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THE IWMF ATTENDS THE ASH ANNUAL MEETING

By Peter DeNardis and Dr. Glenn Cantor

(Editor's note: Dr. Glenn Cantor's articles in this issue were submitted before his untimely death in Alaska. See the "In Memoriam" article on page 10.)

Pete here… In December 2023, I was honored to have the opportunity, as Chair of the IWMF Board of Trustees, to attend my first American Society of Hematology (ASH) Annual Meeting in San Diego, California. Each year, representatives from the IWMF attend the meeting to engage with researchers, partner foundations, and pharmaceutical representatives to find ways to better serve the global WM community. It's also an opportunity to convene an annual meeting of the IWMF's Scientific Advisory Committee. This year, in addition to me, the IWMF was represented by Newton Guerin (IWMF President and CEO), Tom Hoffmann (Vice Chair of Research), Glenn Cantor (IWMF Research Committee), Annette Preston (IWMF Director of Donor Engagement), and Beth Mitchell (Consultant with Scientific Education Support, who also works on behalf of the IWMF, spearheading its efforts outside of North America).

I saw firsthand just how large an event it is, with over 32,000 attendees from 113 countries, most of whom were hematologists. The ASH Annual Meeting is considered the world's most comprehensive hematology event, and just walking around the conference center grounds proved that, as masses of attendees were walking between meeting events—hurrying to the next presentation and exchanging thoughts and observations with colleagues. The streets and hallways were clogged with pedestrians at peak meeting times.

My first evening there, while walking with my wife to have dinner at a nearby restaurant, I heard my name being called. My first thought was perhaps it was a fellow IWMF representative, but the voice sounded different. And I wondered, among the 32,000 attendees, who could possibly spot me walking down the street? The person who noticed us walking by was Dr. Ibrahim Tohidi-Esfahani, one of the driving forces (together with Dr. Judith Trotman, whom I also met with at ASH) behind Australia's WhiMSICAL patient registry. This effort collects patient-reported data from WM patients *(see: https://www.cart-wheel.org/* and scroll down to the WhiMSICAL section).

Once inside the exhibit hall, one is struck by the sheer magnitude of the exhibits, many of which had floor-to-ceiling visual displays to capture your attention as you walked between meeting events.

Of course, the primary purpose of attending ASH is either giving or attending research presentations and poster sessions. The latest and newest results from various research studies are presented here, where those with critical roles to play as medical professionals, patient organization members, and pharmaceutical company representatives can hear first-hand the latest developments that can lead to better diagnosis, monitoring, and treatment for patients with blood cancers and other blood disorders.

As Chair of the IWMF Board of Trustees, one of my "roles" during the conference was to meet with various pharmaceutical foundation representatives to impress upon them the

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critical part we play in providing WM-focused research, education, and patient support, with the objective of obtaining their assistance for our efforts. I spent time with Newton Guerin, Annette Preston, and Beth Mitchell huddled together in meeting rooms, telling our story and relaying what is top of mind in the IWMF patient and caregiver community.

Ultimately, the vast number of abstracts (over 7,400 were approved for oral and poster presentation) proved just how committed the clinicians and researchers are to fighting blood disorders. For WM or WM-related conditions, there were 35 presentations at the event, and IWMF Board and Research Committee members Dr. Glenn Cantor and Dr. Tom Hoffmann made sure to view the presentations and engage with the researchers there.

I came away humbled and very appreciative of not only how committed the clinicians and researchers are to fighting blood cancers and other blood disorders, but also of the efforts taken by researchers, hematologists, non-profit patient advocacy organizations, and pharmaceutical companies to interact with each other to help advance treatments toward a cure for these conditions.

Glenn here…I totally agree with Pete's feelings—awed at the sheer magnitude of the global hematology medical community and humbled and appreciative of the efforts by so many people working together to advance treatments of blood diseases, including WM.

On one of the first days of the meeting, we held a lunch meeting of the IWMF Scientific Advisory Committee (SAC), a group of the world's leading WM researchers and clinicians. It was an opportunity for WM doctors from around the world to put their heads together, discuss different approaches, and form collaborations.

As a side meeting, Dr. Leslie Crews, a recipient of IWMF research funding and a faculty member at University of California-San Diego, hosted a group of WM patients and their partners at her laboratory. She gave a short talk about her research and its potential impact and then took us on a tour of her laboratory. I was particularly impressed by the students, including undergraduates and even a high school student whom she was mentoring. In turn, the students in her lab valued the chance to meet real, live WM patients and hear from us about how important we considered their work. It was also a good opportunity to meet fellow WMers, many of whom I knew only through their email communications on IWMF Connect.

After that, it was "hit the ground running." Before the meeting, each presenter published a short summary of their work called an abstract. I had read the WM-related abstracts and organized a list of presentations that I wanted to attend. What I didn't count on, though, was how huge the meeting was. Going from one presentation to another required walking long distances at top speed, weaving through the packed hallways.

From my point of view, WM research and clinical development are reaching a new stage. Now, thanks to the hard work of many researchers and pharmaceutical companies, we have a basic understanding of what drives the disease. We have a choice of drugs, and doctors a have much better understanding of how and when to use these drugs. WM doctors, by sharing their research and experience, have better ways to manage the complexities of individual patients' medical presentations.

But we're not there yet. WM scientists are now taking a broader look at the problem. We know about some of the molecular abnormalities of WM, such as MYD88, CXCR4, and BTK. But there's clearly more to it. The search is on for other genes that may be involved and different ways in which genes are regulated. Why do some patients not respond to certain drugs or become resistant to their treatment after a period of time? Are there different types of WM which might require different treatments in the future? Why doesn't the body's normal immune system kill the WM cells? Can we do something to improve the way the immune system deals with WM? And are there basic, underlying differences between WM cells and normal cells that—if we understood them better—might lead to new treatments? Answering these important questions are unlikely to give us new drugs in the next year or two but may lead to much better management of WM in the long-term.

Beth Mitchell and Pete DeNardis at the IWMF table at ASH

SUMMARIES OF SELECTED ABSTRACTS FROM THE 65TH ASH ANNUAL MEETING

BY SUE HERMS, RESEARCH COMMITTEE MEMBER

The following are summaries of selected online abstracts of clinical trial results, future clinical trials of interest, and prognosis and survival trends specific to WM or its associated conditions that were presented at the 65th ASH (American Society of Hematology) Annual Meeting in San Diego, CA, on December 9-12, 2023. The abstracts can be searched at: https://ash.confex.com/ash/2023/webprogram/start.html. *The author acknowledges with gratitude the review of this article by the late Dr. Glenn Cantor.*

Prospective Study of Acalabrutinib with Rituximab in Patients with Symptomatic Anti-MAG Mediated IgM Peripheral Neuropathy (Abstract 213) – Peripheral neuropathy occurs in 20-25% of patients with an IgM monoclonal protein, and as many as 50% of these cases are because the IgM monoclonal protein is an anti-myelin associated glycoprotein (MAG) antibody that attacks the myelin sheath surrounding the nerves. While rituximab can be used to treat anti-MAG neuropathy, its activity may be limited and is often associated with an IgM flare that can temporarily worsen the neuropathy. Therefore, researchers from Dana-Farber Cancer Institute, Massachusetts General Hospital, and Brigham and Women's Hospital began a Phase 2 trial using the BTK inhibitor acalabrutinib (Calquence) in combination with rituximab. As of July 2023, the trial had enrolled eight participants. Their anti-MAG titer range was 1:70,000 to 1:819,200 IU/L at the start of therapy. Treatment consisted of continuous oral acalabrutinib (100 mg/twice daily) and once-weekly rituximab in cycles one and four, with cycles consisting of 28 days each. With a median treatment time of 175 days, seven participants were evaluable for response, with 86% achieving a hematological response rate (determined by a decreased IgM level); 57% showed neurologic improvement, as scored in a self-reported disability scale called I-RODS. One participant has been removed from the trial because of significant elevation of the liver enzyme ALT, and two participants have had reversible adverse events, one from a rituximab-related infusion reaction and one from a fainting episode. The trial is continuing enrollment and will report updates.

CD19-Targeting CAR T-Cell Therapy in Transformed Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma: A Descar-T and US Collaborative Study (Abstract 616) – Patients with transformation of their WM to a high-grade lymphoma, such as diffuse large B cell lymphoma (DLBCL), typically have a poor prognosis if they do not respond to chemoimmunotherapy and are unable to tolerate an autologous transplant (of their own stem cells) or relapse after a transplant. Transformation of WM to DLBCL is an uncommon event that occurs when the cancer cells acquire genetic mutations that cause the cells to grow faster and behave more aggressively. CAR T cell therapy targeted to the CD19 antigen on the surface of B cells can lead to durable responses in relapsed or refractory patients with DLBCL that did not originate from WM; therefore, CD19-targeted CAR T cell therapy may represent a promising option in WM patients with transformed DLBCL.

*...CD19-targeted **CAR T cell** therapy may represent a **promising option** in WM patients with **transformed DLBCL.***

This collaborative multicenter retrospective study evaluated the effectiveness and safety of CD19-targeted CAR T cells in 22 DLBCL-transformed WM patients who were relapsed or refractory to prior treatment. Participants were treated during the period 2017-2023 and came from two US centers and from the French national registry called Descar-T, consisting of blood cancer patients treated with CAR T cell therapy.

The study combined results from two different CAR T cell products, Axi-cel and Tisa-cel. After CAR T cell infusion, the best complete response rate in these DLBCL patients was 82%, and the best overall response rate was 95%, but both measures of response declined over six months to 68% each. Seventeen patients (78%) experienced a side effect called cytokine release syndrome (CRS), which is characterized by a system-wide inflammatory response when large numbers of tumor cells are killed, and in two of them, CRS was serious enough to require hospitalization. Immune effector cell-associated neurotoxicity syndrome (ICANS), which is the occurrence of potentially serious neurological symptoms after CAR T therapy, occurred in nine patients (41%). Two of the nine required hospitalization for neurologic complications, including one in the ICU. Other adverse events included infections, low neutrophil count, low platelet count, and anemia. After a median follow-up of 17 months, the one-year progression-free survival and overall survival were 70% and 84%, respectively. Five deaths were reported, four because of progressing disease and one because of COVID-19 infection. The authors suggested that more follow-up is necessary to confirm the long-term effectiveness of CAR T cells in relapsed or refractory DLBCL-transformed WM.

Classical Complement Inhibition by SAR445088 (BIVV020) in Adults with Cold Agglutinin Disease: Safety, Tolerability and Activity Results from the Open-Label,

Summaries of Selected Abstracts, cont. on page 5

Non-Randomized, Single-Dose Phase 1b Study (Abstract 1069) – Cold agglutinin disease (CAD) is an uncommon autoimmune phenomenon that can occur in WM patients, causing anemia when the monoclonal IgM attaches to one's own red blood cells and lyses or destroys them at temperatures cooler than normal body temperature. In this condition, a set of immune proteins called the complement system enhances the destruction of the red blood cells. Currently, CAD may be treated with a drug called sutimlimab (Enjaymo). This Phase 1b trial evaluated a second-generation treatment for CAD called SAR445088, a humanized monoclonal antibody that inhibits part of the complement system pathway. The drug also does not degrade or break down as quickly as its predecessor drug sutimlimab, thereby allowing it to be recycled in the body so that it lasts longer. Twelve patients, enrolled in several international centers, received a single IV infusion of SAR445088 at one of two dosing strengths. The most frequently reported adverse event was blood in the urine, but there were no treatment-related serious adverse events, discontinuations, or deaths. Following their single dose, nine patients increased their hemoglobin level at least 1.5 g/L from their baseline measurement at the start of the trial to Day 106. Total mean bilirubin, which is abnormally elevated in CAD, decreased on the first day, and this decrease was sustained through Day 106.

*...more **sensitive molecular tests** are now being used to **detect** extremely **small numbers** of **cancer cells** in tissue samples...*

Prospective Evaluation of Minimal Residual Disease in Waldenström Macroglobulinemia Across Different Tissues and Treatments: Results of the "BIO-WM" Trial of the Fondazione Italiana Linfomi (FIL) (Abstract 1621) – Minimal residual disease (MRD) is the term given to the presence of small numbers of cancer cells that remain after treatment, even when a patient is in a clinical remission with no symptoms or signs of disease. Achieving a negative MRD after treatment means that no residual cancer cells are detected and that remission is likely to last longer, while a positive MRD means that cancer cells are still detected and relapse is likely to occur sooner. Heretofore, it has been difficult to assess MRD in WM patients with current testing methods. However, more sensitive molecular tests are now being used to detect extremely small numbers of cancer cells in tissue samples, sometimes as low as one cancer cell in a million normal cells. Researchers in multiple centers across Italy and Spain enrolled 300 WM or IgM MGUS patients from 2018 to 2020 in a clinical trial called BIO-WM to establish a biobank of samples and correlate these with clinical outcomes. This ASH report presents the first results of MRD testing in 59 patients in the trial who had received first-line treatment for WM.

Dr. Zachary Hunter of Dana-Farber Cancer Institute

The researchers assessed MRD status by using highly sensitive droplet digital PCR molecular testing to detect the presence or absence of the MYD88 L265P mutation in paired bone marrow, peripheral blood, and cell-free DNA plasma samples collected from each patient at baseline and again at treatment follow-up. The baseline mutation rate detected before treatment was 94% in bone marrow, 80% in peripheral blood, and 90% in cell-free DNA samples. Thirty-one of the 59 treated patients received bendamustine and rituximab (BR), 23 received dexamethasone, rituximab, and cyclophosphamide (DRC) or similar regimen, and five received a single agent therapy. The overall response rate determined by conventional methods was 87% for BR and 96% for DRC regimens. Among all patients, MRD-negativity after treatment was reached in 30% of bone marrow, 89% of peripheral blood, and 54% of cell-free DNA samples. For patients who were still MRD-positive after treatment, the MRD tumor burden shrinkage in the bone marrow was deeper in patients who received BR than in patients who received DRC, and similar trends occurred in peripheral blood and cell-free DNA samples. The median follow-up for these treated patients was 41 months, resulting in a three-year progression-survival rate of 71% and a three-year overall survival rate of 89%. MRD-positivity by droplet digital PCR in the peripheral blood predicted a worse clinical outcome (three-year progression-free survival of 40%), as compared with MRD-negative patients (three-year progression-free

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survival of 73%). The researchers concluded that droplet digital PCR is suitable for MRD analysis in WM, with the use of non-invasive samples such as peripheral blood or cell-free DNA a promising way to predict outcomes.

