutinib did not develop severe disease, even though they were infected with the coronavirus SARS-CoV-2. This is different than Dr. Lionakis' study, where they used acalabrutinib to treat patients who already had severe COVID disease. Whether ibrutinib helped the five WM patients avoid severe COVID disease cannot be determined from such a small study, but it is interesting.

Without larger, randomized controlled trials, it is impossible to know if these patients' resistance to severe disease was due to the drug, or if they would have been resistant or recovered anyway, even without ibrutinib or acalabrutinib.

I am enormously impressed that randomized, controlled trials were organized so quickly. Normally, this type of clinical trial requires considerable time to organize and initiate. It will be important to see the results.



MEDICAL NEWS ROUNDUP

BY SUE HERMS, IWMF RESEARCH COMMITTEE MEMBER

International Workshop on WM Provides Consensus Statement on Management of WM During Pandemic

The International Workshop on WM has provided a consensus statement on the management of WM patients during the coronavirus pandemic. Several of the consensus highlights are summarized as follows: 1) the threshold for initiating treatment should be high during this situation, and watch-and-wait should be the preferred strategy when possible; 2) for patients presenting with anemia and low iron, a trial of intravenous or oral iron (to reduce visits to healthcare centers) is recommended; 3) when treatment is indicated, chemoimmunotherapy and BTK inhibitors remain reasonable options, and oral therapy may be the better option for patients who cannot travel because of risk; 4) dexamethasone, rituximab, and cyclophosphamide (DRC) rather than bendamustine and rituximab may be less immunosuppressive; 5) the use of proteasome inhibitor therapies such as bortezomib and carfilzomib in combination with steroids and rituximab should be minimized, as these typically imply more frequent visits to infusion centers and a risk of immunosuppression; 6) patients on BTK inhibitors should continue treatment because of the possibility that these agents may reduce rates of COVID-19 pulmonary manifestations; 7) use of rituximab maintenance is to be avoided given the lack of survival benefit, the added burden of travel to healthcare centers, and a risk of immunosuppression; 8) a reduced number of chemoimmunotherapy cycles or delaying one or two cycles may be considered in good/intermediate risk patients, or if a good treatment response has already been achieved; 9) telehealth visits and home collection of blood samples should be used where possible; 10) patients with comorbidities, recent infections, and low serum IgG levels may benefit from immunoglobulin therapy, with subcutaneous administration or home health administration prioritized; 11) where indicated, routine vaccination for influenza and pneumococcal pneumonia should be continued; and 12) supplies of oral medications for longer durations should be considered to reduce patient visits to healthcare centers. For the complete consensus statement go to:

http://www.iwmf.com/sites/default/files/docs/publications/Consensus_Statement_on_the_Management.pdf

European Medicines Agency to Review Zanubrutinib for Marketing Authorization for WM

BeiGene announced that its marketing authorization application for zanubrutinib (Brukinsa) for the treatment of WM patients who have received at least one prior therapy or as first-line treatment for patients unsuitable for chemoimmunotherapy has been accepted for regulatory review by the European Medicines Agency (EMA). If approved, the authorization will allow

BeiGene to market the drug and make it available in the European Union, Iceland, Norway, and Liechtenstein.

Italian Study Analyzes Outcomes for Younger WM Patients

A multi-center Italian study, published in the *American Journal of Hematology*, analyzed 160 younger WM patients for outcomes in the era of immunotherapy and targeted therapies. The median age of these patients, diagnosed at 14 Italian centers between 2000-2019, was 49 years. At diagnosis, 70% were asymptomatic. After a median follow-up of 5.6 years, 57% were treated. As initial therapy, 79% received chemoimmunotherapy, 13% chemo-free therapy, and 8% chemotherapy only. At relapse or progression, 6% underwent an autologous stem cell transplant. Altogether, 19% of patients received ibrutinib (Imbruvica) during the course of their disease. The overall survival of younger WM patients was not significantly reduced as compared with an age-, sex-, and calendar year-matched population. Early diagnosis, absence of high-risk features in symptomatic patients, and high efficacy of modern treatments were suggested as the main determinants of this positive outcome.

*Deletion of the long arm of **chromosome 6** is the most frequent chromosome abnormality in WM...*

Spanish Researchers Discuss Impacts of 6q Chromosome Deletion in WM

Spanish researchers discussed the impacts of the 6q deletion in WM patients in an article published in the *British Journal of Haematology*. Deletion of the long arm of chromosome 6 is the most frequent chromosome abnormality in WM, occurring in approximately 50% of patients. These researchers used fluorescence in situ hybridization (FISH) testing to detect the presence of the 6q deletion in bone marrow cells from 225 patients with newly diagnosed IgM monoclonal gammopathies. The deletion was detected in 4% of IgM MGUS patients, 9% of smoldering WM patients, and 30% of symptomatic WM patients and was associated with adverse prognostic features. Asymptomatic patients with the deletion ultimately required therapy more often and had a shorter time to progression to symptomatic disease. When treatment was required, 6q-deleted patients had shorter progression-free survival and shorter overall survival.

New BCL-2 Inhibitor Granted Orphan Drug Designation by FDA for Treatment of WM

Ascentage Pharma's oral BCL-2 inhibitor APG-2575 has been granted Orphan Drug Designation by the US Food and Drug Administration (FDA)

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for the treatment of WM. This designation encourages the development of orphan drugs, which are developed for the prevention, diagnosis, and treatment of rare diseases or conditions, by allowing the US government to provide incentives and policy support. As reported in this column in the July *Torch* issue, APG-2575 has received approvals for multiple Phase 1b/2 clinical studies in China, Australia, and the US for a range of blood cancers, including a trial evaluating it as a single agent or in combination with ibrutinib (Imbruvica) for the treatment of WM. On www.clinicaltrials.gov, the identifier number for the WM trial, called MAPLE-1, is NCT04260217.

Ibrutinib and Venetoclax Combination Associated with Deep Remissions in Previously Untreated CLL/SLL –

In patients with previously untreated chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), a once-daily oral regimen of ibrutinib (Imbruvica) and venetoclax (Venclexta) was associated with deep molecular remissions in both bone marrow and peripheral blood, according to results from the Phase 2 CAPTIVATE MRD trial. Analysis of 164 patients showed a 75% rate of minimal residual disease (MRD) negativity in peripheral blood and a 68% rate in the bone marrow among patients who received up to 12 cycles of the combination. MRD negativity in CLL is defined as having a disease threshold of less than one CLL cell per 10,000 lymphocytes in the blood or bone marrow. The data were presented during the European Hematology Association 25th Congress.

New Data Presented for Impact of Drug Discontinuation and Interruption in CLL Patients Receiving Venetoclax and Rituximab Combination –

New data were presented from the Phase 3 MURANO clinical trial of venetoclax (Venclexta) and rituximab (Rituxan) in patients with relapsed or refractory chronic lymphocytic leukemia (CLL). Because drug discontinuation and interruption occur fairly frequently, the researchers looked at their impact on patient outcomes. Of 194 patients enrolled, 72% completed two years of therapy, while early discontinuation occurred in 28%. The main reasons for discontinuation were adverse events and disease progression. Temporary treatment interruption occurred in 69% of patients, most commonly due to neutropenia (low neutrophil count), with a median duration of interruption being nine days. While early treatment discontinuation was associated with suboptimal outcomes such as reduction in progression-free and/or overall survival, temporary treatment interruption was not.

Acalabrutinib Improves Survival Outcomes in CLL When Compared to Two Other Therapies –

Acalabrutinib (Calquence) improved progression-free survival outcomes when compared to idelalisib plus rituximab or bendamustine plus rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), according to results from the Phase 3 ASCEND clinical trial. Of 310 patients enrolled, 155 received acalabrutinib monotherapy,

and 155 received investigator's choice—either idelalisib (Zydelig) with rituximab (Rituxan) or bendamustine with rituximab. The median follow-up was 61.1 months; at that time, the acalabrutinib group had a significantly longer median progression-free survival (not reached) compared to investigator's choice (16.5 months). The overall response rates were similar between the two groups, and median overall survival was not reached in either group. Altogether, 94% of patients had at least one adverse event, with serious adverse events more common in those receiving idelalisib with rituximab.

Results Reported for Phase 2 Study of Yescarta CAR T-Cell Therapy in Indolent NHL –

Results from an interim analysis of the Phase 2 ZUMA-5 study of the CAR T-cell therapy called axi-cel (Yescarta) demonstrated high overall response rates and complete responses, as well as a manageable safety profile, in patients with relapsed or refractory indolent non-Hodgkin's lymphoma (NHL). The results were presented during the 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Meeting. The trial enrolled 140 patients with either follicular lymphoma or marginal zone lymphoma. After a median follow-up of 15.3 months, 96 patients were evaluable for effectiveness. The overall response rate was 93%, and the complete response rate was 80%, with a median progression-free survival of 23.5 months. All study participants were evaluable for safety, and 85% experienced grade 3 or greater adverse events, the most common of which were neutropenia (low neutrophil count) and anemia. Cytokine release syndrome and neurologic events occurred in 8% and 17% of patients, respectively.

Novel Therapeutic to Begin Phase 1/2 Clinical Trial in Blood Cancers and Solid Tumors –

Cyteir Therapeutics has initiated a Phase 1/2 clinical trial of its oral drug candidate CYT-0851, designed to enroll approximately 200 patients with non-Hodgkin's lymphoma, chronic lymphocytic leukemia, multiple myeloma, and several types of solid tissue tumors. CYT-0851 is based on the discovery that some cancer cells become more dependent on a DNA repair pathway that is mediated by RAD51, a protein that is essential for the continued survival of these cells. Inhibiting this pathway limits their ability to self-repair, leading to overwhelming DNA damage and ultimately, self-destruction—a therapeutic effect known as synthetic lethality. On www.clinicaltrials.gov, the trial identifier is NCT03997968.