Ibrutinib and Venetoclax in Symptomatic, Treatment-Naïve Patients with Waldenström Macroglobulinemia (Abstract 1661) – This is an update after continued follow-up in the Phase 2 clinical trial conducted by Dana-Farber Cancer Institute to assess ibrutinib (Imbruvica) and venetoclax (Venclexta) combination therapy in symptomatic treatment-naïve WM patients. Ibrutinib was dosed at 420 mg daily, with venetoclax added stepwise, starting at the second monthly cycle and proceeding to a maximum dose of 400 mg daily, for an intended total of 24 cycles. Of 45 patients enrolled, all had the MYD88 L265P mutation and 17 had a CXCR4 mutation. Therapy was stopped in March 2022 after the occurrence of four ventricular arrhythmia events, including two deaths, but patients have continued in follow-up. The overall response rate has been 100%, with a major response rate of 96%, including a very good partial response (VGPR) rate of 42%. CXCR4 mutations have been associated with a lower VGPR rate of 29% vs. 50% for patients without these mutations. At 24 months of follow-up, progression-free survival was 76%, and overall survival was 96%. There has been a trend toward longer progression-free survival in patients who attained a VGPR. No treatment-related toxicities, including arrhythmias, occurred after therapy was stopped.

*There has been a **trend** toward **longer progression-free survival** in patients who **attained a VGPR.***

Real-Life Multicentre Study on 547 Patients Affected by Waldenstrom Macroglobulinemia Treated with Chemo-Immunotherapy: Which Is the Best and Most Used First-Line Treatment? (Abstract 1667) – Italian researchers from multiple centers compared the effectiveness and safety of different chemoimmunotherapy regimens used in Italy for first-line WM in a retrospective study of 547 patients treated between 2008-2022. Among all patients, 245 received bendamustine and rituximab (BR); 116 were treated with dexamethasone, rituximab, and cyclophosphamide (DRC); 129 were treated with a variety of other regimens; and 48 received rituximab alone. The main focus of this analysis was on the two major treatment groups, BR and DRC. Patients treated with BR tended to be younger and more fit but also had more aggressive disease. Five-year overall survival was not significantly different between the two groups (87.5% for BR and 93% for DRC), but progression-free survival at five years was better for BR at 79.2%, compared to 54.5% for DRC. Notably, approximately 33% of BR patients received an initial bendamustine dose lower than the standard first-line dose of 90 mg/m^2, with 91% of these patients receiving 70 mg/m^2. Both regimens were well tolerated, although dose reductions were more common for BR.

Single-Center Experience of Carfilzomib-Based Combinations for Patients with Lymphoplasmacytic Lymphoma (Abstract 1684) – The John Theurer Cancer Center at Hackensack University Medical Center of New Jersey conducted a retrospective study of intravenous carfilzomib (Kyprolis)-based therapies given to 37 lymphoplasmacytic lymphoma patients (36 with WM) treated there from 2015 to 2022. Carfilzomib was studied because it is a second-generation proteasome inhibitor associated with a lower risk of peripheral neuropathy than the proteasome inhibitor bortezomib (Velcade). The majority of patients in this study were treatment naïve. The combination of carfilzomib, cyclophosphamide, dexamethasone, and rituximab was given to 34 patients (91.9%), while the remaining patients received carfilzomib, dexamethasone, and rituximab. With a median of six treatment cycles, the overall response rate of the carfilzomib regimens was 97.3%, with 48.6% achieving a very good partial response or better. The median progression-free survival was 51 months, and the median overall survival was not reached. Two patients discontinued treatment because of shortness of breath, a side effect associated with carfilzomib.

Indolent Lymphoma: High CR and VGPR Rate with Fixed Duration Bendamustine, Rituximab and Acalabrutinib in Waldenstroms Macroglobulinaemia (BRAWM) (Abstract 3037) – Researchers involved in this multicenter Canadian trial (called BRAWM) are attempting to determine if combining bendamustine and rituximab with acalabrutinib (Calquence), a second-generation BTK inhibitor, will result in deeper responses and provide a longer duration of response than typical first-line therapies for WM. The trial drugs are being given as a one-year, fixed duration treatment that includes six monthly cycles of bendamustine and rituximab and 12 months of acalabrutinib. The primary outcome measure of this ongoing trial is the combined rate of complete responses (CR) and very good partial responses (VGPR). At the time of this interim analysis, 17 of 35 participants had completed therapy, and their combined CR/VGPR rate was 77%, with none showing progressing disease. Three participants discontinued treatment early for varying reasons. The total number of observed treatment-related adverse events was 188, with the number of moderate-to-serious events at 24, including low neutrophil count with fever, allergic reaction, bowel obstruction, and pneumonia. Participants are now being assessed for minimal residual disease status in their peripheral blood and bone marrow.

Orelabrutinib Monotherapy in Patients with Relapsed or Refractory Waldenström's Macroglobulinemia in a Single-Arm, Multicenter, Open-Label, Phase 2 Study:

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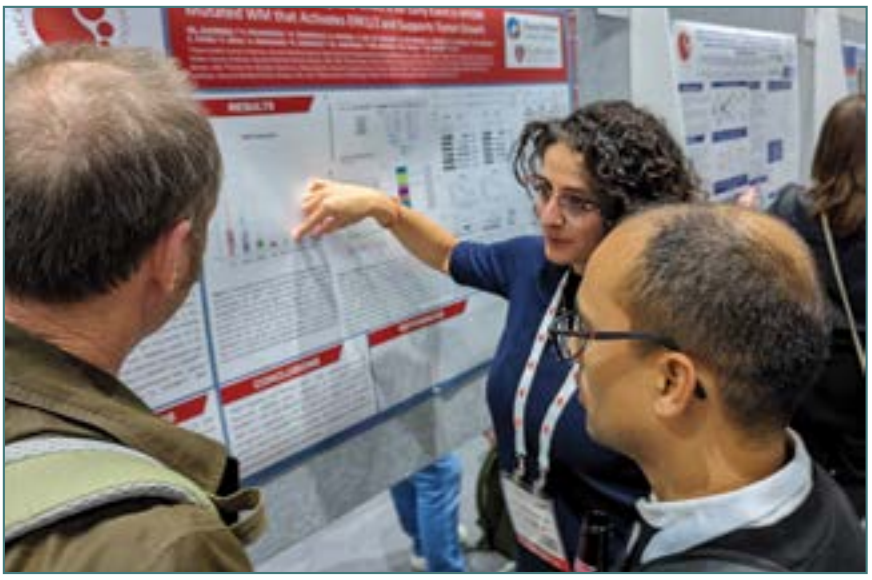
Long Term Follow-up Results (Abstract 3039) – This clinical trial from multiple centers in China administered the BTK inhibitor orelabrutinib to relapsed or refractory WM patients between August 2019-December 2020. At a median 31.9 months of follow-up, 47 patients were evaluated, demonstrating a major response rate of 80.9% and an overall response rate of 91.5%. Using mutational analysis, the group of patients with mutated MYD88 and wild-type (unmutated) CXCR4 had a progression-free survival of 86.2% at 30 months, compared to the groups with either wild-type MYD88 and wild-type CXCR4 or with mutated MYD88 and S388X-mutated CXCR4, both of which had a progression-free survival rate of 75%. Most adverse events were mild; serious treatment-related adverse events occurred in 8.5% of patients and included low neutrophil count, low platelet count, and pneumonia. Four patients discontinued treatment because of adverse events, and one died from treatment-related hepatitis B reactivation.

*The **overall response** rate to **venetoclax** was **73%,** and the median **time-to-best-response** was **four months.***

Clinical Outcomes in Patients with Waldenström Macroglobulinemia (WM) Receiving Ibrutinib on the Phase 3 ASPEN Study ≥ 1 Year After Transitioning to Zanubrutinib (Abstract 3043) – The Phase 3 ASPEN trial compared outcomes of zanubrutinib (Brukinsa) and ibrutinib (Imbruvica) treatment in patients with MYD88-mutated WM. This current extension trial is reporting safety and effectiveness outcomes after at least one year of follow-up in 47 patients from the ibrutinib arm of the original ASPEN trial who were ibrutinib-intolerant and then elected to start zanubrutinib therapy. After a median duration of 15.3 months on zanubrutinib, worsening of adverse events present during ibrutinib therapy occurred in five patients—COVID-19 infections in three patients and anemia and low neutrophil count in one patient each. Of seven patients who experienced cardiovascular events after starting zanubrutinib, all but one had experienced at least one cardiovascular adverse event during ibrutinib therapy. No cardiovascular adverse events led to death; two deaths occurred because of COVID-19 infection. No new or recurring episodes of high blood pressure occurred after patients switched therapy, and no ongoing high blood pressure worsened; also, no new atrial fibrillation occurred, and no ongoing atrial fibrillation worsened. Response was maintained or improved in 44 patients who switched to zanubrutinib. As of June 2023, 40 patients remained on zanubrutinib, and follow-up is continuing.

Outcomes of Patients with Relapsed/Refractory Lymphoplasmacytic Lymphoma Treated with Venetoclax: A Multicenter Retrospective Analysis (Abstract 3045) – A multicenter US study looked at outcomes in 62 patients with relapsed or refractory lymphoplasmacytic lymphoma treated with venetoclax (Venclexta) alone. These were heavily pretreated patients, with 58% having three or more previous lines of therapy. The maximum venetoclax dose was 400 mg daily in 27% of patients and 800 mg daily in 63%. The overall response rate to venetoclax was 73%, and the median time-to-best-response was four months. After a median follow-up of 21.9 months, the median progression-free survival was 30.4 months, and the median overall survival was not reached. Inferior progression-free survival was associated with prior BTK inhibitor therapy, whereas age greater than 65 years at the start of venetoclax therapy and three or more prior lines of therapy were factors associated with inferior overall survival.



Dr. Maria Luisa Guerrera of Dana-Farber Cancer Institute giving a poster presentation

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Tumor lysis syndrome, caused by massive tumor cell death and the release of large amounts of potassium, phosphate, and other substances into the bloodstream, occurred in 7% of patients, while 5% developed a low neutrophil count with fever. Venetoclax dose interruptions and/or reductions occurred in 39%. Venetoclax was stopped in 34%, with the main reasons being progressing disease, planned treatment completion, or toxicity, while 26% remained on venetoclax therapy at the time of abstract submission.

A First-in-Human Phase 1 Study of ABBV-525, a Small-Molecule MALT1 Inhibitor, in Patients with Relapsed or Refractory B-Cell Non-Hodgkin Lymphoma (Abstract 3101) - The MALT1 protein is part of a complex downstream from the BTK protein in the B cell receptor signaling pathway and is considered a potential therapeutic target for several subtypes of B cell lymphoma. A Phase 1 clinical trial of ABBV-525, an oral small molecule inhibitor of MALT1, has just opened to patients with relapsed or refractory mature B cell lymphomas, including WM, and will evaluate its safety, tolerability, and preliminary efficacy. Patients are being enrolled in 25 sites across the US, Australia, Belgium, France, Germany, Israel, Spain, and the UK. The trial identifier on *www.clinicaltrials.gov* is NCT05618028.

A Phase 1, Open-Label, Multicenter, Dose-Escalation Study of SGR-1505 as Monotherapy in Subjects with Mature B-Cell Malignancies (Abstract 3102) – Another oral inhibitor of MALT1, called SGR-1505, is being evaluated in a newly-opened Phase 1 multicenter clinical trial in people with relapsed or refractory mature B cell malignancies, including WM. The trial will study the drug's safety and effectiveness and establish its recommended dose for anticipated future studies. At present, the trial is open at US sites but plans to expand to Europe. On *www.clinicaltrials.gov*, the trial identifier is NCT05544019.

...[ibrutinib] dose reduction can be an effective strategy to manage adverse treatment events...

Real-World Outcomes of CD19 CAR T Cell Therapy in Adult Patients with Relapsed Refractory Transformed Indolent Lymphoma (Abstract 3511) – Transformation of indolent lymphomas, including WM, occurs when acquired genetic mutations cause the lymphoma cells to grow faster and develop into an aggressive lymphoma, such as diffuse large B cell lymphoma (DLBCL). Transformation is generally associated with poor survival outcomes. This multicenter retrospective study looked back at the results from prior CD19-directed CAR T cell infusion therapy used to treat transformed indolent lymphoma (TIL) patients who were relapsed or refractory to therapy. From a total of 788 patients at five US centers who underwent CAR T cell therapy for DLBCL, 212 had TIL—by far, most had transformed follicular lymphoma, but five had transformed WM. Similar toxicities were observed in both the TIL patients and in those whose DLBCL was not the result of transformation from indolent lymphoma. Cytokine release syndrome (CRS), which is characterized by a system-wide inflammatory response when large numbers of tumor cells are killed, was observed in 76% of TIL patients vs. 81% of non-transformed DLBCL patients. Immune effector cell-associated neurotoxicity syndrome (ICANS), which is the occurrence of potentially serious neurological symptoms after CAR T therapy, was observed in 37% of TIL patients compared to 49% of non-transformed DLBCL patients. With a median follow-up of 13.4 months, the median progression-free survival and overall survival were 11.2 months and 41.7 months, respectively, in the TIL group; the same survival outcomes were 7.9 months and 29.7 months, respectively, in the non-transformed DLBCL group. The rates of CAR T cell-related deaths were 9.3% in the TIL group and 7.1% in the non-transformed DLBCL group. The researchers concluded that outcomes in relapsed or refractory TIL patients who had CD19 CAR T cell therapy were similar to those with non-transformed DLBCL who had the therapy.

Real-World Outcomes Following Dose Modifications of First-Line Ibrutinib in Patients with Waldenström Macroglobulinemia (Abstract 3780) – In this real-world study based on Medicare and pharmacy records at their institutions, Dana-Farber Cancer Institute and Mayo Clinic analyzed WM patients from 2014-2020 who received first-line ibrutinib (Imbruvica) therapy and subsequently developed adverse treatment events that may or may not have led to dose reductions and treatment discontinuation. Of 404 such patients identified, 66% had high blood pressure, 14% had atrial fibrillation, and 28% had other cardiovascular conditions before beginning therapy. For this study, ibrutinib dose reduction was defined as a decrease from the starting dose of 420 mg daily within one year from the beginning of treatment. Dose reductions occurred in 14% of these patients, with a mean of 28 days from the start of therapy to the time of their first adverse treatment event and a mean of 137 days from their first adverse treatment event to the time of a dose reduction. At six months of follow-up, 24% of those with a dose reduction discontinued treatment, compared to 46% without a dose reduction. Similarly, after 12 months of follow-up, 36% of those with a dose reduction discontinued treatment, compared to 50% without a dose reduction. The researchers suggested that dose reduction can be an effective strategy to manage adverse treatment events while still maintaining clinical benefit.

First Results from a Phase 1, First-in-Human Study of the Bruton's Tyrosine Kinase (BTK) Degrader BGB-16673 in Patients (Pts) with Relapsed or Refractory (R/R)

Summaries of Selected Abstracts, cont. on page 9

B-Cell Malignancies (BGB-16673-101) (Abstract 4401) – Disease that progresses on BTK inhibitor therapy often has acquired BTK mutations that lead to treatment resistance; therefore, novel agents that overcome resistance are needed. For this multicenter international clinical trial, patients with different types of relapsed or refractory B cell malignancies, including WM, were recruited. BGB-16673 degrades or breaks down BTK instead of blocking its activity, and in pre-clinical work, it degraded wild-type (unmutated) BTK as well as mutated BTK, leading to tumor suppression. To enroll in this ongoing Phase 1 trial, participants must have received at least two prior therapies; in the US and Australia, one of those prior therapies must have been a covalent BTK inhibitor like ibrutinib (Imbruvica), zanubrutinib (Brukinsa), or acalabrutinib (Calquence). BGB-16673 was taken daily by mouth at different dose levels. As of May 2023, 26 patients, including four with WM, were enrolled. In this early report, treatment-related adverse events were reported in 88.5% of patients, with bruising, fever, low neutrophil count, and increases in the enzyme lipase the most common adverse events. No high blood pressure or atrial fibrillation was observed. No one discontinued therapy because of adverse events, but two patients reduced their dose. Of 18 patients evaluated for response, the overall response rate was 67%, with three of the four WM patients responding. At the time of abstract submission, all responders remained in response, and 77% of patients remained on therapy.

Clinical Characteristics, Treatment Approach and Long-Term Outcomes of 678 Patients with Symptomatic Waldenstrom's Macroglobulinemia: Comprehensive Insights from a Spanish Registry of IgM Gammopathies (Abstract 4406) – This retrospective multicenter study included 678 newly diagnosed symptomatic WM patients from 1990 to 2023 who were evaluated at Spanish hospitals and on the Spanish data registry of WM and IgM-related disorders. The most common symptom at diagnosis was anemia, followed by B symptoms (weight loss, fevers, night sweats, fatigue), peripheral neuropathy, and hyperviscosity. Among patients who had samples available for assessing mutations in MYD88 and CXCR4, 75% were identified as positive for MYD88 L265P and 12% as positive for CXCR4 S388X. Plasmapheresis was indicated in 10% of patients. The main first-line treatment regimens were: chlorambucil (37%); dexamethasone, rituximab, and cyclophosphamide (21%); rituximab alone (13%); bendamustine and rituximab (9.1%); BTK inhibitors (7%); and bortezomib, dexamethasone, and rituximab (5.5%). The overall and major response rates for all patients were 67% and 58%, respectively, but the major response rate was higher for bendamustine and rituximab, at 88%, than for the other regimens. At a median follow-up of 96 months, the median overall survival for all patients was 8.7 years, and the median progression-free survival was 6.8 years.

Treatment Selection and Clinical Outcomes in Lymphoplasmacytic Lymphoma / Waldenstrom Macroglobulinemia (LPL/WM) – A Single Center Analysis (Abstract 4421) – A retrospective analysis from Roswell Park Comprehensive Cancer Center in New York looked at treatment selection and outcomes in 127 lymphoplasmacytic lymphoma (LPL)/WM patients seen in consultation at its facility from 2003 to 2023. Of 121 patients with data on treatment strategy, 16.5% were on watch-and-wait. Hyperviscosity was present in 28.1%, and they received plasmapheresis with first-line treatment. The most common first-line treatment used was chemoimmunotherapy (with bendamustine and rituximab the primary choice) in 50.4% of patients, followed by single agent rituximab in 16.5%, and BTK inhibitors in 9.9%. The overall response rate was highest, at 90.7%, in the chemoimmunotherapy group, followed by 87.5% in the BTK inhibitor group and 71.4% in the single agent rituximab group. With a median follow-up of 36.9 months, the median progression-free survival and overall survival were 61.2 months and 159.8 months, respectively, in the chemoimmunotherapy group; 50.2 months and 113.9 months in the single agent rituximab group; and 23 months and not reached in the BTK inhibitor group. The researchers suggested that the shorter progression-free survival in the BTK inhibitor group was likely because of toxicity leading to treatment interruption and change of therapy.

A First-in-Human Phase 1 Trial of NX-2127, a First-in-Class Bruton's Tyrosine Kinase (BTK) Dual-Targeted Protein Degrader with Immunomodulatory Activity, in Patients with Relapsed/Refractory B Cell Malignancies (Abstract 4463) – Although BTK inhibitors are effective in the treatment of B cell malignancies, mutations in BTK that cause resistance to these drugs lead to the need for improved or newer approaches. NX-2127 is an oral once-daily drug that degrades, or breaks down, the BTK enzyme rather than blocking its activity; the drug also boosts T cell function so that the T cells can better attack cancer cells. This US multicenter Phase 1 trial of NX-2127 had enrolled 47 participants, including three with WM, at the time of abstract submission. Participants were heavily treated with several prior lines of therapy. After a median follow-up of 9.5 months, rapid and sustained BTK degradation was observed in all participants. Two of the WM patients were evaluable for treatment effectiveness, one with stable disease and one with progressing disease. The most common adverse events of any grade were fatigue (48.9%), low neutrophil count (42.6%), and high blood pressure (36.2%). Bruising occurred in 27.7% and atrial fibrillation in 12.8%.

In Memoriam

DR. GLENN CANTOR

IWMF Trustee and *Torch* Science Editor

Dr. Glenn Cantor, well-known long-time volunteer for the IWMF, did not survive a snowmobiling accident in Denali, Alaska, on February 16, 2024. This sudden shock reverberated not only among his extended family and close friends, but also within the IWMF.

Glenn lived in Bend, Oregon, with his wife of 43 years, Inge Eriks. He was a devoted family man with two daughters, Alida and Emma, and three grandchildren. He enjoyed the outdoors, photography, bicycling, and birdwatching, and was proud of his service in the Peace Corps in Ecuador and his volunteer work as a veterinarian with the Iditarod sled dog race. He referred to himself as a "skeptical optimist," a description that many of us who knew and worked with him in the IWMF would recognize.

Memories of Glenn from just a few of the many IWMF-related people who knew him are below; they remind us that the entire WM community benefitted in some way from Glenn's tireless work.

Peter DeNardis, Chair of the IWMF Board of Trustees

"The IWMF community is deeply saddened by his passing. Glenn was a tireless volunteer, freely giving his expertise and time to further advance WM-specific research, and to provide guidance and advice to others dealing with Waldenstrom's macroglobulinemia. Glenn had served as an active Board Member since 2020 and was a key member of the IWMF's Scientific Advisory Committee and Research Committee.

"His keen insight and probing questions always led to great discussions at Ed Forums, Board Meetings, and Research Committee meetings and served to further advance the outlook for WM research. His presence will be sorely missed by all: patients, caregivers, researchers, and clinicians alike. His intellect, humor, and insight were unparalleled.

"The IWMF extends heartfelt sympathies to his wife and family. May they take comfort in the knowledge that Glenn had a tremendous impact on everyone he encountered while on his WM journey and mission of helping others, whether in person or virtually around the world."

Dr. Steven Treon, Dana-Farber Cancer Institute

"I want to express my profound sadness on the passing of our dear friend, Glenn Cantor. Glenn was a tireless advocate for WM. I worked with Glenn in numerous capacities as a member of the IWMF Board, SAC, and grant review committees. He was a very thoughtful, kind, and inspiring individual who was always thinking outside the box on ways to advance treatment for WM. His background in veterinary medicine and years in the pharmaceutical industry gave him much insight into new drug development, and he freely shared his wisdom with seasoned and young investigators, greatly benefitting their WM-related studies. He was very excited about fostering the careers of younger doctors and scientists. He recognized the importance of recruiting and preparing the next generation to take on the challenge of finding a cure for WM. He was a presence at the IWMF Ed Forums and the International Workshops on WM, asking thoughtful and provocative questions and stimulating great discussions. Though soft-spoken, his words always carried great meaning. He leaves a great legacy and will be very much missed. May his memory be eternal."

Lisa Wise, IWMF Trustee and Vice Chair, Information and Support

"Glenn was a true mensch and treasured WM buddy. I will never forget when I first met Glenn and his wonderful wife Inge as they walked into the Philly WM Support Group on June 3, 2018. The profound, powerful bond the two of them shared—and the gentle loving care that they showed each other—was palpable to all. They exuded pure warmth and deep wisdom. After making their exciting decision to move to the Pacific Northwest to be closer to children and grandchildren, they also decided to continue Zooming into our group meetings, for which we were grateful! They remained vibrant, engaged, beloved members of our community.

"I will always keep Glenn's generous wisdom, insatiable intellectual curiosity, and warm humor in my heart. He was a dedicated volunteer, cherished friend, and inspiring mentor to so many of us at the IWMF. We will miss him—and the sound of his amazing laugh—very deeply. Last year, I turned to Glenn for wisdom as I was deciding to join a new experimental clinical trial. His clarity, friendship, and words of wisdom were invaluable.

"We send warmest hugs of love and support to Inge, his children, and his grandchildren as our IWMF community mourn this loss by their side."

Shirley Ganse, Editor, *IWMF Torch*

"Those of us who work to put together the IWMF Torch *also feel Glenn's absence acutely. As Science Editor, Glenn's ability to translate technical research into understandable articles for our lay readers was amazing. His exacting standards ensured that information presented in the* Torch *accurately reflected researchers' work and intentions. He was willing to tackle all sorts of subjects, from reports on the various meetings he attended (see page one in this issue), to IWMF-funded research, to explaining interesting scientific questions, such as "Why Can't I Eat Grapefruit?" in the July 2023 issue.* (https://iwmf.com/wp-content/uploads/2023/06/N43999-Torch-July-2023_web.pdf). *Our loss is minor compared to that of Glenn's family, to whom we send our heartfelt words of sympathy and appreciation for the wonderful friend, mentor, scientist, and supporter that Glenn was for the entire WM community."*

WHAT YOU CAN DO

A bold leap forward on Leap Day
On Leap Day, February 29, 2024, the IWMF announced the **"Accelerate the Cure Campaign"**—a bold effort to raise $25 million in five years to accelerate progress toward our vision of "A World without WM." This campaign is designed to move us closer to the ultimate goal that we all dream about: a cure for WM. To read more, see the introductory brochure at *https://iwmf.com/accelerate-the-cure-campaign/*.

Is a cure even possible?
In a word, yes! Read these inspiring statements from two of the leading WM experts in the world. To let the words sink in, read them out loud.

Dr. Stephen Ansell from the Mayo Clinic says, "The generous support of IWMF has set the stage for an acceleration of research toward a cure." And Dr. Steven Treon from the Dana-Farber Cancer Institute states, "At the end of the day, do I believe there is a cure in sight for WM? *Absolutely*."

Don't miss Dr. Treon's hopeful and inspiring video on the subject at: *https://iwmf.com/accelerate-the-cure-campaign/*

Check out the amazing progress we've made so far!
The IWMF has made enormous strides in education, support, and research:

- Early on, the best guess for life expectancy after diagnosis was 3-5 years. Now doctors project 15-20 years. That's great but it's not enough for the folks diagnosed with WM in their 40s, 50s and, yes, even their 30s.
- Originally, there were no treatments. By 1999, there were four treatments. These treatments were harsh and provided short remissions. Now there are over 80 available treatments that provide deeper, longer remissions with fewer side effects, so people diagnosed with WM have a higher quality of life.
- Since 2000, the IWMF has invested over $27 million in WM research. Research funded by the IWMF was critical to discovering and understanding the MYD88 genetic mutation that is found in 90-95% of people with WM and the CXCR4 mutation found in another 30-40%. These findings led to the use of oral BTK inhibitors like ibrutinib and zanubrutinib that have prolonged and improved the lives of people with WM.

But we still need to do more. That's where the **"Accelerate the Cure Campaign"** comes in, and **we need YOU to help make it happen.**

Why the IWMF?
The IWMF is a patient-founded, patient-focused, and patient-led global organization dedicated to Waldenstrom's macroglobulinemia. We are the only global WM-focused organization in the world. There is no one else leading the global charge against WM.

Charity Navigator, the leading organization that rates non-profits in the US, gives the IWMF its highest rating of 4 stars. And within the 4-star category, we get a perfect rating of 100%. That means you can trust us to spend your money wisely!

Why you?
Since WM is a rare disease, we receive no government research funding and limited pharmaceutical research funding. Over **85%** of our funding comes from individuals with WM and the people who care about them, their families and friends. In other words, from people like you.

Why now?
Because we are approaching more research breakthroughs through the IWMF Strategic Research Roadmap and the new WM Clinical Trials Network, we need to keep the momentum for research building. We have the best minds in the world working on our disease. And if we all pull together, we can realistically expect further improvements in our quality of life, longer lives, and yes, even a cure. Your gift will make a difference. But we need your help right **now**.

Why give?
We cannot leave the responsibility of funding to "other" WMers…there are just too few of us. We have made

Accelerate the Cure, cont. on page 13

enormous progress because of the generosity of the WM community in the past. We need you to **pay it forward** and donate. We all have different capacities to give but we all have the same stake in the outcome. Please help ensure our success by making a generous gift or pledge today. Encourage your friends and family to give too. They love you and will be more than happy to support you—you just have to ask. Easy opportunities to ask for their help include donations to the Walk for Waldenstrom's and Facebook fundraisers in honor of your birthday, anniversary, or whatever you choose.

If you've been a regular donor to the IWMF, we thank you from the bottom of our hearts. It would mean the world—a world without WM—if you would increase your giving by as much as you can.

How can you give now?
Support the **"Accelerate the Cure Campaign"** either by making a one-time gift right now or a pledge that can be paid over two to five years. You can donate cash, stocks, mutual funds, or property. There are many ways you can be part of our campaign.

If you don't think you can afford to give very much, consider giving a monthly gift on your credit card, PayPal, or directly from a bank account. Even a small monthly amount will add up over a year or the life of the campaign. And don't be shy, ask your friends and family to help.

Making gifts for the future
Legacy gifts are a way to make a significant donation that you may not be able to afford today. Include the IWMF in your will or estate plan by joining the Ben Rude Heritage Society (BRHS). BRHS gifts provide the IWMF with the strength and the confidence that we can continue to accelerate the cure. These actions can be as simple as calling your life insurance company or IRA/SEP and designating the IWMF as a recipient or by using our FreeWill partner at *www.FreeWill.com.*

For more information, contact Annette Preston, IWMF Director of Donor Engagement, at *apreston@iwmf.com.*

How does this campaign change your dreams for your future?
The IWMF has published Stories of Hope on our website to lift up those troubled by living with WM. We asked three WMers who have published Stories of Hope about what their dreams would be with a cure in hand.


Paul Kitchen

Paul Kitchen's dream: "I dream of a world without WM for my children and grandkids and yours. When Mom had WM in the 1970s, there were no treatments. WM made her life difficult, and it was agonizing for our family. She was gone in just a few years. I've lived with WM for 13 years, and I'm grateful for the treatments that have made this possible. Thanks to IWMF-funded research, my life with WM is much easier than my mom's. But I want more. I want a cure." To read Paul's Story of Hope, see *https://iwmf.com/stories-of-hope/from-canada-paul-kitchens-familial-wm-story/.*


Mary Kitchen


Pete DeNardis with one of his grandchildren

Peter DeNardis' dream: "My first dream was to be around to dance at my daughter's wedding! When I was diagnosed with WM in 2003, my children were very young, and my wish was to live long enough to see them graduate from high school and to walk my daughter down the aisle at her wedding. Now that I've been able to do that, my dream is to be around to dance at my granddaughter's wedding!" To read Pete's Story of Hope, see *https://iwmf.com/stories-of-hope/peter-denardis-there-is-life-with-waldenstroms/.*


Julie Richardson and her daughter

Julie Richardson's dream: When I was first diagnosed in 2020, and my daughter was only 13, I prayed that, as an only parent, I'd just be able to see her to adulthood. Now, my dream involves more beautiful hikes with her, seeing her singing and acting on more stages, travelling together, and, one day—if her life takes her there—being as good a grandmother to her children as my mom has been to her." For Julie's Story of Hope, see *https://iwmf.com/stories-of-hope/julie-richardson-where-hope-is-found/.*

Now go back and read the words of Drs. Ansell and Treon again. Print them out. Copy and share them with your friends and family. Together, we can accelerate the cure and create a "A World without WM." But it is up to us, all of us, each of us. Join us and donate today.