Pneumococcal Vaccination Response Especially Poor in Treated CLL Patients –

Vaccination to prevent pneumococcal pneumonia is recommended for patients with blood cancers; however, response to vaccines has not been well investigated in these patients. An article published in the journal *Leukemia* reported the analysis of antibody response and outcomes in 112 chronic lymphocytic leukemia

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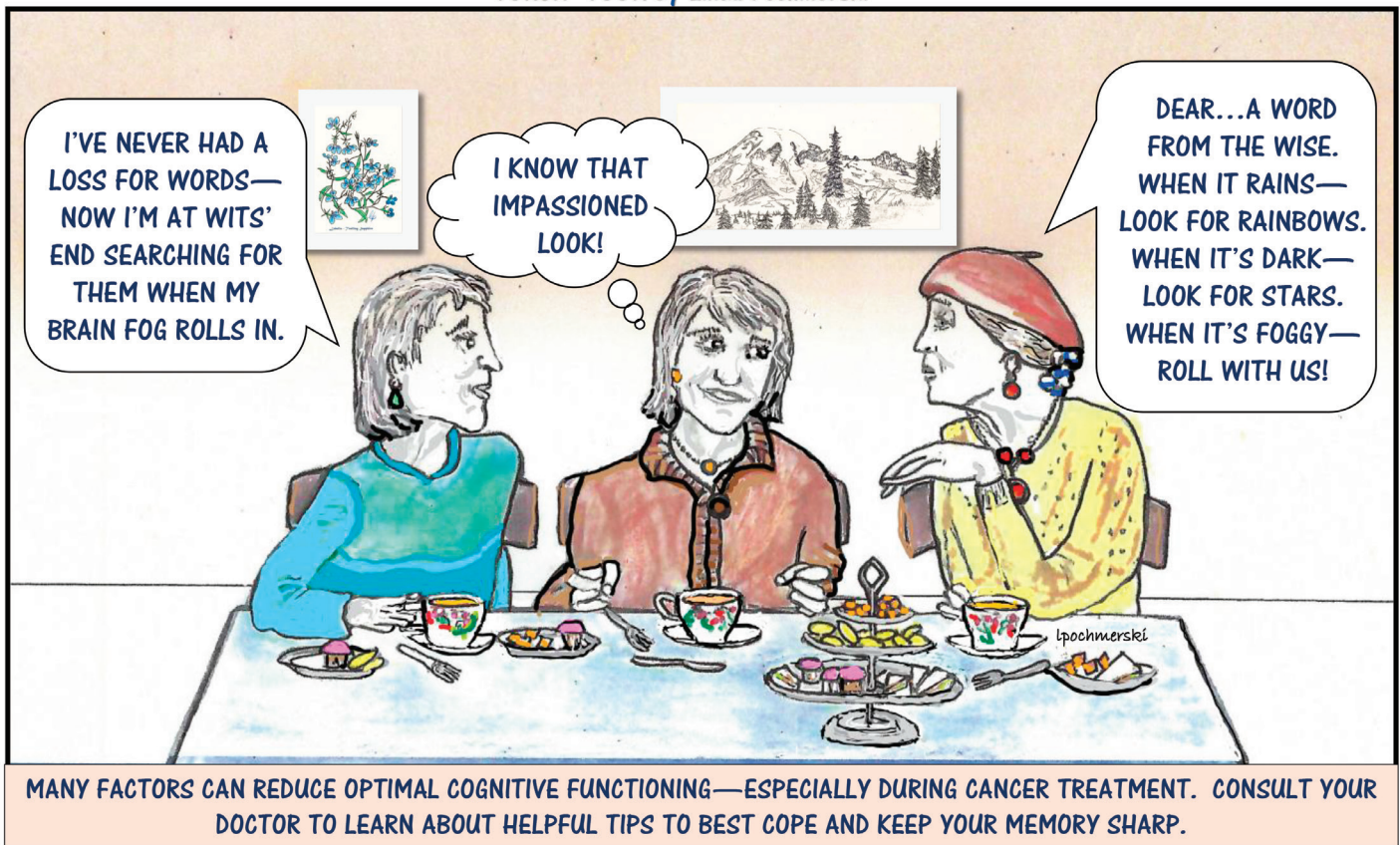
(CLL) patients who received the 13-valent pneumococcal conjugate vaccine (PCV13). The percentage of patients who were treatment-naïve was 19.6%, while 80.4% were previously treated. Nine patients (8%) developed an immune response—eight of these were treatment-naïve and one was previously treated with ibrutinib (Imbruvica) as front-line therapy. No immune responses were observed in patients previously treated with chemoimmunotherapy. Factors associated with a lower immune response were 1) age equal to or greater than 60 years, 2) IgG levels less than 400 mg/L, 3) prior treatment, and 4) signs of disease progression. The researchers suggest that vaccination should be offered at diagnosis to patients with early stage and stable disease who have better resources for an effective immune response.

Prevention of Chemo-Induced Neutropenia Improves with Addition of Another Drug to Neulasta – The combination of plinabulin with pegfilgrastim (Neulasta) reduced the rate of serious chemotherapy-induced neutropenia (low neutrophil count), compared to Neulasta

alone, according to an interim analysis of the Phase 3 PROTECTIVE-2 clinical trial. The trial of approximately 120 patients met its primary end point of improving the prevention of neutropenia early in the first eight days of a chemotherapy cycle, since Neulasta alone typically protects against neutropenia from day nine onward. It also met its key secondary end point of reducing the duration of neutropenia. In the bone marrow, plinabulin boosts the number of primitive stem and progenitor cells that are the source of mature immune cells, including neutrophils, and is being developed by BeyondSpring Pharmaceuticals.

The author gratefully acknowledges the efforts of Grete Cooper, Peter DeNardis, Tom Hoffmann, Pavel Illner, Meg Mangin, Colin Perrott, Richard Savoy, Charles Schafer, Ron Ternoway, and others in disseminating news of interest to the IWMF Connect community. The author can be contacted at suenchas@bellsouth.net for questions or additional information.

TORCH TOON by Linda Pochmerski



“THE WALDENSTRÖMS,” BRAZILIAN CLASSIC ROCK BAND

BY DR. MARCELLO BELLESSO, HEMATOLOGIST, SÃO PAULO, BRAZIL

Editor's note: As discussed on IWMF Connect earlier this year, a classic rock band in Brazil, called The Waldenströms, has five doctors, several of them hematologists, as instrumentalists and singers. Dr. Marcello Bellesso, one of the original members of the band, says he loves to talk and write about the band, so he sent this history of it for the Torch.

The initial idea of a band arose at a scientific meeting in Frankfurt in 2011. It was a presentation of multicentric clinical trials, and we three hematologists met during the event. We found we loved to play songs, and that our musical preferences were similar. “So, why don’t we play together? When will we rehearse? Hey ho, let’s go!”

We wanted to design something that would identify us as a band of hematologists, so that’s why we chose the name “The Waldenström’s.” At that time, we were just three hematologists who love blues and classic rock. Thus, Renato Centrone, Guilherme Perini, and I created a dumb trio (we are terrible singers); we were just two guitarists and a drummer. After a couple of weeks in São Paulo, we started to play together, and we created a strong friendship. Due to some tribulations, Guilherme had to leave, and others joined us.

representing the five members of the band. The colors and design were a joke on the logo of the band Red Hot Chili Peppers. We always play for an audience of friends.

The current band is: Denis Alberto, vocalist and plastic surgeon; Gustavo Loubet Guimaraes, bass player, also a classmate from medical school, trained in infectious diseases and hospital administration; Felipe Bruniera, drummer, a hematology resident at School Hospital where I work; and Renato Centrone, solo guitar player. I play bass guitar.

Before the pandemic, we rehearsed twice a month in a small studio near our jobs. Moreover, our wives love the band, and they have become friends. COVID19 has changed our lives; unfortunately, in the last few months we stopped rehearsing for obvious reasons.

We are looking forward to playing again. We’ve tried to play together through virtual meeting apps, but it isn’t possible due to delays. Perini, Centrone, and I have participated in some multicentric hematology trials, and we have several patients with WM. Although we have told them about the band, we’ve never played for an audience of WM patients. We’d love to do it!



Brazilian classic rock band, The Waldenströms

During the reunion of my college class of 2015, I met a great friend, Denis Alberto. His nickname during medical school was “Pavarotti,” because he always sang very well; even during graduation he went on stage and sang for everyone. “Hey, Pava! Shall we play together?”—and that’s how we stopped being an instrumental band and gained a vocalist.

After the entrance of the vocalist, the frequency of rehearsals increased, and our group found the courage to do a show. We designed our logo, a pentamer that has double meaning: a pentamer IgM (monoclonal protein from WM), as well as

Finally, my message to readers of the *IWMF Torch* is that it’s very important to find something that helps us relax and enjoy our lives. It’s vital for us to have moments when we don’t have to be extremely technical, and we can laugh at ourselves around great friends!

“But it’s all right, now, in fact, it’s a gas!”

To see photos of the band in action and hear their rendition of “Jumpin’ Jack Flash,” go to:

<https://www.youtube.com/watch?v=u7kG2avPIH0&feature=youtu.be>.

FROM IWmf CONNECT: FALL 2020

BY JACOB WEINTRAUB

This has continued to be a most unusual and stressful time in our lives. Cancellation of the Educational Forum in Seattle, and almost every other live event we can think of, has become routine. Many presentations continued online, and fortunately, the Educational Forum was rescheduled as an online program. IWmf Connect discussion online has continued unabated, with many different subjects appearing and reappearing. There are links to clinical studies, human interest stories, and personal reports of treatment, along with encouragement and support. Drugs, such as venetoclax, mavorixafor, zanubrutinib, and acalabrutinib, are all reported on by people who have received these treatments, often as part of a clinical trial.

Given the ongoing nature of the pandemic and issues related to this, we have chosen to limit our inclusion of medical aspects of coronavirus here. But there has been some discussion of ancillary issues that are affected by coronavirus.

You are all invited to join IWmf Connect to participate or just “lurk” and absorb all the different experiences, observances, and opinions.

PERSONAL INTEREST

As always, a number of links were not directly related to WM. But they were very relevant to our own feelings and experiences that resonate within the WM community and involve other aspects of life unique to our community. Some of the topics discussed included travel during the COVID era, personal reports of clinical trials, and use of newer treatments, especially BTK inhibitors, plus treatment with and responses to the “older” agents like bendamustine and rituximab.

IWmf Connect Manager and IWmf Trustee Peter DeNardis posted links to several items.

Two articles address issues related to cancer in the era of coronavirus. Many of us have had to continue with our routine of checkups, treatments, blood tests, and other medical appointments throughout the coronavirus outbreak. Peter stated these articles provide some affirmation of what we go through when we have to make those necessary visits. It isn't just the physical toll it takes on us, but also the mental and emotional toll. We all must be vigilant in tending not only to our physical ailments, but also to our emotional status by cutting ourselves some slack and finding more ways to cherish the small things in our lives.

The first is titled “My Cancer Doesn't Care About the Coronavirus,” from a patient dealing with lymphoma and prostate cancer:

<https://www.nytimes.com/2020/05/17/opinion/coronavirus-cancer.html>

The second article is titled “What I've learned dealing with

my cancer diagnosis during lockdown” (the patient deals with CLL):

<https://www.cnn.com/2020/05/15/opinions/cancer-diagnosis-lockdown-coronavirus-beckett/index.html>

(Note: the video on that page doesn't really match the article—just read the article.)