STEVEN HADFIELD: A WALDENSTROM WARRIOR CHAMPIONS AFFORDABLE PRESCRIPTION MEDICATION

By Art Brewer

In a world where the battle against cancer is waged not only in hospital rooms but also in the corridors of policymakers, Steven Hadfield emerges as a formidable advocate. Amidst his own trials with Waldenstrom macroglobulinemia (WM) and other illnesses, Steven fearlessly champions the cause for accessible and affordable medications, igniting a beacon of hope for countless others navigating the daunting terrain of illness and financial strain.

At the heart of Steven's mission is the conviction that no one should be forced to choose between their health and financial well-being. Through sharing his own experiences, Steven highlights the often-overlooked intersection of health and financial struggles faced by cancer patients. His story resonates as a call to action, urging policymakers, pharmaceutical companies, and the health care community at large to reevaluate and recalibrate the pricing dynamics of life-saving medications.

Steven, a 71-year-old resident of Charlotte, North Carolina, was diagnosed with WM in 2014 after purple lesions appeared on his legs. A blood test revealed that his IgM level was elevated to almost 2,000 mg/dL, and a subsequent bone marrow biopsy indicated he had WM. A second opinion from the Cancer Treatment Centers of America confirmed the diagnosis. His initial treatment consisted of a combination of rituximab, cyclophosphamide, and dexamethasone, which produced a positive response. When WM returned, he began taking ibrutinib (Imbruvica), a BTK inhibitor, and then switched to zanubrutinib (Brukinsa), a second-generation BTK inhibitor, when the ibrutinib caused intolerable bleeding and bruising.

He is still being treated with zanubrutinib, which is delivered monthly, and travels to Dana-Farber Cancer Institute in Boston every three months for WM checkups as well as for pain management. He has severe back pain and neuropathy and finds it difficult to walk at times due to irreversible nerve damage. The gabapentin he took to ease the pain was ineffective, but spinal infusions and a spinal cord stimulator do provide him with some relief. In addition to WM and back pain, Steven suffers from Type 2 diabetes and takes Januvia and Lantus to treat the disease.

Steven's life has been significantly impacted by WM. He was part of the stock team at Walmart for ten years, but lost that job because the retailer did not want to accommodate the restrictions imposed by his doctor. These restrictions included lifting no more than 35 pounds, being on his feet for no more than a couple of hours, and being prohibited from climbing ladders. Now he works as a suite runner at the Spectrum Center (home of the Charlotte Hornets basketball team) and as a suite attendant at Bank of America Stadium (home of the Carolina Panthers football team and the Charlotte FC soccer club). During the summer, Steven works as concession manager at Truist Field (home of the Charlotte Knights baseball team) and has worked part-time in merchandising at Carowinds amusement park for 14 years.

As you can imagine, the cornucopia of drugs that Steven takes is not cheap—the zanubrutinib alone costs $17,000 per month. Without assistance, he would not be able to afford these drugs. Fortunately, he has medical insurance and receives a grant from the Leukemia & Lymphoma Society (LLS) to help defray his medical expenses. He is also resourceful in finding creative and less expensive ways to travel to Boston for his quarterly appointments. Diagnosed with multiple diseases, Steven is a living example of how pharmaceuticals can be both a lifeline and a financial burden.

Undeterred by his personal struggles, Steven is a fervent advocate for affordable healthcare, particularly in the realm of prescription drugs. His journey has propelled him into the spotlight, where he passionately champions the cause of lowering drug prices, believing that access to essential medications should be a right, not a privilege.

For several years, Steven has collaborated with patient support groups, nonprofit organizations, and policymakers to push for systemic changes that ensure affordable access to prescription drugs. By amplifying their voices, he aims to create a ripple effect that sparks conversations, influences policies, and ultimately transforms the landscape for cancer patients. He has collaborated a great deal with LLS and also advocates for the American Cancer Society. In addition, he is active in Patients for Affordable Drugs, an organization focused on achieving policy changes to lower the price of prescription drugs.

On August 29, 2023, at the request of Patients for Affordable Drugs, Steven had the honor of introducing President Joe Biden at the White House before Biden delivered remarks attacking the pharmaceutical industry over the cost of drugs. The Biden administration has unveiled a list of the first ten medicines that will be subject to price negotiations with Medicare, part of a landmark program to reduce drug spending under the Inflation Reduction Act passed in 2022. Januvia and ibrutinib are two of the drugs on the list.

"I missed seeing the Guns N' Roses concert to meet the President, but it was definitely worth it," Steven said.

Steven Hadfield: A Waldenstrom Warrior, cont. on page 15

Steven Hadfield introduces President Biden and advocates for affordable drugs.
Screenshot taken from https://www.meidastouch.com/news/putting-a-face-to-the-impact-of-the-inflation-reduction-act

"Biden hugged me and told me to keep fighting to get help for the American people."

For a video of Steven's remarks in the White House, go to: *https://www.meidastouch.com/news/putting-a-face-to-the-impact-of-the-inflation-reduction-act.*

A few weeks after his visit to the White House, Steven participated via Zoom in a congressional hearing with the US Department of Health and Human Services about the cost of drugs. During this hearing, Steven talked about his experience with Januvia.

Steven's efforts have also had an impact in his home state of North Carolina. He traveled to the state capital of Raleigh, where he spoke with state representatives and senators to help get Medicaid expansion passed in the state. North Carolina was one of the few states that had declined to expand Medicaid coverage. Thanks in part to Steven's advocacy, as of December 1, 2023, an estimated 600,000 adults were eligible for full Medicaid coverage under the expansion.

Steven loves sports and attends a lot of athletic events for free because of his various jobs. He also loves to go on cruises and is planning to travel to the Caribbean in July with his wife and grandchildren. As an immunocompromised individual, he takes adequate precautions when traveling. "I make sure to take all my medications with me and wear a mask," Steven said. "I also have my updated shots for COVID, the flu, pneumonia, RSV, and shingles." He has a sensor in his arm to monitor his insulin levels, which is a lot better than pricking his finger five times a day, he added.

Steven's journey serves as an inspiring testament to the resilience of the human spirit and the power of advocacy in the face of adversity. As he continues to fight his personal battle against WM and diabetes, he remains unwavering in his commitment to championing a cause that extends far beyond his own struggle—the fight for accessible and affordable drugs for every patient grappling with the formidable challenges of a serious illness.

Have Your Say

The *Torch* welcomes letters, articles, or suggestions for articles. Please contact *IWMF Torch* editor Shirley Ganse at *shirleyganse@hotmail.com*

CHINA: THE FIRST SPECIALIZED CLINIC FOR INERT (INDOLENT) LYMPHOMA ESTABLISHED AND OPENED: BRINGING GOOD NEWS TO WM PATIENTS

By Yao Huifeng (Roger Yao)

On January 5, 2024, the first specialized outpatient clinic for inert (indolent) lymphoma in China, called the Specialized Outpatient Clinic for Inert Lymphoma at the Chinese Academy of Medical Sciences Hematology Hospital, was grandly established in the Renaissance Tianjin Hotel. On the same day, the inaugural meeting of the Chinese Anti-Cancer Association's Professional Committee of Integrative Rehabilitation of Hematology Tumors was also held there. The conference attracted 148 experts and physicians from all over the country and representatives of patient organizations.

Over the years, the Lymphoma Specialty of the Chinese Academy of Medical Sciences Hematology Hospital, under the leadership of Prof. Qiu Lugui, has been dedicated to the research and treatment of inert lymphoma, which has won wide acclaim from patient groups and recognition from domestic and international counterparts.

As a type of non-Hodgkin's lymphoma with relatively slow disease progression, inert lymphoma has complexity in classification, diagnosis, treatment, and a relatively long treatment cycle. Patients expect to receive diagnosis and treatment advice from a team of specialized physicians and participate in the full-cycle management of their disease. With the first specialized outpatient clinic for inert lymphoma in China, the Chinese Academy of Medical Sciences Hematology Hospital integrates excellent expert resources with years of experience in inert lymphoma

Director Yi Shuhua at the newly established specialized outpatient clinic

to provide more convenient, professional, and targeted diagnosis and treatment services for inert lymphoma patients. While serving the Beijing-Tianjin-Hebei region, it also covers the whole country, so that more patients can receive systematic and standardized treatment in the specialty clinic.

To solve the problem of inconvenience for patients in remote areas to go back and forth for medical treatment and follow-up, the Inert Lymphoma Specialized Outpatient Clinic has established up-and-down referral alliances with provincial and municipal hospitals nationwide, which simplifies the process of medical treatment for patients and

Members at the inaugural meeting of the Chinese Anti-Cancer Association's Professional Committee of Integrative Rehabilitation of Hematology Tumors

China: The First Specialized Clinic, cont. on page 17

realizes the goal of homogeneous diagnosis and treatment nationwide. This initiative provides patients with the convenience of local treatment and follow-up, while at the same time providing them with treatment plans and advice on full-cycle management of their condition from the nation's most specialized physicians and experts.

On January 5, 2024, Yao Huifeng, a representative of the WM Patient Organization, participated in both of the inaugural meetings and delivered a speech at the Specialized Outpatient Clinic for Inert Lymphoma meeting:

"As a relatively rare part of the inert lymphoma group, we WM patients are very much looking forward to the newly established Specialized Outpatient Clinic for Inert Lymphoma, and we hope that more and more hospitals in various provinces and cities, especially those in remote areas, can establish referral and cooperation mechanisms with the Specialized Outpatient Clinic for Inert Lymphoma at the Chinese Academy of Medical Sciences Hospital of Hematology. This will enable WM patients and other inert disease patients to have more convenient access to standardized, regulated, and high-quality diagnosis and treatment services.

"The WM Patient Organization would like to thank Qiu Lugui, Yi Shuhua, and other specialists from the Hospital of Hematology, Chinese Academy of Medical Sciences, for their attention and support to WM patients over the years, as well as the many scientific lectures and free in-group Q&A sessions held for WM patients over the past three years. We hope to continue to receive the support from inert lymphoma specialists for our future patient education activities."

At the inauguration ceremony, Yao Huifeng, on behalf of the WM patient group, invited four hematologists from the Hematology Hospital of the Chinese Academy of Medical Sciences, Qiu Lugui, Yi Shuhua, Xiong Wenjie, and Yan Yuting, to become WM Health Science Volunteer Physicians and presented certificates to them.

China WM Support Group Leader Yao Huifeng and Prof. Yi Shuhua

On January 10, the Tuanbo Campus of the Chinese Academy of Medical Sciences Hospital for Hematology officially opened to the public, marking the beginning of the country's first specialized outpatient clinic for inert lymphoma.

Overview of specialty clinic information

- Scope of Clinic: Diagnosis and treatment of inert lymphomas such as chronic lymphocytic leukemia, follicular lymphoma, splenic marginal zone lymphoma, lymphoplasmacytic lymphoma/ Waldenstrom macroglobulinemia, lymphoma of the condylomata, hairy cell leukemia, hairy cell leukemia variant, T-macrogranulocyte lymphocytic leukemia, and other inert lymphoma diseases
- Physician Team: Yi Shuhua (Chief Physician), Wang Tingyu (Deputy Chief Physician), and others
- Time: Every Wednesday morning
- Place: Tuanbo Hospital, Chinese Academy of Medical Sciences (No. 28, Tuanbo Avenue, Jinghai District, Tianjin, China)

DRUG DISCOVERY AT THE TREON LABORATORY HIGHLIGHTED AT ASH

BY DR. GLENN CANTOR, *TORCH* SCIENCE EDITOR AND IWMF TRUSTEE

The American Society of Hematology (ASH) Annual Meeting is a large, prestigious conference where scientists show, often for the first time, key discoveries from their laboratories. For me, one of the highlights of the ASH meeting was seeing data on new drug discoveries from Dr. Steven Treon's lab in the Bing Center for WM at the Dana-Farber Cancer Institute at Harvard University.

For years, Dr. Treon's lab has been central in some of the major discoveries about WM and its biology—the discovery of gene changes (mutations) in MYD88 and the importance of how MYD88 transmits a signal to another protein called BTK. This led the way to the first successful use of ibrutinib, a BTK inhibitor, for WM treatment. The lab also discovered the importance of CXCR4 mutations, which led to several successful Phase 1 studies with CXCR4 inhibitors, and more.

As the lab developed a better understanding of WM and its biology, it became apparent that there is more to it than just MYD88, BTK, and CXCR4. One important discovery, initially by Dr. Guang Yang in Dr. Treon's lab, was the role of another signaling molecule called HCK. For a number of years, the lab has been exploring the dual roles of BTK and HCK, which together signal to the WM cells that they should survive in the bone marrow and expand their numbers, causing disease.

*One **important discovery**... was the **role** of another **signaling molecule** called **HCK.***

But as Dr. Treon explained to me, even as this knowledge has accumulated, it remains frustrating to continually rely on "hand-me-down drugs," drugs originally developed for other cancers and re-purposed for WM. Now, with a better knowledge of the specific molecular pathways that cause WM, he and his group have taken the bold step of discovering and attempting to develop their own drugs, specifically intended to treat WM. Since both BTK and HCK are important in WM, the lab decided to try to invent a new drug that would attack both BTK and HCK at the same time.

Medicinal chemists are chemists who specialize in the invention and synthesis of new drugs. Dr. Treon's first step was to set up a collaboration with an experienced medicinal chemistry group, run at the time by Dr. Nathanael Gray at Harvard University. Now, they have taken the effort to the next level by hiring a talented medicinal chemist, Dr. John Hatcher from the Harvard group, to join the Treon lab at the Bing Center and actually work side-by-side with the rest of the Treon lab members. Meanwhile, Dr. Hatcher continues to collaborate with his chemistry colleagues and take advantage of expert advice from Dr. Sara Buhrlage and other Harvard medicinal chemists.

An essential aspect of drug discovery is the synthesis of a large number of molecules, which are then tested in the laboratory for desired properties. The molecules that perform the best are then selected as starting points, from which a large number of next-generation variant molecules are generated. The cycle is repeated many times. Again, the new, next-generation molecules are subjected to laboratory tests, the best ones are selected, and these third-generation molecules are used as templates for making additional modifications.

Critical to this process is not only a skilled medicinal chemist who can prepare numerous variations of a molecule but also knowledgeable biologists who can identify the desirable properties that are necessary and help to design efficient tests for those properties. The advantage of having a medicinal chemist working directly in Dr. Treon's lab is that he can take advantage of the skills and knowledge of other lab members to better understand exactly what qualities the new drug must have.