One other link posted by Peter is titled “How to Embrace Pain and Let it Transform You.” These are wise words from a fellow cancer “thrivor.” The last paragraph from the article in *Lymphoma News Today* states “Yet this year and all that has unfolded have been an even deeper reminder to myself and everyone around me that we can't control anything. And we certainly can't go through this life without facing suffering. And sometimes that suffering becomes the alchemy, the gift that transforms us into better, kinder, happier, and more open and loving people.” <https://lymphomanewstoday.com/2020/06/08/suffering-how-reach-acceptance>

Finally, **Grete C** posted a link to a “Patient Power” video interview featuring our own Peter DeNardis. This title is “Waldenstrom Patient Stories: Finding Strength.” Several members posted very positive responses to this interview, one saying it was better watching rather than just reading. **Linda P** posted that action along with a positive attitude are optimal together. A link to the transcript is at: <https://patientpower.info/waldenstrom-macroglobulinemia/patient-stories/waldenstrom-patient-stories-finding-strength>

BALANCE

Cheryl H posted a question about her difficulty with balance. She went through chemo ten years ago, but during the last two years she has been terribly off balance all the time. She has had an MRI and had her ears checked. She is 74 years old and is reluctant to go to rehab.

Jan W answered with a suggestion to use a walker to help with stability. Jan felt that until Cheryl finds a solution to her imbalance, she needs to protect herself from falling and injuring herself.

Eileen S responded that she also has balance problems. She thinks this is from a combination of neuropathy and weakness in her feet/ankles. She suggested Cheryl contact her primary care doctor about a physical therapy referral, either virtual or in-person. She also agreed that a walker would be beneficial.

Steve P added that peripheral neuropathy led to his diagnosis of WM 15 years ago. He had neuropathy in his feet, and their loss of sensation made balance difficult. He still needs to pay extra attention to how he is standing, and he holds on whenever possible.

Betty Ann B posted that she has some trouble with her

From IWmf Connect, cont. on page 19

balance, and both tai chi and yoga classes really help. She indicated a “gentle yoga” class has been best for her, but yoga organizations can make additional recommendations. Tai chi builds strong thighs, which help with mobility and every day activities. She is 78, and her classes have other seniors.

Kathy W suggested water Pilates and water yoga, which help a lot. The Silver Sneakers group has online chair balance classes.

Finally, **Judy K** added some suggestions. She has had significant balance problems for many years, mainly due to spinal issues, but likely also from her WM. She finds that stairs, walking, and working in the yard help with balance. She always uses a cane when outside and recommends finding a good physical therapist.

TRAVEL

Travel precautions are discussed periodically in this forum. However, with the coronavirus pandemic, any travel requires special precautions.

Jean C posted that she is going to see her granddaughter for the first time since she was born. Parents have been social distancing and working from home, and Jean has been taking all precautions, including virus testing, which was negative. She wishes others safe travels.

Bonnie B added that she lives 1,100 miles away from her daughter and granddaughter. Daughter very much wanted Bonnie to come and visit. She and her husband have largely sheltered in place except for essential errands. She decided to make the drive in one day. She drove 14 ½ hours solo in her minivan “bubble.” She stopped only for gas/bathroom and had a disposable mask for every stop, socially distanced and sanitized at the restroom and again at her car. She took her own food and drink. When she got to her daughter’s, she headed straight to the shower and clean clothes. Now with her daughter and granddaughter, she was enjoying the visit, with lots of TLC. She dreads the drive home and hopes by the time she wants to visit again, it will be safe to fly.

Kathleen A posted that it is possible to travel safely by auto. She and her husband have been practicing these measures since he was diagnosed in 2012. They have many grown children and grandchildren, and they never visit if anyone is not feeling absolutely well. Kathleen and her husband have used masks and hand sanitizer during all these years. She is the oldest of nine children and has tried to stay close with her siblings. They had a family gathering over July 4. All traveled by auto, bringing along their own food, masks, and hand sanitizer. They celebrated outdoors and prepared all food with gloves and masks. Anyone who was not feeling absolutely healthy stayed home. On the way home, she and her husband had to break up the trip with a stay at a Marriott Residence Inn, where they have full kitchens, and she could prepare food. While at the family gathering, they rented an RV, which the owner brought to the campgrounds and

setup for them. Then they sanitized the inside. It was an exceptional vacation and break from the stresses at home.

CRAMPS

This is one of those pesky but potentially disabling symptoms that is discussed recurrently in the group.

Lea H posted the initial question. She has lived with ILS (irritable leg syndrome), plus cramps for many years. When younger, she would “walk it off,” but that often would take a long time. Now when she has cramps during the night, she makes a hot drink, which often helps. One of her New Zealand friends with WM found his cramps stopped after treatment with bendamustine and Rituxan, but her treatment did not help. She was asking for help.

Kathy C noted that she was diagnosed with WM ten years ago. Her first symptom was terrible leg pain during the night. Nothing helped except getting the IgM down with Rituxan treatments. Pain has recurred twice when her IgM went up, though only into the 800s. She has just completed a four-month course of bendamustine and Rituxan. Pain did not change as her IgM came down, though it is present only in one leg. She has had no relief taking gabapentin, so her doctor is looking for other etiologies.

Laura B added that she has had cramps and thought she was staying hydrated. However, while all her labs were in the normal range, she added an electrolyte solution like Pedialyte daily, and drinking more water than usual, and she has not had cramps in months.

Some have advocated drinking pickle juice for cramps.

Meg M posted a link to an article that does a thorough review of the use of pickle juice for leg cramps. “Pickle Juice for Cramps; Does it Work?”

<https://www.healthline.com/health/pickle-juice-for-cramps>

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.

WM HIGHLIGHTS FROM THE EUROPEAN HEMATOLOGY ASSOCIATION 25TH CONGRESS

BY GLENN CANTOR, SCIENCE EDITOR

This year, the European Hematology Association (EHA) 25th Congress was held virtually in June. This gave participants from around the world the opportunity to listen without the expense (and risk) of international travel. Here, I will discuss a few of the key WM presentations.

Christopher Oakes, The Ohio State University. “Developmental epigenetic modifications underlying malignant B cells distinguish biologically distinct subtypes of WM.”

Epigenetic analysis revealed a different way to categorize WM patients. If confirmed, this may provide an additional tool to understand the differences among WM patients and potentially individualize treatment.

The WM community benefits from the tremendous advances in identifying genetic changes (DNA mutations) in WM patients, including the MYD88 L265P mutation and CXCR4 mutations. Patients can be categorized according to whether they have these mutations. This enables doctors to better determine prognosis and is changing the face of WM treatment.

Dr. Oakes presented a different way of categorizing patients, which may lead to further insight into disease progression and better treatments. Using epigenetic tests, his group found two subtypes of WM disease, called “memory B-cell-like” (MBC-like) and “plasma cell-like” (PC-like). These two subtypes of WM have different patterns of gene expression and different clinical features. It remains to be determined if this work will lead to treatments that are different, depending on which subtype of WM a particular patient has.

Epigenetics is the study of structural changes that regulate how genes are expressed. Most cells in the body share the

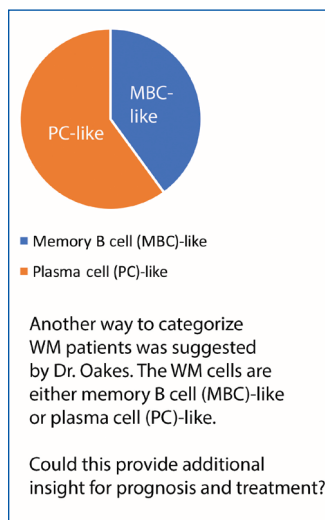
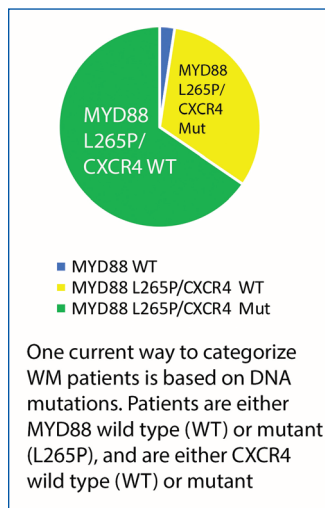
same DNA, the same genome. However, different types of cells must use these genes differently, so that one cell becomes a liver cell while another becomes a skin cell. This is accomplished during early development by regulating how DNA is compacted into the small space within a cell nucleus. After extensive folding to enable DNA to fit inside cells, areas of DNA are either in an “open,” exposed state or in a “closed,” inaccessible state. This allows certain genes, the ones in the open areas, to be expressed, while the genes in the closed, inaccessible areas are silenced. Epigenetic changes, by governing which areas are open or closed, allow the same underlying DNA genome to be expressed in multiple different ways, depending on the cell type. Epigenetic changes also govern the appropriate development and fate of cell types throughout the body.

In cancer cells, epigenetic changes can cause different genes to be expressed or silenced, even if their DNA sequence is exactly the same as the sequence of people without cancer. Knowing this, Dr. Oakes set out to test whether WM cells had epigenetic changes. Specifically, he looked at an epigenetic change called DNA methylation, in which a methyl group (consisting of an extra carbon and three hydrogens) is added to one of the DNA nucleotides, called cytosine, in certain stretches of DNA called CpG islands. This DNA methylation represses or shuts down gene expression. In the work reported at the EHA Congress, Dr. Oakes used a new and powerful method to map up to 850,000 CpG sites throughout the genome and determine their methylation status.

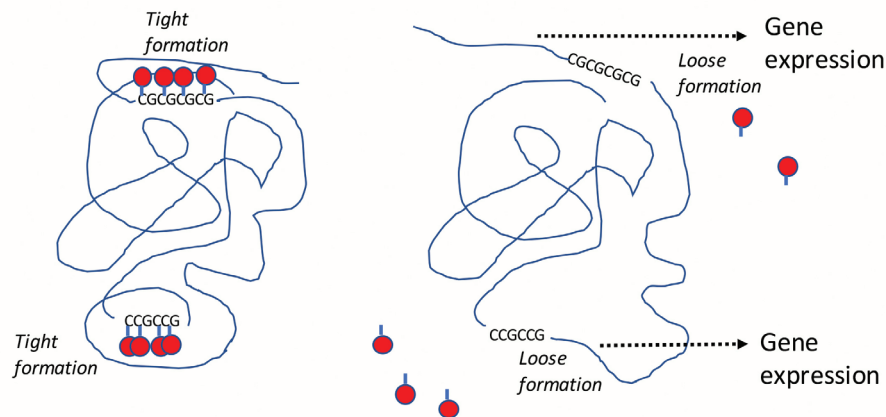
Surprisingly, he found that WM cells had extensive areas—hundreds of thousands of sites in the genome—with low DNA methylation, where the normal process of DNA methylation was impaired. Importantly, he found that WM patients fell into two specific patterns or subtypes, each with distinct areas of the genome with reduced methylation. This reduction in DNA methylation opens up the opportunity for WM cells to abnormally express many genes. Which genes are abnormally expressed depends on which pattern of epigenetic changes the patient has.

Dr. Oakes compared the demethylation patterns in cells from WM patients to different types of normal B cells and plasma cells, including bone marrow cells at different stages of maturity, and to cells from other hematologic cancers such as multiple myeloma and chronic lymphocytic leukemia. This led to the conclusion that one group of WM patients, about 40% of the total, had WM cells which are most similar to a type of B cell called a memory B cell (MBC-like), while another group of WM patients, about 60% of the total, had WM cells more similar to plasma cells (PC-like).

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Dr. Oakes' work shows two types of WM cells. About 40% of patients have WM cells that are memory B cell-like and about 60% have WM cells that are plasma cell-like.



Methylation (red circles) of cytidines (C) in CpG sites keeps DNA in tight formation. The DNA structure is closed or inaccessible, and nearby genes are silenced.

Removal of methyls (red circles) from cytidines (C) allows DNA structure to open up (loose formation). Nearby genes can be expressed.

The behavior of cells—including whether the cell is cancerous or not—depends on which genes are expressed. When DNA is tightly wound or compacted (tight formation), genes cannot be expressed. One feature that keeps DNA in this silenced form is the presence of methyl groups (red circles) on some of the DNA bases (cytidines) in specific locations (CpG sites). When the methyl groups are removed, the DNA opens up (loose formation), and nearby genes can be expressed. The memory B cell-like WM cells have a different pattern of methylation than the plasma cell-like WM cells. This causes different patterns of gene expression and may explain some of the differences among WM patients.

The implication is that the MBC-like WM cells seem to have many of the features of memory B cells, while the PC-like WM cells seem to have many of the features of plasma cells. This is important because the WM cells still retain many of the genetic, biological, and clinical features of their respective cell of origin.

This intriguing study was done with only 36 patients, a rather small number. In IWMF-funded research at the Dana-Farber Cancer Institute, Dr. Zachary Hunter is also doing epigenetic mapping, along with concurrent analysis of DNA mutations, changes in RNA expression, changes in protein expression, and clinical history. The work at Dana-Farber examines a much larger number of patients, approximately 300. It will be fascinating—and important—to see if the two groups, Dr. Oakes' and Dr. Hunter's, converge on similar findings.

Importantly, if Dr. Oakes' work is confirmed, it may provide an additional tool to understand the differences among WM patients. Hopefully, this will provide more individualized treatment recommendations in the future.

Meletios Dimopoulos, National and Kapodistrian University of Athens School of Medicine, Greece. "ASPEN: Results of a Phase 3 randomized trial of zanubrutinib and ibrutinib for patients with WM," and Alessandra Tedeschi, Niguarda Cancer Center, Milan, Italy. New treatments (part of a Satellite Symposium: Expert discussion: "Challenges and new opportunities to manage and treat patients with WM, a complex B cell malignancy")

- A recently completed Phase 3 trial compared zanubrutinib (Brukinsa) and ibrutinib (Imbruvica) head-to-head. The trial did not show statistically significant improvement in efficacy with zanubrutinib, but it did show that zanubrutinib was associated with a higher rate of a very good partial response, was safer, caused fewer adverse events, and was more tolerable than ibrutinib.

Several talks at the EHA summarized new results on zanubrutinib from the ASPEN trial. ASPEN is a Phase 3 trial to directly compare zanubrutinib, a new second generation BTK inhibitor, with ibrutinib, the standard-of-care BTK inhibitor.

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Zanubrutinib and ibrutinib have approximately equal potency, but zanubrutinib is more selective. One feature of ibrutinib is that it not only inhibits BTK, the desired target, but also inhibits a number of other cellular proteins (called kinases), including EGFR, ITK, JAK3, HER2, and TEC. These off-target effects can cause some of the adverse effects seen with ibrutinib. In contrast, zanubrutinib was designed to inhibit BTK more selectively and have much less off-target reactivity to other kinases (2.4-fold to 51-fold less, depending on the kinase), in an effort to reduce toxicity.

In ASPEN, a large head-to-head trial, 201 WM patients with the MYD88 mutation were randomized to receive either zanubrutinib (160 mg twice daily, n=102) or ibrutinib (420 mg once daily, n=99). The treatment groups were arranged ("stratified") so that each treatment group had patients with similar CXCR4 mutation status and similar numbers of prior therapy.

In clinical trials, a primary endpoint is declared before the trial begins, and then the data are evaluated at the end to see if the primary endpoint was met. In the ASPEN trial, the primary endpoint was to determine if zanubrutinib was more efficacious than ibrutinib, as measured by the proportion of patients with either a complete response (CR) or very good partial response (VGPR), as determined by an independent review committee. Additionally, the trial assessed safety.

With zanubrutinib, 28.4% of patients had a CR or VGPR, while with ibrutinib, 19.2% of patients had a CR or VGPR, with a p value of 0.092. Because the study had a pre-established p value of less than 0.05, the study did not meet the primary endpoint of more efficacy.

There has been considerable attention paid to the conclusion that the study did not meet the primary endpoint of increased efficacy. What is particularly important, though, from a patient's perspective, is the safety data. With zanubrutinib, only 2% of the patients developed atrial fibrillation or flutter, while with ibrutinib, this was seen in 15% of the patients, a statistically significant difference. The number of patients in the ibrutinib group with atrial fibrillation or flutter increased with time during the 33-month period of observation.

There were less dramatic safety improvements with zanubrutinib in the percentage of patients with other adverse events, including diarrhea (zanubrutinib 21%, ibrutinib 32%), major bleeding (zanubrutinib 6%, ibrutinib 9%), and hypertension (zanubrutinib 11%, ibrutinib 17%). One feature that was worse with zanubrutinib was neutropenia (low blood neutrophil counts) (zanubrutinib 30%, ibrutinib 13%). The significance of this is puzzling, since neutropenia typically results in increased susceptibility to infections; however, in the ASPEN trial, the rate of infections was similar (zanubrutinib 66%, ibrutinib 67%).

Another important parameter was that fewer patients receiving zanubrutinib dropped out of the trial because of

adverse events (zanubrutinib 4%, ibrutinib 9%) or had dose reductions during the trial (zanubrutinib 14%, ibrutinib 24%). When evaluated with a standard survey for Quality of Life, the patients with VGPR who were treated with zanubrutinib reported a better quality of life than those treated with ibrutinib.

In the question period, Dr. Dimopoulos said he thinks that zanubrutinib, if approved, will challenge ibrutinib as the standard-of-care for WM, because of its equal activity but better safety and tolerability. Dr. Tedeschi was asked about combination therapy in the future, such as venetoclax (Venclexta) together with a BTK inhibitor. She thought this will be the future trend, if toxicities from dual therapies are not higher. A potential advantage of dual therapies may be deeper responses and the ability to discontinue drugs after a period of time, rather than administering as lifetime therapy.

Karima Amaador. "Ixazomib, rituximab, and dexamethasone (IRD) in patients with relapsed or progressed WM: Final analysis of the HOVON124/ECWM-R2 trial"

- Ixazomib (Ninlaro), a second-generation proteasome inhibitor, showed safety and efficacy in combination with rituximab (Rituxan) and dexamethasone (Decadron) in a Phase 2 study

*...there has been considerable effort to find safer
proteasome inhibitors that are less neurotoxic.*

Bortezomib (Velcade), a proteasome inhibitor, has been used for many years in WM patients with very high IgM levels. However, bortezomib often causes peripheral neuropathy. As a result, there has been considerable effort to find safer proteasome inhibitors that are less neurotoxic. One second generation proteasome inhibitor under consideration is ixazomib.

In HOVON124/ECWM-R2, a Phase 2 trial in The Netherlands, Belgium, and Greece, WM patients were treated with a combination of ixazomib, subcutaneous rituximab, and dexamethasone. Interim results have been described previously; the purpose of this talk was to present the final data after 24 months of follow-up.

Treatment consisted of eight 28-day induction cycles. In each cycle, ixazomib (4 mg) was given orally on days 1, 8, and 15, and oral dexamethasone (20 mg) on days 1, 8, 15, and 22. From cycle 3 onwards, rituximab was added on day 1; the first dose was intravenous (375 mg/m²) and all subsequent doses were given subcutaneously (1,400 mg). After the induction phase, patients with at least a minor response (MR) received two years of rituximab maintenance therapy (1,400 mg subcutaneously every three months), with no additional ixazomib.

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Initially, 59 patients were enrolled. Of these, 45 completed the eight induction cycles, with three discontinuations due to toxicity and six due to progressive disease, while 41 continued on maintenance therapy.

Notably, there was a rapid response to ixazomib after only two cycles, before rituximab was started, as demonstrated by a significant decrease in IgM and increase in hemoglobin. IgM and hemoglobin continued to improve, although more gradually, during the remaining cycles.

The MYD88 mutation was present in 36 (88%) patients, and CXCR4 mutations were present in 12 (38%). There was no statistically significant difference in progression-free survival (PFS) based on CXCR4 status, although there was a tendency for the CXCR4-mutated patients to have shorter PFS ($p=0.064$). Additional samples are still being analyzed.

The overall response rate (ORR) after induction was 71%, including 15% very good partial response (VGPR), 46% partial response (PR), and 24% minor response (MR). After a median follow-up of 24 months, the progression-free survival (PFS) was 56%, and the overall survival (OS) was 88%. Serious adverse events occurred in 16 patients and were mainly infections. Peripheral neuropathy was present in 21 patients at the beginning of the trial. Of these, three worsened; two from grade 1 to grade 2 and one from grade 2 to grade 3. Thirteen patients developed new onset of peripheral neuropathy, but it was grade 1 in 11 patients and grade 2 in two patients. Altogether, there was new onset or worsening of peripheral neuropathy in 16 patients (grade 1, 69%; grade 2, 25%) and was reversible in 10 of the 16 patients.

Dr. Amaador emphasized the ease of treatment using subcutaneous rituximab, rather than intravenous rituximab. Patients were given an initial dose of IV rituximab, but then after that received subcutaneous rituximab, which only takes 5-7 minutes to administer. She said that none of the patients in the study had hypersensitivity reactions to rituximab given subcutaneously. With the combination IRD treatment, there was no IgM flare, a problem seen with rituximab given as a single agent.