It is not an easy process. The molecule that the lab is trying to discover must not only attack both BTK and HCK at the same time, but it must do so selectively. It is desirable to only target BTK and HCK, while sparing the wide variety of other similar signaling molecules in the cell, molecules that normal cells may rely on to carry out their functions.

But that is not enough. A successful molecule must have many other properties. The molecule must be "potent," meaning that only a very small amount is needed to carry out its function. The molecule cannot be toxic, or at least, it must have manageable toxicities that are acceptable to doctors and patients. If a drug is going to be given as a pill instead of an injection, it must be stable in the stomach and intestines and then be able to pass through the wall of the intestines and through the liver to enter the body's blood supply. Once it gets into the blood, the molecule has to reach a certain concentration, so that it is effective against

Drug Discovery at the Treon Laboratory, cont. on page 19

the WM cells, but not at so high a concentration that it causes unintended damage. In the blood, the molecule must be stable for a period of time, but eventually it must be capable of being degraded. Once the molecule is degraded into pieces, the pieces themselves must also not be toxic. After the drug is manufactured, it has to be stable on the shelf or in a bottle, so the pills don't chemically change or become inactive before a person can take the pill. Those are just a few of the properties a newly-discovered molecule must have. Not surprisingly, medicinal chemists go through many rounds of selection before they land on the right molecule.

At the ASH meeting, Dr. Treon's lab disclosed some of their first efforts. In a poster presented by Dr. Shirong Liu, a lab member, they showed data from a series of molecules that can attack both HCK and BTK and inhibit the growth of WM cells. A bonus is that the molecules also are active against cells from a related disease, diffuse large B cell lymphoma (DLBCL).

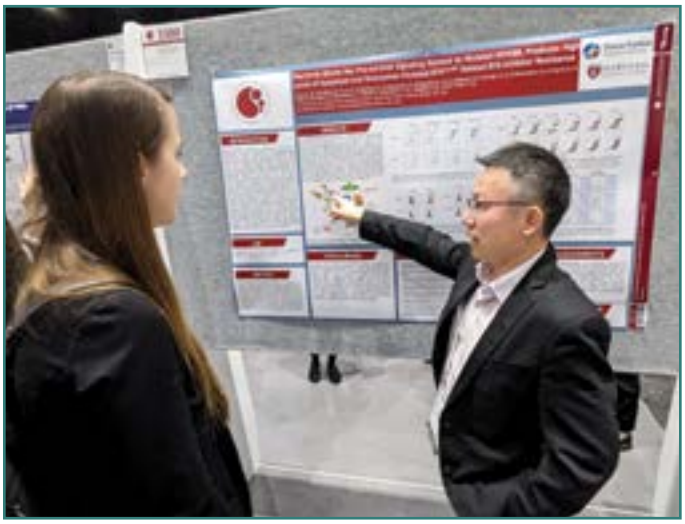
They chose an interesting approach, one that is being used by a number of medicinal chemists at many pharmaceutical companies in recent years. Previously, BTK inhibitors have been in a class called "kinase inhibitors." BTK and HCK have what are called "active sites," areas of the proteins that carry out their signaling function. Ibrutinib, zanubrutinib, and acalabrutinib all work by obstructing the active site of BTK. BTK still exists in the cell, but it is "inhibited"—it is non-functional because its active site is gummed up. Pirtobrutinib works in a generally similar way, but instead of binding to the active site, it binds elsewhere on the BTK protein, which likewise inhibits the BTK function.

Instead, Dr. Hatcher is using a different approach. He is trying to discover molecules that do not just inhibit but completely degrade BTK, as well as HCK. They are doing this by taking advantage of cells' normal "garbage disposal" machinery. Normal cells in the body must have a means of getting rid of old or unwanted proteins. Otherwise, the cells clog up and eventually die. In the case of the new molecules from the Treon lab, first, the molecule attaches to a specific region on BTK and HCK. Then, the other end of the molecule binds to a different molecule that is present in cells and that causes BTK and HCK to become coated in a cellular chemical called ubiquitin. When molecules are coated with a large number of ubiquitins, they are recognized by the garbage disposal system of the cell, called the proteasome, which chops the ubiquitinated protein, in this case BTK and HCK, into small, non-functional pieces. This type of degrader drug is called a PROTAC, which is an acronym for "proteolysis targeting chimera."

Dr. John Hatcher, a medicinal chemist at the Treon Lab

In the ASH poster, Dr. Liu, Dr. Hatcher, Dr. Treon, and their colleagues showed data on some of the BTK and HCK PROTACS that they have discovered. The molecules are potent, meaning only a small amount is necessary; relatively specific, in that they affect only a small number of proteins other than BTK and HCK; inhibit pro-survival signaling and proliferation of WM cells in the laboratory; do not inhibit healthy lymphocytes; and, in experiments with mice, successfully pass through the intestinal wall to reach the bloodstream. It is an encouraging start, and I look forward to further development of this set of molecules in the Treon lab.

In another poster at the ASH meeting, Dr. Shirong Liu presented other work from the Treon lab. In addition to attempting to discover new molecules, they are also going back and testing the activity of existing drugs, with the intent of using them in WM if they show suitable properties. Interestingly, their screens identified a drug called pacritinib that has been FDA-approved since 2022 for use in another bone marrow disease called myelofibrosis. While pacritinib is not known to inhibit BTK (or HCK), it does inhibit a protein called IRAK1, which is also part of the MYD88 signaling pathway. Because WM cells have excessively active MYD88 signaling, it is reasonable to think that pacritinib might be able to slow down or kill WM cells. The Treon lab found that pacritinib worked together (synergized) with BTK inhibitors such as ibrutinib and also with the BCL2 inhibitor venetoclax, giving hope that a combination therapy might be much more effective against WM. A nice feature of pacritinib is that it worked, at least in the laboratory, even against WM cells that had become resistant to the BTK inhibitor drugs such as ibrutinib or



Dr. Shirong Liu of the Treon Lab presenting a poster on pacritinib at the 2023 ASH Annual Meeting

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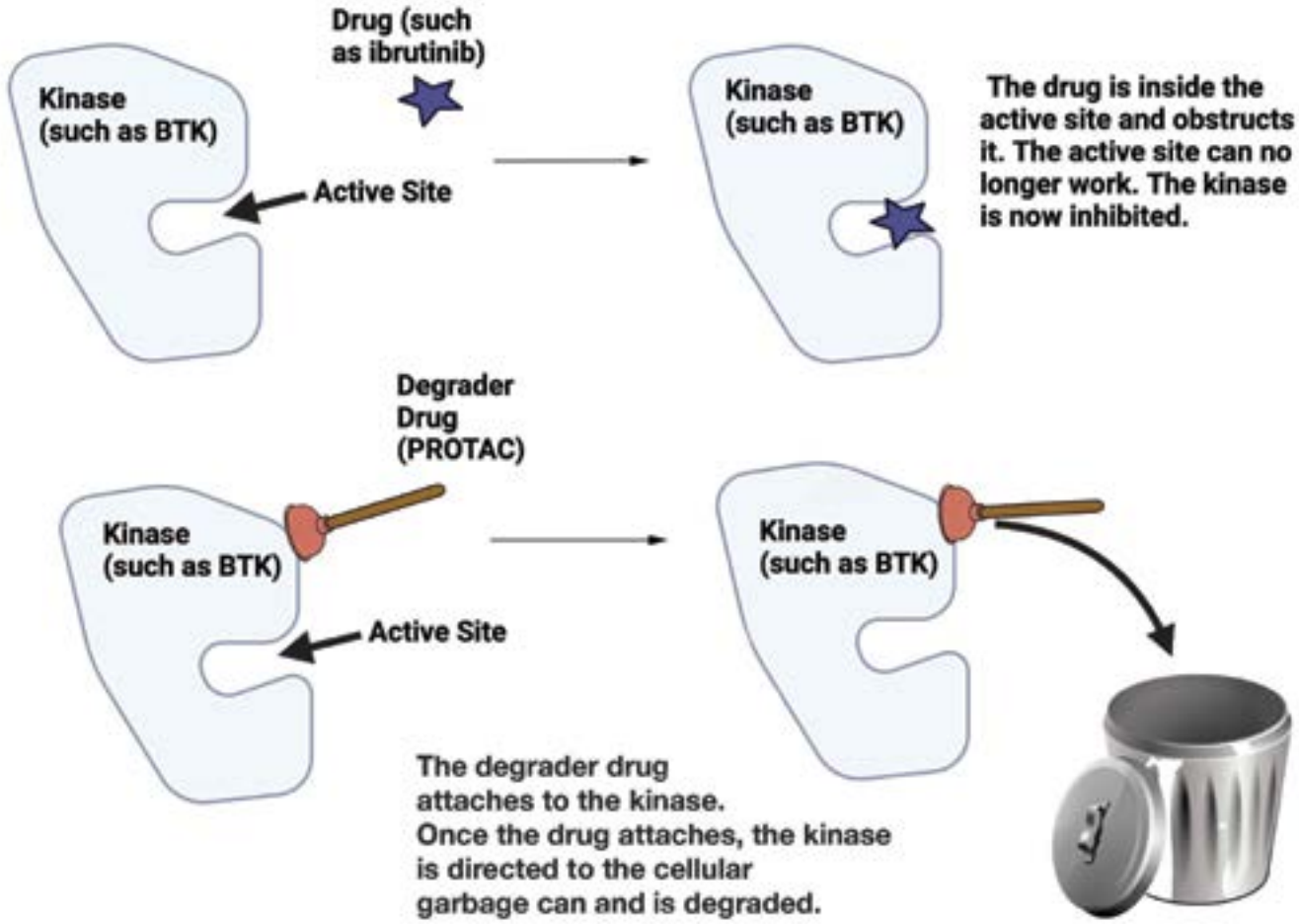
zanubrutinib. The laboratory discoveries described in Dr. Liu's poster have led to plans for a Phase 2 clinical trial of pacritinib at Dana-Farber Cancer Institute for WM patients who have become resistant to BTK inhibitors. If successful, pacritinib might be repurposed as another tool for doctors to use in better managing WM.

MECHANISM OF ACTION OF A KINASE INHIBITOR VS. A DEGRADER DRUG (PROTAC)



BTK is a protein inside cells called a kinase. Its active site can be obstructed by drugs such as ibrutinib or zanubrutinib, which are called kinase inhibitors (shown here as a star). Dr. Hatcher is using a different approach. He is trying to design a degrader drug or PROTAC (proteolysis targeting chimera), shown here as a toilet plunger. After the drug attaches to the protein, in this case BTK or HCK, at a location other than the active site, a chain of events results in the protein being taken to and chopped up (degraded) by the proteasome, the cell's garbage disposal machinery (shown here as a garbage can). Figure created with Biorender.com.

WHAT YOUR HEART ASKS AND YOUR POCKET CAN AFFORD

By Anne Moffat, Toronto, Canada

Anne Moffat

In June of 2013, I retired from 40 years of teaching. Two months later, I was diagnosed with lymphoma, and two months after that, the diagnosis was narrowed to lymphoplasmacytic lymphoma, or Waldenström's macroglobulinemia.

Waldenström's macroglobulinemia. I had to practise that one until it rolled off my lips mellifluously. I started looking online. First, I searched for information on the unfamiliar terms used in the laboratory report: IgM, lambda light chains, neutrophils, RDW, blah, blah, blah. Then I found case studies from online medical journals describing unusual cases of WM involving hideous complications of every sort. Those were ominous. Next, I discovered information about Dr. Jan Waldenström, the Swedish physician who described the disease in 1944. On the various cancer centre sites, I found simple descriptions of this lymphoma as well as information on standard treatments. I researched the treatments and happened upon information about BTK inhibitors, including Dr. Steven Treon's research, and this finally led me to the IWMF. I was excited to learn there was an organization providing information and support to us WMers, and I was very impressed to learn the whole organization was run by people with Waldenström's. I joined the club, the club no one wants to join.

The IWMF proved a lifeline for me, as WM is such a rare disease. What a relief to find this source of information and connection! I wanted to know absolutely everything about the disease, the research, and the treatments, and the IWMF provided a path for me to learn all this and connect with others in the same boat. I discovered the *IWMF Torch,* our quarterly magazine, and was amazed at the quality of information and the excellent writing, all produced by WMers. From the IWMF, I discovered a similar Canadian organization, the Waldenström's Macroglobulinemia Foundation of Canada (WMFC), which I immediately joined also. On several occasions, I drove four hours to Toronto to attend fundraising events for WM research, and there I connected with then-president Arlene Hinchcliffe, as well as other WMFC members. At one of these events, I met a fellow WMer, Walter, who at 88 was still going strong. That was encouraging. I joined the Toronto Support Group. I began donating to the WMFC and subsequently to the IWMF, both for research and for the wonderful support the organizations provide to us WMers.

With better understanding of WM, I relaxed and went back to my newly retired life of exercise, socializing, travelling, and visiting with family. I vowed to be more present in every moment of life. In 2016, I attended the IWMF Ed Forum in Providence, RI, where my recently married daughter was then living. At the Ed Forum, I met WMers from all over the world, and most importantly, I met Drs. Steven Treon and Jorge Castillo, both of whom were presenting at the conference. I was stunned by the commitment and interest of all these doctors and researchers. When I approached Dr. Treon to talk about genetic testing for MYD88 and CXCR4 mutations, he invited me to come to Dana-Farber Cancer Institute in Boston to be tested. At the time of my diagnosis, Ontario was not doing this genetic testing, so I didn't know my status but was keen to find out, as it might affect prospective treatment. I made an appointment with Dr. Castillo, drove to Boston (a two-day trip for me), and had a bone marrow biopsy that revealed I had both genetic mutations. I felt so grateful to have discovered the IWMF and to have met these amazingly dedicated WM doctors. Additionally, Dana-Farber itself is an incredible experience and a first-rate institution.

Early in 2017, with my hemoglobin steadily declining, my doctor in Sudbury wanted to start treatment. In April, I began therapy with bendamustine plus rituximab and dexamethasone and experienced almost every possible complication, but I shall spare you the details because I had a good result: my IgM dropped from about 2,600 to 300 mg/dL. I stopped rituximab maintenance therapy after a year of perpetual pneumonia, and I have been doing well since. I still regularly pick up respiratory infections that lead to pneumonia, but COVID was a blessing for me, as isolation meant I remained quite healthy. With COVID running rampant in the spring of 2020, I organized an outdoor aerobics class that is still going strong, summer and winter, here in Northern Canada. At the same time, most of my activities went online. For years I hadn't been able to attend my book club or go to the gym for exercise classes lest I contract a respiratory infection,

Outdoor aerobics class

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Anne Moffat and her grandson Eric

and with COVID, I could suddenly do everything on Zoom. I may be the only person whose social life improved during the pandemic!