Christian Buske (moderator), Roger Owen, Veronique LeBlond, and Alessandra Tedeschi. Expert Discussion: “Challenges and new opportunities to manage and treat patients with WM, a complex B cell malignancy”

I was interested in the discussion of different standard-of-care treatment approaches in Europe compared with the US.

*In the US, **ibrutinib** is now a dominant first line **treatment**. In Europe, ibrutinib is **not approved yet** for first line treatment...*

In the US, ibrutinib is now a dominant first line treatment. In Europe, ibrutinib is not approved yet for first line treatment (except in patients who cannot tolerate chemotherapy). As a result, rituximab in combination with chemotherapy is much more common for first line treatment throughout Europe.

Dr. LeBlond pointed out that in the US, rituximab is sometimes used as a single-agent treatment because of concerns that combination with chemotherapy introduces toxicity. Single-agent rituximab is not used often in France, since the progression-free survival (PFS) with rituximab only is short.

In patients who are resistant or refractory to rituximab-based treatments, most European physicians prefer ibrutinib as second line treatment. Dr. LeBlond also mentioned using rituximab/bendamustine as second line if the first line was rituximab/bortezomib.

The speakers said that a major goal is limited duration of treatment, rather than lifetime treatment. Limited duration of treatment would help avoid development of resistance, reduce toxicity, and improve the quality of life of the patients. All of the speakers emphasized the importance of combination treatments in the future. A Phase 2 trial is beginning now in France to evaluate venetoclax (a BCL-2 inhibitor) in combination with zanubrutinib, a second-generation BTK inhibitor. Others mentioned CXCR4 inhibitors as components of combination therapy. While there are high hopes for synergistic effects and increased efficacy, the toxicity of combination treatments will be a key consideration.

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

Imagine a Cure: A World Without WM

Help us support and educate everyone affected by Waldenström's macroglobulinemia (WM) while advancing the search for a cure. Together, we will reach our new campaign goal of \$50,000,000.

Your gift makes a tremendous difference to our global WM community. Please, give generously.

Imagine a Cure Campaign Progress Report as of September 2020



What kind of legacy will you leave?

"A person's life is measured by the effort made for the benefit of others."

BEN RUDE, IWMF PRESIDENT 2000-2005

The Ben Rude Heritage Society recognizes those who have made provisions for a future gift to the IWMF, such as a bequest, listing the IWMF as a beneficiary for a life insurance policy or qualified planned asset (such as a 401k or IRA), or a life income agreement such as a Charitable Remainder Trust. Legacy gifts represent an important component of the IWMF's financial future. Since the establishment of the Ben Rude Heritage Society in 2008, a number of bequests have been received, and the gifts of these generous donors have allowed the organization to expand our programs and research commitments significantly over the years. Members of the Ben Rude Heritage Society are dedicated to supporting research, education, and support for countless patients and caregivers, at home and around the globe. There is no minimum requirement to join the Ben Rude Heritage Society—some members have included provisions ranging from \$1,000-\$1,000,000—but every single gift makes a difference to the future of the IWMF and to those who benefit from our research and support.

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With the help of an advisor, you can include language in your will or trust specifying a gift to be made to the IWMF as part of your estate plan. A bequest may be made in several ways:

- Gift of a dollar amount
- Gift of a specific asset
- Gift of a percentage of your estate
- Gift of the residue of your estate

One benefit of joining the Ben Rude Heritage Society by making a charitable bequest is that it enables you to further the work of the IWMF long after you are gone. Better yet, a charitable bequest can help you save estate taxes by providing your estate with a charitable deduction for the value of the gift. With careful planning, your family can also avoid paying income taxes on the assets they receive from your estate. For more information on estate gifts or to join the Ben Rude Heritage Society, contact Director of Development and Communications Jeremy Dictor at 941-927-4963 or JDictor@IWMF.com.

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 our 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. We generally have 10 to 12 research projects underway with new projects under consideration each year.

The David and Janet Bingham Research Fund of the IWMF supports the following current research projects:

Factors Regulating Immunoglobulin-Producing B-Cells in Patients with WM- Part V

Targeting MYD88 Signaling in WM

The Elting Family Research Fund of the IWMF supports the following current research projects:

Anti-Tumor and Immune Microenvironment Responses Following a First-In-Human DNA Fusion Vaccine for Asymptomatic WM/LPL

Modulation of T-Cell Function by Metabolomic Signature of the Bone Marrow Microenvironment in WM

Non-Invasive Diagnostics and Monitoring of MRD (Minimal Residual Disease) and Clonal Evolution of WM

Novel Antibody-Targeted Interferons in Combinatorial Therapies for WM

Single-Cell Next-Generation Flow and Sequencing to Unravel the Pathogenesis of WM and to Design Genetically-Driven Human-Like Experimental Models

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

From Biology to Treatment: Prognostic Factors, Bone Marrow Microenvironment, Genomic and Proteomic Profile of Light Chain Amyloidosis in WM

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

Anti-Tumor and Immune Microenvironment Responses Following a First-In-Human DNA Fusion Vaccine for Asymptomatic WM/LPL

The Carolyn Morris Research 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 Member Services or Research or a combination of the two.

Baker Family Research Fund of the IWMF	Gary Green Research Fund of the IWMF	Gail Murdough Member Services and Research Fund of the IWMF
Yoshiko Button Member Services 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 Kathryn Wolgemuth Research Fund of the IWMF
Dr. Morie A. Gertz Research Fund of the IWMF	Dennis and Gail Mathisen 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)	JAN HERGESHEIMER	MARGUERITE C. REGAN, PHD*
JEAN-MARC AUDIBERT*	SUZANNE L. HERMS	PAUL AND JANICE RIPPAS
BARBARA A. BACKER RN	ARLENE HINCHCLIFFE	ROGER AND BARBARA ROBINETTE
MARTIN BAER*	ELINOR HOWENSTINE*	MARGARET ROCKELMAN*
C. EDWIN BAKER*	WANDA L. HUSKINS AND	JOEL ROSENBLIT
JACK BAKER	JEFFREY A. PRUPIS	LAURIE RUDE-BETTS ◇
JANET BAUSSER*	DR. EUNICE JOHNSON*	CYNTHIA RUHL
DAVID M. BENSON	STANLEY KAUFMAN*	ELMO R.* AND DOLORES E. SCHMID*
BEVERLY J. BLOSS	SHAN ELIZABETH KEARY	MICHAEL AND CAROL SESNOWITZ
VIVIAN AND ROBERT BOAS ◇	NANCY KERR*	ALLAN SHAW*
ELSA AND GARY BRADLEY	THOMAS KEYS*	DR. GUY R. SHERWOOD
ARLOU BRAHM*	EVELYN KLIEN*	ELLEN SMITH
WILLIAM O. AND ELLEN	GLENN AND MARCIA KLEPAC	RAY SOBOROWICZ*
KANER BRESNICK ◇	GEORGE KNIPELBERG*	KEN AND LINDA SOLOW
RUTH L. BROWN*	CHARLES KOCH	CORDELIA AND PETER STEARNS
L. DON AND MARY BROWN	DR. ROBERT A. AND	JUDITH LEE STERLING AND LESLIE
PETER CARR	CHARLENE M. KYLE	CHARLES WILSON
GERALD PRESTON CLANCEY*	MICHAEL E. LUTTRELL	JOHN AND DIANE TIPLADY
CHRISTINA CONLEY*	LENNY MARTIN	RUBEN TROSS*◇
MRS. IVY COOPER*◇	JUDITH ANN MAY	MATHILDE JOHANNA VAN GOGH*
ROBERT* AND ANNE COULBOURN*	KATHARINE E. MCCLEARY AND K.	TAMARA VINCENT
NORMAN W. CRANDALL JR.	EDWARD JACOBI*	DR. JACOB WEINTRAUB
TONY DYE*	KATHLEEN L. MINER	VIRGINIA A. WILLIAMS*
FREDERICK A. EBELING*	ANNE AND PETER MITRO ◇	PENNI WISNER
JEAN ELLIS*	ELEANOR MOORE*	JAMES P YEAGER*
RAYMOND* AND BETTE FISHMAN*	MAYNARD MORRIS	GREGORY FITZWATER AND
MARLYN FRIEDLANDER AND	SAM AND GAIL MURDOUGH	MARILYN ZOLLNER-FITZWATER
GILBERT SCHERER	GUIDO AND IDA NEIROTTI*	RALPH ZUCKERMAN*
CINDY L. FURST	BARRY NELSON	
JEB GELBER	LINDA NELSON	
NEWTON GUERIN	BRANDT NORQUIST*	
LESLIE C. GUTHRIE, JR.*	JAMES AND BETTE ORTOLEVA	
CARL HARRINGTON	HOWARD F. PRASS*	
RALPH AND JANE HENDRICKSON	ALAN PRESTELL*	

SUPPORT GROUP NEWS

EDITED BY CHRIS STAY

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.

CALIFORNIA

Orange and San Diego Counties



The Orange and San Diego Counties Zoom meeting had several new attendees.

Fifteen people attended this group's August meeting, five of whom were new to Zoom meetings. Some live three hours away from where the nearest support group used to meet and were very happy to be able to attend from home. Most of the time was focused on introductions of new people and on follow-up with others who had had recent surgery. Everyone discussed what they are doing to protect themselves from COVID-19 while negotiating some social, but physically distant contact. This group, which normally meets twice a year, is Zoom meeting every four weeks during the COVID-19 pandemic.

Julianne Flora-Tostado reporting

ILLINOIS

Chicago Area/SE Wisconsin

The Chicago Area Support Group, including SE Wisconsin, had its summer gathering on Zoom Saturday morning, August 29, following the IWMF Virtual Educational Forum and the Walk for WM. Fourteen families showed up for the "Morning Zoom Coffee" to discuss the Ed Forum and their personal situations. The Walk for WM was briefly discussed by Don after he sent out an email describing the event and his family's participation. The two-hour meeting ran overtime with discussions ranging from treatment options, COVID-19 impact, and one member's

experience of being diagnosed with COVID while on ibrutinib. He has recovered since his June diagnosis, after staying on ibrutinib and also using hydroxychloroquine. He is still showing signs of fatigue, but, thankfully, he never went to the hospital.

Our group is planning our fall meeting in October or November, and we will most likely have a guest speaker on Zoom. Contact Don Brown if you have questions, or watch the IWMF website for details on the fall meeting.

Don Brown reporting

INDIANA

Sue Pruce is stepping in as the new leader of the Indiana Support Group. She is a recently retired nurse with professional experience in many areas of nursing. She was diagnosed with WM in 2010. Her daughter, who works for an oncology drug company, directed her to the IWMF, which Sue says was her saving grace for information about the disease. Now she feels she has a lot to give to support group members since she has dealt with WM for over ten years. Sue loves spending time with her family and grandchildren. She says, "We have a convertible, and with COVID-19 and social distancing, taking rides is so refreshing and keeps me sane!"