During the spring of 2021, in the IWMF "Waldenstrom's Weekly" newsletter, I noticed that Ann MacMullan was offering a chair yoga class for WMers via Zoom and immediately added this to my calendar. In our first session, Ann told us her father had WM and she was donating a series of classes in his honour. As the three-month series was concluding, we learned from IWMF Information & Support Director Shelly Postek that one of our number had donated some money to pay for the classes to continue, something we cheered, because this class and our post-yoga chat had become important to all of us. Ann had created not only the perfect chair yoga class for WMers, but also a wonderful chat group where we had become supportive friends. I so enjoyed the classes and attendant chat that I organized my weekly activities around them, and when this second round of classes was coming to an end, I sent a donation to the IWMF to keep classes going. I have continued to send donations designated for this IWMF Wellness Program that is now offering many more supportive activities to help WMers keep moving and deal with the many issues we daily experience. I hope news spreads throughout our community about this fabulous IWMF Wellness Program and that many more WMers join us.

For me, the IWMF has been a portal to knowledge and support. With everything I have learned about Waldenström's macroglobulinemia from IWMF publications like the *Torch*, and from IWMF-sponsored seminars and the annual Ed Forum, I have become more curious about the science and less anxious about the outcome. The science fascinates me. In my next life, I now plan to return as a medical researcher.

How fortunate I am that since my diagnosis ten years ago, I have seen my children marry and have welcomed three delightful grandchildren into my life! I feel grateful and blessed to be alive, and I'm enjoying my family and friends and the world around me. Strange as it may sound, I also feel grateful for my Waldenström's experience, as it has heightened and intensified my appreciation of every interaction with my family, my friends, and my more recently acquired Waldenfriends.

For the last ten years, with what "the pocket can afford," I have supported the WMFC and its contributions to research both in Canada and the United States. More recently, I have supported and will continue to support the IWMF in making the lives of those with Waldenström's macroglobulinemia better and brighter. My heart asks me to do more.

MEDICAL NEWS ROUNDUP

By Sue Herms, IWMF Research Committee Member

US FDA Approves Liquid Formulation of Ibrutinib – The US Food and Drug Administration (FDA) has approved an oral suspension (liquid) formulation of ibrutinib (Imbruvica) for the estimated 5% of users who have difficulty swallowing tablets and capsules. The oral suspension is off-white and supplied in an amber glass bottle with a pre-inserted bottle adapter and a child resistant closure. It comes with two 3-mL reusable oral dosing syringes. Each mL of the liquid formulation contains 70 mg of ibrutinib.

Iopofosine 1131 Phase 2 Trial for Relapsed or Refractory WM Meets Primary Endpoint – Cellectar Biosciences announced that its Phase 2 CLOVER WaM clinical trial evaluating iopofosine 1131 for the treatment of relapsed or refractory WM patients has met its primary endpoint with a major response rate of 61% (the sum of partial, very good partial, and complete responses), including a complete response rate of 8%. Iopofosine is a fixed, four-dose course of therapy that is completed in 75 days; it consists of radioactive iodine 131 combined with a small molecule phospholipid that is engineered to target cancer cells. The drug was studied in 45 WM patients who had received at least two prior lines of therapy, including BTK inhibitors. At a median follow-up of eight months, the median duration of response had not been reached, and 76% of patients remained progression-free. Grade 3 (severe) or greater adverse events included low platelet counts in 55% of patients, low neutrophil counts in 37%, and anemia in 26%. No treatment-related adverse events led to discontinuing the drug, and there were no treatment-related deaths in the trial. Cellectar says it plans to request accelerated new drug approval from the FDA. In a related finding, iopofosine 1131 demonstrated complete clearance of central nervous system development (called Bing-Neel syndrome) in a WM patient enrolled in the trial, providing evidence that the drug is able to cross the blood-brain barrier.

Phase 2 Trial of Ibrutinib and Ixazomib in WM Reports Results – An article in the *British Journal of Haematology* reported Phase 2 trial results for ibrutinib (Imbruvica) in combination with the oral proteasome inhibitor ixazomib (Ninlaro) for the treatment of WM patients. The trial, conducted at Mayo Clinic in Florida, was intended to be limited to a maximum of 24 cycles and included treatment naïve and relapsed or refractory patients. The primary endpoint of the trial was the complete response rate, but no complete responses were achieved and trial enrollment was closed early. In 21 evaluable patients, the overall response rate was 76.2%. After a median follow-up of 25.7 months, the median progression-free survival was 22.9 months. The most common adverse events were anemia, fatigue, nausea, low platelet count, vomiting, peripheral sensory neuropathy, peripheral motor neuropathy, and diarrhea. Adverse events caused 28.5% of patients to discontinue treatment.

Phase 4 Observational Clinical Trial of Zanubrutinib in WM Has Opened – A Phase 4 US-based observational trial of zanubrutinib (Brukinsa) therapy in WM patients has been opened to gather additional data on the drug's effectiveness and safety in groups of people not well represented in previous clinical trials of the drug. The trial plans to enroll 111 WM patients on zanubrutinib who will be assigned to one of two groups based on their MYD88 mutation status. One group will include patients with the MYD88 L265P mutation who are from racial and ethnic minority groups and are either treatment naïve or have relapsed or refractory disease. A second group will include patients who are MYD88 wild-type (unmutated) or who have non-L265P mutations in MYD88 and are either treatment naïve or relapsed/refractory. Dose and duration of zanubrutinib therapy are at the discretion of the prescribing physician. Data collection will occur at screening, every three months during the first year of treatment, and every six months thereafter. The identification number on *www.clinicaltrials.gov* is NCT05640102.

*An **increased risk** of **secondary cancers** was noted for WM **patients aged 50-74...***

Study Analyzes Risk of Secondary Cancers in WM – A multicenter study published in the journal *Clinical Hematology International* analyzed the incidence and risk of secondary cancers occurring in WM patients by using the Surveillance, Epidemiology, and End Results (SEER) database of cancer patients in the US. A secondary cancer was defined as the occurrence of a different cancer appearing at least one year after the diagnosis of WM. Of 4,112 WM patients identified from 2000 to 2018 in the database, secondary cancers were reported in 699 (17%), which was a 53% higher risk compared to the general population. An increased risk of secondary cancers was noted for WM patients aged 50-74 years and for those over 75 years, but not for patients younger than 50. The average age for occurrence of a secondary cancer was 74 years. This study demonstrated a significantly increased risk for Caucasians, American Indians/Alaska Natives, and Asian/Pacific Islanders but not for African Americans. Among secondary solid cancers, the highest risks were for various kinds of skin cancers, mouth cancer, brain cancer, respiratory cancer, and gastrointestinal cancer. Among secondary blood cancers, the highest risks were for extra-nodal non-Hodgkin's lymphoma, other non-

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Hodgkin's lymphomas, acute leukemias, and multiple myeloma. The researchers noted that the reasons for secondary cancer development in WM are somewhat unclear, but are likely because of genetic predisposition in those with a family history of WM or related disorders, dysregulation or impairment of the immune system, and/or the use of certain treatments for WM such as chlorambucil and nucleoside analogs (such as fludarabine).

Chinese Researchers Study Optimal Second-Line Treatment Strategies for Relapsed WM – Over time, treatment strategies for WM have gone from cytotoxic chemotherapy drugs to rituximab- or bortezomib-based regimens to the current era of BTK inhibitor-based regimens. However, the best second-line treatment strategy for relapsed WM remains unclear. This article, published by Chinese researchers in *Blood Science*, analyzed the outcomes of first- and second-line therapies in 377 WM patients to determine the best choices for second-line therapy. After a median follow-up of 45.4 months, 89 of these patients had relapsed and received second-line therapy; 53 were eligible to be evaluated for treatment response. The overall major response rates of first- and second-line therapies were comparable at 65.1% and 67.9%, respectively, while the median overall progression-free survival for second-line therapy was generally shorter than for first-line therapy (40.7 months vs. 56.3 months, respectively). However, patients who had first-line cytotoxic chemotherapy drugs and chose more targeted rituximab-based, bortezomib-based, and BTK inhibitor-based therapies for second-line treatment demonstrated a higher overall major response rate, longer progression-free survival, and longer overall survival than those who chose second-line cytotoxic chemotherapy.

Biomarker Analysis Published from Phase 3 ASPEN Study in WM – Researchers from the Phase 3 ASPEN trial that compared zanubrutinib (Brukinsa) and ibrutinib (Ibruvica) in WM patients have published their biomarker analysis of pre-treatment bone marrow samples from 98 zanubrutinib-treated and 92 ibrutinib-treated patients with mutated MYD88 and from 20 zanubrutinib-treated patients with wild-type (unmutated) MYD88. The most common mutations other than those in MYD88 were in CXCR4 (25.7%), TP53 (24.8%), ARID1A (15.7%), and TERT (9.0%). In general, patients with CXCR4 mutations who were on BTK inhibitors had a lower rate of combined very good partial responses and complete responses (VGPR+CR), as well as a longer time to response, than CXCR4 wild-type (unmutated) patients. However, the nonsense mutations in CXCR4 were associated with an improved progression-free survival in zanubrutinib-treated patients compared to ibrutinib-treated patients. In those with TP53 mutations, zanubrutinib-treated patients had a higher VGPR+CR rate and a longer progression-free survival than ibrutinib-treated patients. This analysis appeared in the journal *Blood Advances*.

Review Article Discusses Transformed DLBCL in Indolent Lymphoma Patients – A review article in the online publication *Science Direct* discussed transformation to diffuse large B cell lymphoma (DLBCL) in patients with indolent lymphomas (such as WM). Transformation is thought to develop as a result of additional genetic changes in the original cancer that cause it to grow faster and behave more aggressively. Typically, transformation requires treatment with aggressive chemotherapy and possibly stem cell transplant and is associated with a poor prognosis. The article noted that transformation should be suspected in patients who have a sudden deterioration in symptoms, include new onset of B symptoms (fevers, night sweats, weight loss, fatigue), rapidly enlarging lymph nodes, and laboratory tests showing rising LDH levels and high blood calcium levels. In its discussion of transformation in WM, the article stated that there are limited studies on the subject, but there is evidence to suggest wild-type (unmutated) MYD88 confers a higher risk for transformation to occur. One study from Dana-Farber Cancer Institute on transformed WM was cited, reporting a 5-, 10-, and 15-year cumulative incidence transformation rate of 1%, 2.4%, and 3.8% in a group of WM patients who were both treatment-naïve and previously treated. Extra-nodal (outside the lymph nodes) involvement, particularly of the central nervous system, tended to occur with WM transformation.

Phase 1 Trial of Nemtabrutinib Reports Early Results – Early Phase 1 clinical trial results for the BTK inhibitor nemtabrutinib were reported in the journal *Cancer Discovery*. Nemtabrutinib is an oral, reversible inhibitor of BTK, including C481S-mutated BTK (a cause of treatment resistance in patients on ibrutinib and certain other BTK inhibitors). This Phase 1 trial of 48 relapsed or refractory patients with chronic lymphocytic leukemia (CLL) or non-Hodgkin's lymphoma reported an overall response rate of 75% in the patients with CLL who were on a 65 mg daily dose of the drug. Grade 3 (severe) adverse events occurred in 89%, and the most common adverse events were low neutrophil count, low neutrophil count with fever, and pneumonia.

Pirtobrutinib Is Granted Accelerated Approval for Relapsed or Refractory CLL/SLL – The US Food and Drug Administration (FDA) has granted accelerated approval to pirtobrutinib (Jaypirca) for people with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) who have received at least two prior lines of therapy, including a BTK inhibitor and a BCL2 inhibitor. Approval was based on the Phase 1/2 BRUIN trial in CLL and SLL that achieved an overall response rate of 72%. The most common adverse reactions in trial participants were fatigue, bruising, cough, musculoskeletal pain, COVID-19 infection, diarrhea, pneumonia, abdominal pain, shortness of breath, hemorrhage, fluid retention, nausea, fever, and headache. Serious infections occurred in 32% of patients, including fatal infections in 10%.

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BTK Degrader Receives FDA Fast Track Designation for Relapsed or Refractory CLL and SLL – The US Food and Drug Administration (FDA) has granted Fast Track designation to the BTK degrader NX-5948 for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) after at least two lines of prior therapy, including a BTK inhibitor and a BCL2 inhibitor. The decision came after the drug's developer, Nurix Therapeutics, presented Phase 1a/b clinical trial results for the drug treatment in CLL and SLL patients during the American Society of Hematology (ASH) annual meeting in December 2023. Fast Track designation is designed to improve the efficiency of product development and accelerate the review of treatments for serious conditions. BTK degraders, also known as PROTACS, work differently from BTK inhibitors and are being studied in WM. For more about how degraders work, see Dr. Glenn Cantor's article on page 18 of this issue.

French Researchers Discuss Severe Infection Risk in Blood Cancer Patients on Ibrutinib – A multicenter French study appearing in the journal *Annals of Intensive Care* discussed the incidence of severe infections requiring intensive care unit (ICU) admission from 2015-2020 in 69 blood cancer patients receiving ibrutinib (Imbruvica) treatment. Ibrutinib is an inhibitor of the BTK pathway, and this inhibition increases the risk for infections, including opportunistic ones. Opportunistic infections do not typically occur in people with normal immune systems but are more common or more severe in people who are immunocompromised. The median time from start of ibrutinib therapy to ICU admission in these patients was 6.6 months. Invasive opportunistic fungal infections accounted for 19% of total infections and included invasive aspergillosis, *Pneumocystis* pneumonia, and cryptococcosis. Acute respiratory failure occurred in 71% of patients, 41% required mechanical ventilation, and 29% died in the ICU. By day 90, the mortality rate reached 55%. The authors noted that ICU physicians should be more aware of and screen for opportunistic infections in ICU-admitted patients on ibrutinib.

FDA Requires Black Box Warning After Safety Investigation into Risk of T Cell Cancers Associated with CAR T Cell Therapy – The US Food and Drug Administration (FDA) is requiring label updates with a black box warning for all six commercial CAR T cell therapies it has approved to treat relapsed or refractory blood cancers, such as B cell leukemias, diffuse large B cell lymphoma, follicular lymphoma, mantle cell lymphoma, and multiple myeloma. The warning is specifically for the risk of developing T cell cancers, which appear to occur as a result of genetic mutations in the CAR T cells used in these therapies. The CAR T cell therapies included in the warning are Yescarta, Tecartus, Carvykti, Breyanzi, Abecma, and Kymriah. Despite this safety warning, the FDA has stated that the overall benefits of these products continue to outweigh their potential risks. The European Medicines Agency (EMA) has launched a similar safety investigation, but it was not completed at press time.

Study Analyzes Impact of Body Mass Index on Survival After Cancer Diagnosis – A study from researchers in China and the US, published in the open access journal *Innovation*, analyzed the impact of body mass index (BMI) on survival after a cancer diagnosis. BMI is a numerical calculation that helps assess whether someone has a healthy body weight based on his or her weight and height. The current recommendation encourages patients with cancer to keep a normal BMI of around 22.5, based largely on previous studies indicating that excessive body weight increases the risk for developing cancer. This study, however, attempted to determine from actual mortality statistics whether the normal BMI recommendation is valid for those who have already been diagnosed with cancer. The researchers analyzed the MD Anderson Cancer Patients and Survivors Cohort database of 111,430 patients who were diagnosed with cancer and tracked their mortality rate over 7.2 years of follow-up. After attempting to remove potential biases such as smoking and other co-morbidities (co-existing medical conditions), their analysis revealed that a BMI lower than 22.5 was associated with shorter life expectancy across most cancer types, including lymphoma, leukemia, and multiple myeloma, while, interestingly, a higher-than-normal BMI was associated with longer life expectancy. In this study, the optimal BMI for cancer patients was reported to be 29.6 to 34.2 (overweight to mildly obese). The researchers suggested that extra weight in cancer patients may confer a survival advantage because it serves as a nutritional reserve to overcome the negative metabolic impacts not only from cancer growth itself, but also from treatments for cancer.