NEW YORK

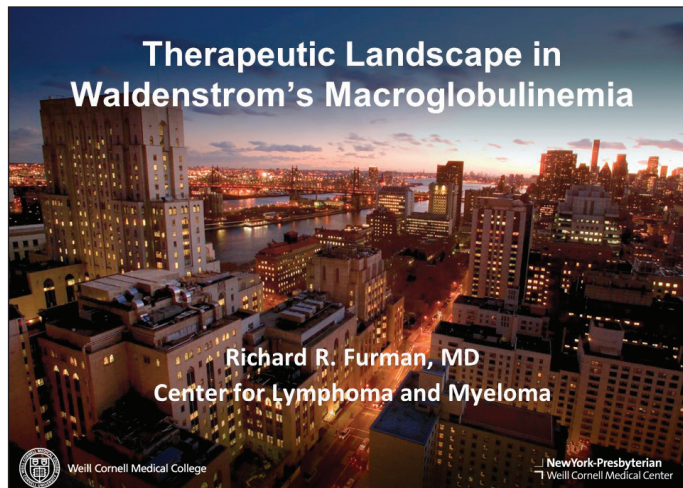
Eastern NY/Western New England

More than 250 people from over 30 states and 14 countries registered for Dr. Richard Furman's August Zoom conference. Dr. Furman is the distinguished research professor at Weill Cornell Medical Center's CLL Oncology Center, and his Zoom talk, "Novel Agent Treatment Options for Waldenstrom's," explores the emergence of novel agents for the treatment of Waldenstrom's, CLL, and other blood cancers. His practice is on the forefront of this exciting revolution in treatment modalities. As a project by the Eastern New York and Western New England Support Group, a number of us are putting together a Zoom program to explore the topics Dr. Furman discussed. We welcome participation by those with some time for doing this kind of thing. The link to his talk is at https://youtu.be/9SLQR_ncYdA. If you are

Support Group News, cont. on page 28

interested, contact Mel at wmcure@yahoo.com to receive a copy of the summary of Dr. Furman's presentation prepared by Pat Getz (Santa Fe) and Winny and Kees Van de Velden (the Netherlands).

Mel Horowitz and Pete Skinner reporting



The Eastern NY/Western New England Support Group gained a world-wide audience with Dr. Richard Furman's presentation.

WESTERN NY

The support group of Western NY met via Zoom in July and included 17 participants. The guest speaker was Dr. Jeremiah Moore, PharmD, BCOP, University of Rochester, James P. Wilmot Cancer Center. Questions submitted ahead of time from group members included queries about medication options, the best time to take meds, possible interactions with other meds and over-the-counter supplements, safety of vaccines, CBD (cannabidiol), COVID-19 treatments, and financing medications. The group was quite appreciative of the information shared and the time Dr. Moore spent with them.

Lynn and Tom Milliman reporting



The Western New York Support Group hosted Dr. Jeremiah Moore of University of Rochester, James P. Wilmot Cancer Center at their July Zoom meeting.

EASTERN OHIO, WESTERN PENNSYLVANIA & WEST VIRGINIA

In early June, an enthusiastic group of 15 WM patients and caregivers connected online to try out the new Zoom

meeting format. As folks joined, one by one, they felt uplifted in seeing each other for the first time since late 2019 before the COVID-19 lockdown. Zoom definitely solves the distance problem...one member who could not travel to in-person meetings joined in and a former member who moved away was able to reconnect with WM friends. Group sharing covered WM-related quality of life issues, evaluation of personal treatment responses, and navigating the COVID-19 risks with day-to-day life. One member stressed the importance of finding joy in the moment during these challenging times!

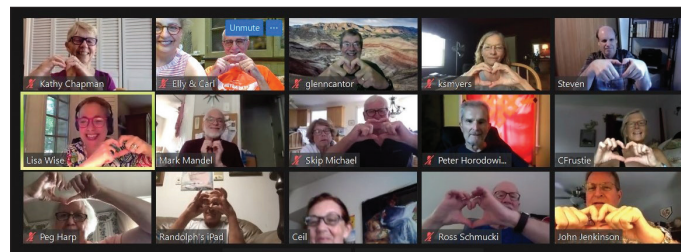
Marcia Klepac reporting

OREGON & SOUTHWEST WASHINGTON

This group has continued meeting via the Zoom video conferencing platform and has had members joining in who otherwise live too far to attend the meetings in person. At the June meeting, they checked in with everyone and had a general discussion about living through a pandemic.

The August meeting brought a presentation from Glenn Cantor, a member of the group, but also a member of the IWMF Research Committee and Science Editor for the *Torch*. Glenn discussed the development of vaccines from smallpox vaccines to polio and shingles vaccines, the ways in which vaccines cause a strong immune response, and about all the current efforts to develop a vaccine to fight the COVID-19 virus. Glenn's talk was incredibly timely, informative, and straightforward. With all Pharma scrambling to create a viable vaccine, knowing the efficacy of the drugs developed will be a challenge given the numbers of people needed for double-blind trials. This was an important takeaway for WMers.

Cindy Jordan reporting



The Philadelphia WM Support Group sends love to the WM world.

PENNSYLVANIA

Philadelphia

Philly WMers were invited to two meetings this past quarter to share time connecting, catching up, offering support, and seeing familiar faces. Thirty-two WMers connected online during the June Zoom meeting. A fellow WMer joined from the UK to share his personal experiences and recent recovery from COVID-19. The group enjoyed submitting questions in advance and

Support Group News, cont. on page 29

answering them together using Zoom's "polling" function so that they could gather real-time anonymous information about unique and different WM experiences. In August, 20 WMers joined together to discuss how they are navigating social isolation and negotiating staying in their own safe "bubbles" or venturing out as the world emerges. Everyone had a different approach to suit their individual medical needs. Topics discussed included: the challenges of social distancing (especially from grandchildren), the ache of missing family and communal celebrations, and the hurdles of coping with a secondary cancer. The group also enjoyed sharing their favorite vacation memories and fun trip photos with each other to give a boost to our current "Staycation Summer."

Lisa Wise reporting



Philadelphia WMer Skip Michael remembers a favorite vacation pastime with his grandchildren.

TEXAS

Denton

The Denton (North TX and OK) Area Support Group met in July via Zoom with 11 people sitting in on the call. Two new-to-the-group people joined and shared their WM history. The rest of the group updated their status with many questions asked and points of common interest found. Dawn Guerrero, LLS coordinator of patient outreach for North Texas, Oklahoma, and Arkansas, joined the group to talk about the many great services LLS has to offer for WM patients, including online information sources, personalized help, and their financial aid programs. The group also noted the upcoming IWMM Virtual Education Forum dates and the Walk for Waldenstrom's fundraiser.

Cathy Hartman reporting

Houston

The Houston group of six families met in June for their "Wine and Whine" session. One Houston couple beamed in from their log cabin in New Mexico, while another couple joined from Marble Falls, about four hours from Houston. When they did the individual wellness checks, a few reported starting a chemo protocol, but all were still feeling fine. The group offered their safety protocols

for dealing with COVID-19. Most have their groceries delivered. All wear gloves and masks when (infrequently) out of their homes. The meeting's premise was to discuss wine, but member Wolfgang instead gave a German tutorial on beer as food. A fun part of the call was inspired by some international members who showed how to raise a glass to cheer in German, Hungarian, Spanish, French, and Greek.

Barbara and John Manousso reporting



The Houston Support Group held a "Wine and Whine" Zoom meeting in June.

WASHINGTON

Northwest Washington/Seattle

Twenty-two people met on a Sunday afternoon for our Zoom meeting on August 2. We were pleased to welcome Dr. Jeffrey Matous, of the Colorado Blood Cancer Institute, to the group. For an hour and a half he answered questions submitted before the meeting, and he also took some online questions. The subjects ranged from the pros and cons of IVIG treatment, to the availability of zanubrutinib and alcaabrutinib, stopping ibrutinib, paraprotein interference with lab values, and normal aging symptoms, such as fatigue, vs. WM symptoms. Discussions were wide-ranging, and everyone was pleased that we were able to tap Dr. Matous's expertise.

Shirley Ganse reporting



The Seattle Area Support Group peppered Dr. Jeffrey Matous with numerous questions during a Zoom meeting in August.

INTERNATIONAL SCENE

EDITED BY ANNETTE ABURDENE

AUSTRALIA

Australia, like the rest of the world, is adapting to the reality of living with COVID-19. Our news on activities and developments in the Australian Waldenstrom's community covers funding for WM research, impact of COVID-19 on support group meetings, and Australian Blood Cancer Action Plan.

IWMF/LLS Strategic Research Roadmap

WMozzies have responded to the enthusiastic IWMF invitation to provide funding for the IWMF/LLS Strategic Research Roadmap. We are proud to be part of the international support, which includes the Waldenstrom's Macroglobulinemia Foundation of Canada (WMFC), the Leukaemia Foundation of Australia, and Waldenström France. We are strongly committed to the long-term vision of "A World Without WM." WMozzies joined with the Leukaemia Foundation of Australia in a campaign to raise AUD \$150,000 (US \$100,000). Three months into the campaign, over one-third of the two-year goal has already been raised. The generous support of WMozzie Peter Carr, a member of the IWMF Ben Rude Heritage Society, is greatly valued. As a matched funding partner, Peter matched dollar for dollar all other donations.

Impact of COVID-19 on support group meetings

No face-to-face support group meetings have been held in the past six months due to the Australian government COVID-19 restrictions. WMozzies are still exploring Zoom opportunities for local support group meetings. Participation in IWMF and affiliate Zoom meetings by WMozzies is proving very worthwhile. Notwithstanding the time zone challenges, Zoom has enabled all interested WM Australians to have online access to the latest international WM news. Noteworthy are presentations by Dr. Richard Furman at Upper New York State, Dr. Shirley D'Sa for WMUK, Dr. Zachary Hunter speaking at an Atlantic Support Group Zoom meeting, and a Toronto Support Group meeting with Dr. Steven Treon.