US FDA Issues Emergency Use Authorization for IV Drug to Prophylactically Prevent COVID in the Immunocompromised – At press time, the US Food and Drug Administration (FDA) issued emergency use authorization for a monoclonal antibody called Pemgarda to help prevent COVID-19 infection in immunocompromised people unlikely to benefit from vaccination. Pemgarda is administered as a single one-hour intravenous infusion, to be followed by two hours of observation by a health care professional. The most common side effects in clinical trials were mild-to-moderate infusion-related reactions. Infusions can be repeated every three months as needed.

The author gratefully acknowledges the efforts of Grete Cooper, Peter DeNardis, Julianne Flora-Tostado, Tom Hoffmann, Richard Savoy, Ron Ternoway, and others in disseminating research news of interest to the WM community. The author can be contacted at suenchas@bellsouth.net *for questions or additional information.*

KIA ORA (HELLO) FROM NEW ZEALAND

By Mel Arnold, Member, NZ Waldos

In our last *Torch* article, we mentioned we had been doing some advocacy to increase the number of funded treatment options for WM in New Zealand. As detailed in several reports, New Zealand is consistently ranked one of the lowest countries for medicine access within the Organisation for Economic Co-operation and Development (OECD), and with an average time of seven years from funding application to funding decision, we knew this challenge was going to be a difficult one.

I had the privilege of collating the lived experiences of WM patients in New Zealand to showcase that, yes, although WM is a slow-growing condition with a great prognosis for most, the one-size-fits-all approach to treatment does not suit us all, and for those of us, our lives can be so much richer with the opportunity to access other treatment options.

Two applications were submitted to the Pharmaceutical Management Agency (Pharmac) in 2018 for the funding of ibrutinib for first-line and refractory/relapsed WM. These were graded as low and medium priority respectively and, therefore, had not moved much within the system. Our aim was to write to Pharmac to request the applications be reassessed and reprioritised to a grading that reflected the unmet need for further treatment options in New Zealand (currently our only funded treatment option for WM is chemoimmunotherapy).

Our perspective paper to Pharmac included:

- Lived experiences of WM patients in New Zealand who courageously shared insights into their cancer journey.
- Research published in the past several years not available for consideration at the time of the initial Pharmac application review.
- A list of support from WM physicians, researchers, and supporting organisations.

Within one week of our Pharmac submission, we received a response from the CEO. After several further discussions, Pharmac agreed to not only reassess the initial ibrutinib applications, but also to review all other more recent applications currently sitting in Pharmac for WM (bortezomib and zanubrutinib) in light of the new information provided within our perspective paper. While there is still a long journey ahead, we are thrilled with this outcome and hoping the reassessments will bring us closer to having additional funded treatment options. Unfortunately, Pharmac was unable to provide a timeline for this; however, we are monitoring the situation and following up accordingly.

I have had some success on a personal note too. In my Story of Hope last September (see *https://iwmf.com/stories-of-hope/from-new-zealand-mels-story/*), I mentioned that as chemoimmunotherapy was not suitable as my second-line treatment, I managed to import a generic ibrutinib from overseas, which caused my IgM to decrease significantly and my haemoglobin and other markers to sit healthily within normal range. It is hard to imagine that just over six months ago prior to starting a BTK inhibitor, I was so fatigued and weak that I couldn't walk my kids to school! And today, I am out on daily bike rides with the kids, continuing the running of our business, resuming my biopsychology study, getting involved in the kid's sports, going on family adventures, and feeling fit, healthy, whole, and optimistic.

When I thought it couldn't get any better, I was granted compassionate access to zanubrutinib. This journey in itself helps highlight the amazing WM community we have: from Dr. Jorge Castillo, who supported us through my first-line treatment; to Dr. Mathias Rummel, who took an interest in my story and personally contacted BeiGene to see if I would be eligible for their Compassionate Access Program and encouraged me and my haematologist to apply; to Professor Judith Trotman, who managed to squeeze me in short

Mel Arnold and her children, enjoying strawberry picking and fruit ice creams

Kia Ora *(Hello) From New Zealand, cont. on page 27*

notice into her busy schedule for a consult to discuss some questions I had prior to starting zanubrutinib; to Lea Hullett, our local WM affiliate leader who has been supporting all our WM patients since 2017 and offered tremendous support in the development and review of the perspective paper. Furthermore, not only am I grateful to the dozens of WM physicians and researchers who supported our cause, but also to Dr. Shirley D'Sa, who generously agreed to peer review our perspective paper.

I liken the support from the IWMF and these wonderful WM experts to a reference I made in my previously mentioned Story of Hope:

> The human body is a beautiful synergistic complex system, comprised of trillions of cells working around the clock with a shared goal of keeping you healthy and alive. Appreciating this fact and acknowledging that this cancer is an unfortunate occurrence with no malicious intent can help us move from victim mode on to our journey to wellbeing.

The WM community is a beautiful synergistic complex network, comprised of hundreds of WM experts working around the clock with a shared goal of keeping us (WM patients) healthy and alive. Appreciating this fact and acknowledging that they are there for support and have our back can help us move from fear mode on to our journey to wellbeing.

When time allows, I wish to continue supporting Lea and the IWMF in the enhancement of WM care and treatment options in New Zealand. I see multiple opportunities to expand both patient and haematologist knowledge in WM in New Zealand, with the aim to achieve greater health outcomes, equity, and quality of life for our wonderful WM patients.

WHAT DOES THAT MEAN?

If you're reading through the *Torch,* listening to a presentation on WM, or talking to your doctor about treatment, do you wonder what some of the medical terms mean?

Complete response (CR) – A way to measure the response to treatment for WM. The criteria are a normal quantitative serum IgM; the absence of monoclonal IgM; the absence of WM cells in the bone marrow; and no enlarged lymph nodes, enlarged spleen, or WM masses in other tissues.

Major response – A way to measure the response to treatment for WM. It is any response that meets the criteria for a partial response, very good partial response, or complete response.

Overall survival (OS) – The length of time during and after diagnosis or treatment that someone remains alive.

Partial response (PR) – A way to measure the response to treatment for WM. The criterion is a reduction in quantitative serum IgM between 50-90%.

Progression-free survival (PFS) – The length of time during and after treatment that someone lives with a disease but it does not get worse.

Refractory – Not responding to treatment.

Relapse – The return of disease after someone was treated and had a response.

Time to Next Treatment (TTNT) – The interval from the beginning of a treatment to the time of the next treatment.

Very good partial response (VGPR) – A way to measure the response to treatment for WM. The criterion is a reduction in quantitative serum IgM of at least 90%.

In Memoriam
DR. ENRICA MORRA

By Dr. Steven Treon

Dear Members of the Waldenstrom's Macroglobulinemia Community:

I wanted to share with you the sad news that our colleague and friend, Dr. Enrica Morra, recently passed away. Dr. Morra was the Co-Chair of the 6th International Workshop on Waldenstrom's Macroglobulinemia (IWWM), which was held in Venice, Italy, in 2010 and a recipient of the Jan Gösta Waldenström Award for Lifetime Contributions to Waldenstrom's Macroglobulinemia at the 8th IWWM in London, UK, in 2014.

Dr. Morra obtained her medical degree at the University of Pavia, and in the same institution she received post-graduate certificates in both hematology and oncology. Since 1973, she worked as a physician in the Hematology Department of the University of Pavia and in 1994 became Head of the Hematology Department and Bone Marrow Transplant Unit at Niguarda Hospital, Milan. She also chaired the Oncology-Hematology Department in the same institution from 2000.

Her career was marked by close collaboration with scientists, but her major focus was on giving effective care to patients suffering from hematological malignancies. Dr. Morra's main research interests were on the biological and therapeutical aspects of acute leukemias and lymphomas. She also was the principal investigator of Phase 2 and 3 clinical trials in acute leukemias and lymphomas. She was a member of the scientific board of the Italian Society of Hematology and Experimental Hematology and was also a member of the European and American Societies of Hematology.

Dr. Morra taught and supervised at the Postgraduate School of Hematology at the University of Pavia and Milano, and she first established and coordinated the Hematology Network of the Lombardy Region, Italy. In her later years, the major focus of her research was on monoclonal gammopathies (MGUS) and Waldenström macroglobulinemia (WM). She led a vibrant clinic devoted to the care and study of patients with MGUS and WM at Niguarda Hospital in Milan that attracted patients throughout Italy. She also organized the first patient support groups for WM in Italy. Her research efforts provided fundamental contributions to our understanding of clinical characteristics and factors predicting evolution of IgM monoclonal gammopathies.

Dr. Morra also mentored a new generation of WM faculty, including Drs. Alessandra Tedeschi and Alessandra Trojani, who continue her pioneering work in the discovery and care of patients with WM.

We will miss her kind and gentle nature, her mentorship, her advocacy for patients, and the tremendous wisdom and experience she brought to our field. May she rest in peace.

Dr. Enrica Morra at the 8th IWWM, London, UK, 2016

FROM THE FACEBOOK WM SUPPORT GROUP: SPRING 2024

By Betty Ann Morton

Greetings to the IWMF community. The Facebook WM Support Group page is thriving. As **RS** wrote in early February 2024, "We just reached 6,500 members in the group! Thank you all for helping make the WM and IWMF communities strong." Group members include both WMers and their caregivers. Almost 70% are in the United States, and significant numbers reside in Canada, the United Kingdom, Australia, Italy, and many other countries. At least one of our recent new members opened a Facebook account just to be able to join this group.

Facebook is always available, and since WMers are an engaged and knowledgeable group, multiple new posts appear every day, along with supportive, informative, and useful responses. Most days over 2,000 members post, reply, react, or view the page.

WMers have various health concerns, some related to their WM or perhaps to treatments they have received. Osteopenia and osteoporosis were discussed recently. These conditions are common in older adults, which is the usual age group for WMers, and some WM treatments that include steroids are a risk factor for osteoporosis.

NLK wrote, "I have been a member of this group for over a year, but this is my first post. I am a 71-year-old woman and have had osteoporosis for years. After trying several drugs for it with no improvement, I was encouraged to have a zoledronate (Reclast) infusion. The testing for this infusion uncovered that I had MGUS. I proceeded with two infusions, one year apart. They improved my osteoporosis somewhat, and I had no side effects. Four years later (two years ago) my MGUS developed into a WM diagnosis. Other than fatigue, I have no symptoms and am in watch-and-wait. I was scared to move ahead with more Reclast infusions, because I didn't understand WM or how fast things might change for me. However, my latest bone density test shows no improvement and my endocrinologist encouraged me to have another infusion. My oncologist agreed. I also just fell and broke a hip. I am trying to decide if I should have another Reclast infusion. My question is, (finally, I know) have any of you heard that a Reclast infusion could be helpful to WM patients?"

ES replied, "I don't know if it would be of benefit to the cancer, other than strengthening the bone, but I wouldn't shy away from it. I'm on denosumab (Prolia) now, having had sacral fractures while on alendronate (Fosamax) for osteoporosis. It has helped my bones. I've not been told that it would be problematic, so I can't see why you'd want to skip it, unless they might consider some alternative like Prolia if they or you are concerned that you're not getting much added benefit from the Reclast. Prolia is a twice-yearly injection. They may be similar in the way they work; I don't really know."

MCM added, "I'm sorry osteoporosis is causing you problems. I don't know how treating osteoporosis would improve WM. But it's very important to treat osteoporosis because it has the potential to shorten your life more than WM. Bone fractures in an older adult increase the risk for loss of independence and even dying prematurely. A recent study found that older adults who break a bone have an increased risk for death that lasts for up to ten years after the fracture. Here's a comprehensive article that presents an overview of existing osteoporosis drug therapies and new drug development." As she often does, **MCM** concluded her response with a link to scientific information on the topic: *https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9408932/.*

On another subject, **CP** wondered about WMers' experiences with surgery. "Has anyone had elective surgery after being diagnosed with Waldenstrom? For example, bunion surgery?" **JW** replied, "Don't believe everything you read on Google. Lots of misinformation there. In my 22 years with WM, I have had a cervical discectomy and fusion at C6-7 and a radical prostatectomy and node dissection for prostate cancer. The discectomy was somewhat urgent, though not emergent, and the prostatectomy was clearly needed. No hesitation on the part of the surgeons. Surgeries were done at Mayo Clinic hospitals without any complications." Many WMers shared their experiences with successful surgeries. Reassurance and information are often helpful.

Another common topic is how a person might feel while undergoing WM treatment. In **TR**'s words, "I had my first B&R (bendamustine and rituximab) infusion a week ago on Tuesday. By Friday I felt like I was hit by a truck. That lasted about four days. Then maybe hit by a car. I am still feeling really knocked out. Is there a point when you start to feel better? Also does it get worse, better, or the same after the next treatments?"

JJ described her experience. "The same happened with me for the first round of B&R. Each successive round got significantly better. I always took the first week after treatments off. I'd say by week three post-treatment you'll start feeling yourself again, and by week four post-treatment you'll feel fantastic…and then it starts all over again. It's a rollercoaster of a ride but so worth it. It's been roughly a year and half since my B&R ended, and I feel wonderful."

"I didn't have it as difficult as your first treatment, but my first one was rough. For subsequent treatments it got easier even though due to low counts it took eight months. My learning lessons: water, water, water, and I ate bland (chicken, rice) pre- and post-treatment. I am an avid exerciser, so I tried to at least walk the few days pre-/post-treatments and did my

From the Facebook WM Support Group, cont. on page 30

regular exercise the three weeks in between. That said, we all have unique stories, so sending best wishes!" **SRC** replied.

MCM explained some of the science, "The first Benda-R infusion often kills a lot of B cells, causing a cytokine storm. Many WMers have reported lesser reactions following subsequent infusions. Most folks report feeling better gradually over the next few months of infusions as IgM goes down and other lab results go in the right direction."

Along with discussions about WM treatments and their possible side effects, there are many posts asking for suggestions for dealing with WM symptoms. During the past winter, **LMC** wrote, "I have a new symptom in the past couple of months. I've always been cold, but about a dozen times over the past couple of months, my feet have gotten really cold when I'm in bed trying to fall asleep. They can't be warmed up with wool socks or lots of covers. It's uncomfortable and prevents me from falling asleep. Each time, I have had to use electricity to fall asleep, either an electric blanket or, more recently, electric socks. Could this be cryoglobulins or am I just getting old? I'm having my blood drawn. Should I ask for the cryoglobulin test?" Among the many suggestions were a rice bag heated in the microwave, an electric heating pad, an electric mattress pad, and heated socks. For more information about cryoglobulinemia (and cold agglutinins), WMers suggested the July 2022 issue of the *Torch* (at *https://iwmf.com/wp-content/uploads/2022/08/N27358-Torch-July-2022_web.pdf*).