Australian National Strategic Action Plan for Blood Cancer

WMozzies has been an active member of the Partnerships for Change to achieve the goal of zero lives lost to blood cancer. The National Strategic Action Plan for Blood Cancer has been developed with support from the federal government and led by the Leukaemia Foundation and Professor John Seymour (IWMF Directory, Australian WM specialist) with support by all leaders in Australia's blood cancer community. WMozzies recognise the value of this community-led national action plan and look forward to working with other members of the blood cancer community

on its implementation. The shared vision is:

- Zero lives lost to blood cancer by 2035, underpinned by zero preventable deaths from blood cancer, regardless of geography or background, underpinned by equitable access to quality, safe, and best practice treatment and care for all Australians.
- Patients and their families are empowered to make choices for their wellbeing. Patients and their families know what questions to ask at every stage of their cancer journey.
- Patient autonomy and choice are valued and supported. Through collaboration with patients and leaders in the blood cancer community, the national action plan identifies four major priorities to improve outcomes for people living with blood cancer and their families:
- Empower patients and their families.
- Achieve best practice.
- Accelerate research.
- Enable access to novel and specialized therapies.

Andrew Warden, WMozzies, reporting

CANADA

In May, two new members were added to the WMFC Board of Directors, which provides more national representation—Jim Mason from Halifax, Nova Scotia, and Joe Lewicki from British Columbia. We have also added several new statutory members. Support group leaders and co-leaders are now statutory members. They will represent the membership across the country and will be a great asset to increased communication between WMers and the Board.

Support group meetings have been happening across the country via Zoom due to COVID-19. Our newest support group in Montreal had its first meetings on Zoom. Other Zoom meetings have taken place in Vancouver, Calgary, Toronto/Oakville, (with Dr. Steven Treon speaking about the next generation of BTK inhibitors for WM), Ottawa, and Halifax (with Dr. Zachary Hunter speaking about treatments in WM and the research project that is being supported by the WMFC and the IWMF).

We have also added a national support group for people who are not part of a local group, due to being isolated, travel limitations, and/or for health reasons. Dr. Jorge Castillo spoke about WM treatments at our second national Zoom meeting held on August 12.

We had our first support group leaders' meeting on July 13.

International Scene, cont. on page 31

These meetings are an opportunity to share information and provide ongoing support to our amazing volunteer SG leaders. We also hope to identify additional ways we can serve WMers across the country. The consensus of the group was to continue with these meetings four times a year.

In July, the WMFC launched a fundraising campaign targeted for research. The four research projects we are currently supporting are:

- Dr. Ruben Carrasco's development of a WM mouse. We started this project in 2012 and renewed Dr. Carrasco's funding for the second stage in 2018.
- Dr. Steven Treon's Epigenomic Roadmap of WM project which has been fully funded because of the generosity of a Canadian WM family.
- Dr. Christine Chen's research to develop a blood test to confirm WM, thereby avoiding painful bone marrow biopsies.
- Our newest project supports Dr. Zachary Hunter of the Bing Center at the Dana-Farber Cancer Institute. His research project will study 300 WM patients to analyse their DNA, RNA, and epigenomic changes over time. Dr. Hunter will collaborate with other researchers to determine if WM treatments could be more effective if tailored to each patient's evolving genetic makeup. We have committed to fund half of this project with the IWMF over the next two and a half years.

Betty McPhee, WMFC, reporting

UNITED KINGDOM

Many aspects of the coronavirus lockdown have now eased across the UK. However, owing to recent localised spikes in infections, delays to some easing of restrictions as well as localised lockdown measures have been reimposed in parts of England by the UK government. The Scottish government, Welsh government, and Northern Ireland executive remain responsible for introducing and lifting restrictions in their respective territories and have similar powers to impose local lockdowns if required.

For those people identified as being "clinically extremely vulnerable" and advised to take extra precautions (known as "shielding") during the peak of the pandemic, the UK government has also recently advised that, because the rates of transmission of coronavirus in the community have fallen significantly, shielding advice for those people living in England will no longer be necessary. This announcement was understandably met with confusion and anxiety, particularly for those WM patients and their families who have been cautiously shielding for many months. In response, updated guidance for WM patients from Dr. Shirley D'Sa, WMUK trustee and leading UK WM expert from University College London Hospital, was quickly shared to help our

community navigate the balance between staying safe, and maintaining physical and mental health, whilst retaining a sense of normality by performing usual activities. WMUK continues to monitor the situation and provides updates via our website, social media platforms, Facebook community page, email forum, and e-newsletters.

COVID-19 and WM Webinar

With face-to-face meetings and events still restricted, WMUK was delighted to host its first webinar on Friday, 19 June. Held in partnership with Lymphoma Action, we welcomed over 260 people to hear our panel of UK experts answer some of the most commonly asked questions around COVID-19 and WM. WMUK Chief Executive Lindsey Bennister said, "We hope that the webinar was useful for people affected by WM. Following the success of this first session, we are now looking to host further webinars around this and other topics relevant for people affected by WM. We would like to offer our sincere thanks to our panel of UK experts: Dr Shirley D'Sa and Helen DeMarco, our co-host Stephen Scowcroft and the team at Lymphoma Action, as well as everyone who participated in the webinar and submitted their questions to the panel in advance." You can find a video of the webinar, as well as some additional questions we asked our speakers, on the Resources section of our website

WMUK Factsheet: Testing for coronavirus

Dr. Shirley D'Sa has written a helpful and informative factsheet for the WM community, "Testing for Coronavirus," which is available on our website <https://www.wmuk.org.uk/resources/testing-coronavirus-factsheet>

Ibrutinib for patients with WM in Scotland

WMUK is participating in the Scottish Medicine Consortium (SMC) upcoming assessment of ibrutinib in combination with rituximab in August.

The SMC decides which new treatments are available and funded through NHS Scotland for a range of diseases including cancer. Currently, ibrutinib is not available in any combination for patients in Scotland, and we are working very hard to change this.

A huge thank you to WM patients in Scotland for providing us with their experiences of treatment and care to support our submission and provide us with evidence for the SMC process.

WMUK Patient-Doctor Summit 2021

We are pleased to announce the date for the next WMUK Summit; it will take place at the Edgbaston Park Hotel and Conference Centre, University of Birmingham, on Saturday, 26 June 2021. Registration will open early in January 2021. In the meantime, if you would like to register your interest (no obligation), please email us at info@wmuk.org.uk and we will add you to the Summit mailing list.

International Scene, cont. on page 32

COVID-19 impact on charity fundraising

COVID-19 has had a significant impact on rare and less common cancer charities. A recent survey of Cancer52 members found that a majority had seen a significant drop in income and were worried about their long-term future. Losing charities that represent and support people with rare and less common cancers risks weakening the patient voice and cutting this vital support. Whilst it continues to be a challenging time for a small organisation like WMUK, we have been heartened to hear the creative ways in which our determined WM community members have rallied to raise vital funds for the charity—from making one-off or regular donations, to taking on innovative challenges to help raise funds and awareness of WMUK. Each helps us continue to support those affected by WM, at a time when it's never been more needed.

R4AR JOGLE 2020 – John O’Groats to Lands End Challenge

At the time of writing, the WMUK is incredibly grateful for the support of 13 intrepid cyclists who pedalled their way from John O’Groats to Lands End, in support of The Rory Morrison WMUK Registry and two additional charities: The Brain Tumour Trust and Headcase Cancer Trust.

Taking part in the ride were Honor and Reuben Morrison, who cycled in memory of their dad, Rory Morrison, the much-admired BBC Radio 4 newsreader who died in 2013 of WM, when they were only 15 and 12 years old. The Rory Morrison WMUK Registry (RMR) is dedicated to the memory of Rory and was set up to collect information to help understand the WM landscape in the UK and to gain an accurate picture of this complex disease. Its ultimate aim is to help improve treatment and one day find a cure.



UK cyclists pedal their support for the Rory Morrison WMUK Registry and two other charities.

In total, 13 riders, including cousins, uncles, aunts, and friends completed the whole of R4AR. Setting off on Monday, 17th August and cycling over 12 days, the group arrived at Lands End on Friday 28th August, after having covered over 1,000 miles and climbed over 60,000 ft—twice the height of Mount Everest! To continue support for the #R4AR2020 team please visit their fundraising page at <https://uk.virginmoneygiving.com/fundraiser-display/showROFundraiserPage?userUrl=R4AR2020&isTeam=true>

If you would like to keep up to date with the latest news from the WM community in the UK, you can sign up to receive updates from WMUK at <https://www.wmuk.org.uk/sign-up>.

Leigh Hibberdine, WMUK
operations manager, reporting

BETWEEN JUNE 1, 2020, AND AUGUST 31, 2020, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM’S MACROGLOBULINEMIA FOUNDATION WERE MADE IN HONOR OF:

Team Aarhus
Walk for WM 2020
Sammie Moshenberg
Samuel B. Wechsler

Sylvia Almstadt
William and B. Thompson

Edward J. Baer, Jr.
Cynthia Baer

Charles F. Baish III
Kathleen M. Baish

Abby Black’s Birthday
Leigh Black
Leisha Black
Craig Heimbach
Leslie Hepburn
Diane Hillis

David Kosztowny
Emiel Rickman

Ron Branscome’s
Walk for WM 2020

Juanita Barnett
Jeffrey Branscome
Fred Branscome, Jr.
Janice Brunson
Debbie Cartwright
Janel Donohue
Tracey Hess
Sharon Reik
Patricia and Doug Wall
Annette Wise
Jane Yaun

Chuck Caroselli
Eleanor Caroselli

Chevy Chase, MD
Walk for WM 2020
Ellen Cronin

Chaz’s Birthday
Blythe Anderson Chase
Charlie Cunningham
Gail Glamm
Bill Grilich
Carie Kemenyes
Christine Latimer
D.L. Meckes
Kathy Method
Linda Park
Vicki Sandell
Jude Szczepanski
Brian Taylor
Alice Willis
Brooke Willis

Colorado & Southern WY
Walk for WM 2020
Carol Roberts

Connecticut
Walk for WM 2020
Susan P. Davis
Linda Rainwater
Barbara and Bob Ulkus
Liese Zitzkat

Bill Cox’s
Walk for WM 2020
Phyllis McCarron

Karen Dailey
Aaron Dailey

Honor List, cont. on page 33

BETWEEN JUNE 1, 2020, AND AUGUST 31, 2020, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN HONOR OF:

Dallas, TX

Walk for WM 2020

Judy Francis

Peter DeNardis's

Walk for WM 2020

Guy and Pam Baleno
Michael Bartko
C. Brenner
Cheryl Cook
Diane Drazazinski
Sarah Drudy DeNardis
Louella Edwards
Liz Flush
Francine Faith Fox
John Gelormino
Linda Haberman
Sue Herms
Carolyn Kaikaka
Yvonne Keafer
Dave Laffey
Fay Langer
Eileen McLaughlin
Kathy Moonan
John Paasch
Tara Pallas-Sheetz
Bill Paul
Bill Rupp
Narahari Sastry
Greg and Mary Lou Shirilla
Sandra Stimmler
Cheryl Walton
Thurman Wingrove
Beverly Zern

Denton, TX

Walk for WM 2020

Cathy N. Hartman

Andrea Dictor

Jeremy Asher Dictor

**Audrey Doocy's
Birthday**

Anonymous
Marilyn Beck
Patricia Brandt
Laura Dantes
Audrey Doocy
Donna Gates
Mary McKenna
Katie Shoven
Deborah Stern

Eastern MA

Walk for WM 2020

Lauren Wendel
Eileen Sullivan

**Eastern OH,
Western PA, & West VA**

Walk for WM 2020

Marcia Klepac
Vicki Vlad-Marino

**Eastern PA & Southern NJ
Walk for WM 2020**

Glenn and Inge Cantor
Kathy and James Chapman
John and Frances Gallagher

Jane and Ralph Hendrickson
John and Ann Jenkinson
Carl Lisman
Mark Mandel
Christopher and
Julie Moakley
Randolph Schonour
Josh Weiner
Michael Weiner
Lisa Wise

**Laurence Elliott's
Birthday**

Joan Abrams
Debbie Laypo
Rob Lunny
Gordon Penn
Donna Silverman Levin
Scott Swayze

Deb Fine's Birthday

Lennon Tulsa
Dan Westphal

**Kathy Fulham's
Walk for WM 2020**

Mary Atkinson
Malcolm Austin
Kathryn Fulham
Robyn Haines
Peppi Kearney
Ilyan Keay
Edward Sudol
Kim Tweedie
Andrew Warden

Pat Getz's Birthday

Teri Caputo
Sharon Jennings
Patricia Kearns
Jeanne Simonoff

Ed Goldberg

Bruce and Jacki Barron

Gary Green

Norma and William Green

**Newton Guerin's
Walk for WM 2020**

Newton Guerin

Ali Handal

Margie Marsted

David Handelman

Matthew J. Handelman

**Carl Harrington's
Walk for WM 2020**

Sydney Boisbrun
Jack Burns
Carl Harrington
John and Ann Jenkinson
Roy Langhans
Richard Lilley
Bill Paul

Marquita Henry

Sam M. Glasgow, III

**Tom Hoffmann's
Walk for WM 2020**

Linda Evans

Jack Honaker

Brock and Midge Estes

Natalia Irving's Birthday

Siochanta Farm
Michelle Laroche
Elizabeth Meyer
Nancy Meyer

**IWMF's Walk for
Waldenstrom's 2020**

Anonymous
Anonymous
Edward Bartlett
Michael and Maggie Bayer
Julie and Wade Davidson
Carol and Martin Edelman
Cindy Fahy
Gerald Haram
James Houser
John Justice
Linda and Clyde Kenneaster
Patricia Kirkness
Bruce and Kathie Matloc
Anne Moffat
Robert Mowbray
Lawrence Oakford
Carolyn Olsen
Philip Porush
Michelle Postek
Adrianna Spain
Carl and Susan Stoel
Janet and Andrew Westrich

John Justice's Birthday

John Justice
Arlene Ogata Swinderman
Mark Rosenberg
Maggie Smith
Beverly Starck

**David Kahn's 5K
Waldenstrom's Walk 2020**

Jessica Aber
Suzanne Aber
Diane Andreotes
Art Arevalo
Tom Bird
Kelli Bishop-Bendle
Craig L. Brodeur
Bonnie Brook
Mary Campbell
Andrew Carnase
Mike Chapman
Laura Diaz
John Drago
Michael Dry
Jake Emerson
Scott Fouts
Eleftheria Fraone
Linda Gish
Kim Gore
Crystal Gould
Kevin and Kathleen Hogan
David Kahn
Jay Kahn
Samantha Kahn
Ronald Kennedy
Grayson King
Laura Koester

Pamela Kuphal
David LaBlanc
Evan Levine
Matthew Litchman
Carter Loetz
Amy and Ray Lugar
Patti MacDonald
Luke Marchant
Kathy Martz
Dan McCabe
John Mizzi
Pedro Mora
David Nevin
Susan Ogradnik-Smith
Molly Paisley
Sharon Pontes and Dennis
Murphy
Chuck Quealy
Peter Roblin
Kim Rodriguez
Jenny Rosas
John Scroope
Rick and Kelli Seeger
DeAnn Sheldon
Amy Speen
Phyllis Speen
Christine Tibor
Mary-Jane Tryssesoone
Mitch Watson
Deborah Wilson
Rebecca Wolfa

**Sarah Kirschner's
Walk for WM 2020**

Patricia Cohen
Amy Flaum
Stephen Herschler
Leann Kardell
Julia Kimble
Ron Kirschner
Susan Mackler
Judith Palmer
Karen Smith
Ben Stoltzfus

Stanley Koutstaal

Murilyn Koutstaal

Dr. Steven Krause

Karen and Jerry Eisman

**LA/Orange County/San
Diego, CA**

Walk For WM 2020

James Bailey
Peter Betts
Marla Chao
Wei Chao
Kathie Coen
Julianne Flora-Tostado
Beth Grant
Joseph and Maureen Janda
Deena Kuper
Jim Lambert
Eliot and Connie Levy
Jason Levy
Brenda McCroskey
Blanche Moss

Honor List, cont. on page 34

BETWEEN JUNE 1, 2020, AND AUGUST 31, 2020, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN HONOR OF:

Margaret Nicholas
Susan Piervin
David Senn
Ronnie and LouAnne Smith
Liz Wexler
Gloria Wolen
Diane and Albert Zonana

Janet Livingston
Eleanor Caroselli

**Lower Eastern MI
Walk for WM 2020**
Marian Guyton

Mark Lund
Dr. Edward and Mrs. Gloria
McEllistrem

**Elena Malunis's
Walk for WM 2020**
Michael Bourgo
Arnold Eisman
Sue Herms
Marcia Klepac
Dr. Guy Sherwood
Dominique Smith

Lisa Marie's Birthday
Joshua Seemann
Cole Slaikau

Penny Massoth Beckman
Amy Weiner

**Team Liz McCutchen
Ft Collins, CO
Walk for WM 2020**
Annette Baez
Misty Baker
Dorothy Buckley
Gina Christensen
Geraldyn Colonna
Betsy and Rocky Craig
Lori and Klaus Cross
Annette Foyer
Sarah and Sam Gallo
P. J. Hall
Kristina Jones
Barbara Kingston
Ann Kirchhoff
Nancy Kuehl
Valerie Negron
Joseph Olmstead
Karen Passafaro
Debbie Patton
Katie Randolph
Abbie Reade
MaryBeth Swanson
Ashley Tindall
Jessica Vince
Aleah Zinalabedini

**Jaclyn McDonald's
Birthday**
Becky Cibulka
Sandy Cibulka
Jenn Dougherty

Ruth Hendricks
Jaclyn McDonald
Shannon McDonald
Erika McGrath
Jeff Neubauer
Rocco Perla
Elspeth Wissner

Sara McKinnie
Bill Bass

Ilene Medovich
Linda Theiben

Anne Moffat
Jane Moffat

Anne Mullany
Charles Mullany

My Wife and Family
Bernard Tyrrell

W. Thomas Myers
Sara Franklin and Family

**Northwest/Seattle Area,
WA - Walk for WM 2020**
Mary Conway
Doug Edmonds
Shirley Ganse
Sue Herms

**Oregon & Southwest WA
Walk for WM 2020**
Glenn and Inge Cantor
Bernard and Bonny Carlton
Sylvia Elmer
Cindy Fahy
Ann Hammond
Robert Jensen
Cindy Jordan
Ruth Lizotte
Maria and Joe Navarra
Carrie O'Neil
Kate Stine

James Ortoleva
Charles and Joyce Erff

Harriett Pawliger
Anonymous

Derelys Presley
Charles Presley

**Guy Richards's
Walk for WM 2020**
Detlev Altvogt
Brad Chilton
Matt Eaton
Peter Ganyard
Dave Gardner
Christina Harr
Wendy Jordan
Cheryl Kirk
Michael Klatt
Steven Lykins
Holly Mihok
Patricia Miller

Andreas Miltenberger
Sharie Murray
Norris Pyle
Kenneth Schneider
Brian Seabold
Albert Solderitsch
Deborah Stephens

**Julie Richardson's
Walk for WM 2020**
Todd Adams
Kathleen DiLella
Cathe Dykstra
Holly Eckert
Sandy and Randy Johnson
Ann Keeler
Mom and Dad
Vicki Pilgrim
Carolyn Reed
Beth Roberts
Lisa Tedder
Ruth and Charlie Wallace
Kim Winston

**Team Sarles
Walk for WM 2020**
Pamela Sarles

Karen Schange
Stephen Schange

Bradstreet Walter Smith
Anonymous

**South Carolina
Walk for WM 2020**
Sue Herms

**South Florida
Walk for WM 2020**
Charles Koch

**Stuart's Journey with
BNS - Walk for WM 2020**
Christopher Gavin
Stuart Quick

Maureen Sullivan
Joseph Hauswirth

**Texas Wallies
Walk for WM 2020**
Rick Armstrong
Jean Brock
Jenny Devolites
Richard House
Susan LaForce
Kristina Rojdev

**Karen Thompson's
Birthday**
Craig Aasved
Karen Thompson
Jack Wilbur
Jane Wood

Alexiss Turner's Birthday
Josh Garcia
Vicki Hammonds

Allison Hurd
Amanda Katherine
Jessica Oliver
Kelly Wall Caskey

Elaine Van Bloom
Fred and Dolores
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Daryll Wartluft
Ed and Lisa Anderson

**Western NY
Walk for WM 2020**
Sue Dingee
Patricia Jacobs
Linda Lipp
Joe LoRe
Tom and Lynn Milliman

Merle Weston's Birthday
Warren Hill
Reuben Lewy
Rene Rosechild
Beata Syska
Ruthy Zisook Hill

Walter West's Birthday
Ginger Bissell
Miles Brite
Kathleen Leard
Diana Olsen
Debra Underwood
Tamara Weaver

Lisa Wise
Natalie Fox
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Office Walkers for
WM 2020**
Donna Cutillo
Beverly Docteur
Robert Eanell
Kelly Margolin
Sara McKinnie
Robin Tucker
RaeAnn Uber

**X4 Pharmaceuticals
Walk for WM 2020**
Michele Rhee

BETWEEN JUNE 1, 2020, AND AUGUST 31, 2020, THE FOLLOWING CONTRIBUTIONS TO THE INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION WERE MADE IN MEMORY OF:

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Peggy O'Donnell

Kathryn Gurland

**Bobby Ollerhead
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Macroglobulinemia Foundation

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