SC observed his WM birthday by posting, "Just a brief message to say thank you to everyone in this group, especially the admins who have an encyclopedic knowledge of this disease. Today is a year since diagnosis. So grateful for everyone here. Thank you." In response to the group's questions about how things were going, **SC** elaborated, "Now that is a question. Overall my diagnosis was easier to accept because I've watched my dad's journey with WM. My diagnosis has come 20 years before his, but I suspect his was around for longer. But it still threw us off-kilter initially, as I'm sure it does to everyone. If we were by ourselves at diagnosis, it would have been more challenging, I'm sure.

"Initially I just wanted to be fixed. Do something! Thanks to the group and the doctors, we came to understand that watch-and-wait is a good place to be. But I think the group and resources provided were better than the doctor's. At least initially. I'm still riding and fixing bikes as much as I can in my semi-retirement. If I can keep riding 5,000K per year, I can accept my situation more easily.

"I'm very aware that every time I'm at the cancer center there are many around me that have a more difficult journey. My first hematologist was expecting a worse diagnosis. Grateful that I'm watch-and-wait, unlike many others in the group.

"I'm encouraged when I see evidence that the WM community has provided the support that newly diagnosed people are searching for when they come across this group."

SG related her experience, "I just wanted to express my gratitude towards this wonderful support community. Initially, when I got to know that I may have WM (sometime around this time last year), I was seven months pregnant with my first human baby (I have a fur baby who is equally important and loved). At that point, I was nervous, scared, confused, and angry at the prospect of not being there for both of my sons and my husband, of course—he has been such an incredible support to me.

"After the delivery of my son in March of last year, I had routine bloodwork, CT scan, and multiple biopsies—they weren't able to detect anything in my BMB and lymph node biopsy. They then went on to biopsy a skin lesion, which confirmed a low-grade lymphoma, similar to WM. The whole ordeal took six months, and I was exhausted by the end of it.

"My treatment started almost immediately—within five days from the day of the confirmation of the third biopsy. It was necessary to start treatment, as I had developed a lot of symptoms: multiple swollen lymph nodes, night sweats, and anemia.

"Today was the first day of my sixth cycle of BR, and I feel so much better now. I have an incredible medical care team; they are such superstars, and I am so lucky to have them on my side. I can be there for my family just the way I had hoped for and feel so positive from all the posts I see here on a day-to-day basis.

"I am really loving motherhood and want to be there for my family as much as I can in the best way possible. Thank you once again to all of you for being so nice. I have gained so much from all of you, and I wish to express my sincerest appreciation for you. Love and Light!"

Note: WMers and their family members and support people are welcome to join this group. We all need friends. To join the Facebook WM Support group, go to *https://facebook.com/groups/wmsupportgroup*. In order to join, people must answer two membership questions. Since the group is private, only group members are able to see the posts. If you need additional help with the process, please contact the IWMF office 941-927-4963 or email to *office@iwmf.com*.

Spotlight ON SUPPORT GROUPS

EDITED BY SHARON RIVET

EDITOR'S NOTE:

After a year-long search, the Torch *welcomes Sharon Rivet as the new Editor of Support Group News. Please send ideas for future stories about your support group and its members and activities to Sharon at* shaycr62@gmail.com*. We look forward to reading more about IWMF support groups, perhaps also some that we haven't heard from before!*

JEANNE HARTIG, LEADER WATCH & WAIT/MGUS SUPPORT GROUP

In the spring of 2023, like so many who have WM, Jeanne was diagnosed with Waldenström's after an MRI for an unrelated condition. Her primary doctor ordered additional blood work and sent her to a hematologist who confirmed the diagnosis. She remembers, "I left their offices utterly alone, without any information about where to find emotional support or what the next steps were beyond more blood work. I had entered the watch-and-wait stage of WM without a map. So I immediately began to research WM online, reading peer-reviewed articles and looking for answers to my many questions. And that's when and where I discovered the IWMF. It was a lifeline when I felt I was drowning in fear and anxiety. Having that support was especially important for me, since I have no close family and a small (but wonderful) circle of close friends."

Retired for about three years as a senior university administrator responsible for communications and brand management, Jeanne was looking forward to many, many years of travel and pursuing her hobby—photography! "My mother lived to be 96 and my grandmother 98, both in good health, so knowing I have WM forced me to recalibrate what my own future will look like. I have had the good fortune to travel the world and, at the end of 2024, I will have been to more than 100 countries. Travel is important to me and I want to do as much of it as I can while I can!"

Jeanne Hartig

Jeanne did not want anyone else to feel alone like she did when she received her WM diagnosis. "I volunteered to start and lead a new support group for those of us with WM and MGUS who are asymptomatic and/or find themselves in the watch-and-wait category. I'm looking forward to talking and listening to others who are also at the very beginning of this journey and seeing if, together, we might be able to build a safe place to share how we are feeling."

MICHAEL TURNER, CO-LEADER, PEOPLE OF COLOR SUPPORT GROUP

Michael Turner is a 20-year survivor of Waldenstrom's. He is from Queens, NY, and resides in Arizona. "I served in the Navy Submarine Force and worked for, and retired from, the NYC Fire Department (FDNY) as an Electronic Communication's supervisor. I have an MA in Urban Studies from Queens College, City University of NY (CUNY). My wife and I have been together more than 44 years. We have one daughter, two sons, and three grandchildren; we'll soon be great-grandparents!"

Michael Turner

Michael's WM journey has been rather long and twisted; however, he is glad to have the opportunity to share some of the challenges as well as successes. "Dr. Treon was my first Waldenstrom physician. I am one of his original patients whom we jokingly refer to as 'three percenters,' meaning one of the 3% of patients who are African American with a diagnosis of WM. When he stopped seeing patients, I was referred to Dr. Castillo. Although I have not seen either of them for some time, I remember those visits quite well. They allowed me to move forward with a clearer understanding of how to be a proactive patient."

Michael volunteered to co-facilitate the People of Color IWMF Support Group, along with Paula Eastmond. He is also a member of the Patient Advisory Board of the Chronic Lymphocytic Leukemia (CLL) Society and a member of the Leukemia & Lymphoma Society (LLS), and he volunteers where and when he can with various churches' food

Spotlight on Support Groups, cont. on page 32

dispensing events. Michael's goal this year is working with Habitat for Humanity again. "It has taken me some time to realize how fortunate I am. Because of this, I look for ways that I might help others. Needless to say, both before and during WM, I have been exposed to many challenges. It is a fight that is not easy; however, that is not an excuse. I was asked to co-facilitate this rather small group and am willing to lean into it. There comes a time in life when you should give back. I hope to attend the IWMF Ed Forum this year for the first time, and I hope to see YOU there."

INAUGURAL MEETING OF THE WATCH & WAIT/MGUS SUPPORT GROUP

By Jeanne Hartig, Support Group Leader

This first meeting of the Watch & Wait/MGUS Support Group, on March 3, 2024, drew an international audience, with participants from Mexico, Israel, England, Belgium, and Canada, as well as at least a dozen states of the US.

The participants ranged from those who have remained essentially asymptomatic and requiring no treatment for decades, to those who suddenly find themselves experiencing indicators that their WM is quickly progressing. For those who have been asymptomatic for years, their message was "WM is not a death sentence." For those recently diagnosed, it is "watch, wait, and worry," or as one participant said, "forget the three Ws. I call it active surveillance." Two of the best ways of expressing this were one participant saying that at the beginning it felt like the Sword of Damocles was hanging over his head to another participant saying when she feels something is off, she immediately wonders if it's her WM progressing—or just life.

How they got their diagnosis ranged widely, with MyChart or its equivalent being the way some people heard first. One person got the diagnosis online on a Friday afternoon. One person said her doctor gave her the diagnosis and then said "google it" if she wanted more information. Others waited months for a final diagnosis to be delivered by their physician.

Reactions to their initial diagnoses ranged from angry to puzzled to not being surprised (one woman was already dealing with a rare form of breast cancer, so her reaction was, of course, now I have two rare cancers. Why should I be surprised?). Over time, some said they felt themselves become calmer and better able to handle the uncertainty. They also realized this diagnosis was an opportunity to get their affairs in order and start living the lives they wanted to live.

Their relationship with their hematologist/oncologist is clearly important—and sometimes they needed to cycle through physicians to find a good match. This is where the discussion of going to Dana-Farber Cancer Institute and the Mayo Clinic surfaced, as patients looked to these two entities above all others for expert care that could not be found locally, even if they lived near a teaching hospital. How to pay for that care was broached.

When to start treatment was an issue, with people concerned about their doctors' recommending they start early even in the absence of symptoms. Specific questions ranged from the cost of certain drugs, to whether the presence of neuropathy meant treatment was now necessary, or whether it's worth getting the COVID booster every year after being diagnosed. There was praise for the resources and information provided by the IWMF from those who had availed themselves of it.

Going forward, attendees wanted to keep meeting, with some advocating for smaller groups in recognition of time differences. There were enough West Coast (Oregon, California, Washington State) people on the call to warrant their own subset. Same thing with the East Coast and Midwest. There was also a suggestion that a doctor conduct a Zoom call with the people in this group, so they could ask specific questions about how WM and MGUS progress.

Spotlight on Support Groups, cont. on page 33

THE JOY OF EXERCISE SUPPORT GROUPS

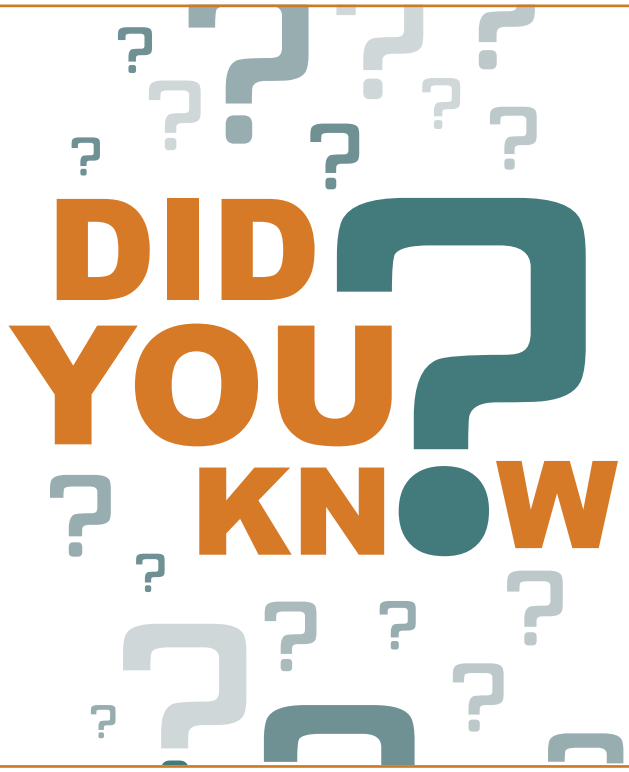
By Beverley Andrade

Beverley Andrade

I don't recall exactly when I first stumbled upon IWMF's Chair Yoga. At that time, it was the very first of the organization's ever-growing list of offerings to us WMers. I know I was still living in England, and because of my fatigue and the late time slot (five hours ahead of Eastern Time), I was only able to do the recordings, which I am still so grateful for. But I'm sure I started very soon after these wonderful classes were first offered. Since moving to Canada in March 2022, I have been participating in real time via Zoom, and it has made my experience so much richer.

During our unrecorded chat sessions, both before and after each class, I have become part of a very sincere and supportive "family." Our roots reach out to each other, and there is comfort and joy knowing we are not alone. Besides Chair Yoga, I also try to participate in Cardio Flow, Yoga Nidra, and Sound Meditation and always save those recordings so I can "catch up" if not able to attend on Zoom. It's fun to see faces from one offering pop up in another! Although I have never met, in the flesh, any of these amazing women and men who are on their WM journey, I do feel we have a bond, and we are all watching out for each other. Recently I connected with another friend from class who shared with me grief support, which was so helpful. These classes are the highlight of my life, and I am immensely grateful for them and thank Ann Grace McMullan from the bottom of my heart.

Besides WM, I also have Bing-Neel syndrome and demyelinating peripheral neuropathy with anti-MAG antibodies. I feel fortunate that I suffer no pain, just chronic fatigue and unbelievable frustration with my barely-functioning hands. During chat, we talk about these things and the symptoms that others suffer and try to help each other. I recall one chat session when I produced all my "props" to help work my hands (pliers, beans, coins, paperclips to lift in and out of a tub, extra-large-handled scissors, etc.). During class we do balance exercises, wrist circles, flicking fingers like removing water from our hands—all these things are so essential, not to mention the body stretching. The "bee's breath" is such a calming exercise, and the singing bowls are my very favourite for relaxation. I am so blessed to have these offerings and this support group!



THE IWMF IS HELPING TO DECREASE THE FINANCIAL BURDEN OF WM

The IWMF provides financial assistance for travel and lodging to individuals diagnosed with WM who have a scheduled WM-related medical appointment or consultation with a health care provider, want to undergo eligibility screening for a clinical trial, or have a first clinical trial visit not paid for by the trial sponsor. The National Organization for Rare Disorders (NORD) administers the fund. For more details on the IWMF Travel & Lodging Assistance Program and to contact NORD, go to:

https://iwmf.com/wp-content/uploads/2024/01/IWMF-TL-revised-2024-3.pdf

RECENT IWMF BOARD APPOINTMENTS

Saurabh Seroo, Co-Leader of Waldenstrom India along with his mother Rajini Seroo, a WM patient, is the newest IWMF Board Trustee.

Saurabh began his career at Deloitte Consulting, where he spent almost a decade building technology solutions for international clients. He subsequently served as COO of an Indian e-commerce startup and is presently a public market securities investor. He also spent five years as Campaign Leader for Teach for India, where he worked to raise funds and provide resources for lower income schools in partnership with Deloitte.

Saurabh lives in Bangalore, India, from where he and Rajini—bringing her perspective as a patient to the fore—have led Waldenstrom India since 2017. They also attended the October 2023 European WM Patient Forum in Amsterdam and were delighted to meet their colleagues in person for the first time, after many years of connecting over Zoom.

Rajini Seroo and Saurahb Seroo at the recent European WM Patient Forum in Amsterdam

Carl Harrington

Carl Harrington has been appointed as the Vice Chair of Fundraising and Chair of the Fundraising Committee. Carl is the Chair Emeritus for the IWMF and served as the volunteer president and CEO for eight years, from 2013 to 2020. During this tenure, he was key to creating the IWMF Strategic Plan, including the vision, mission, values, and global imperatives, as well as the IWMF-LLS Strategic Research Roadmap initiative. His leadership brought significant fundraising and revenue increases. Currently, as Chair of the IWMF Global Patient Initiative, he actively promotes the IWMF vision and mission worldwide. Carl was diagnosed with WM in 2006 and has been in watch-and-wait ever since.

BEN RUDE HERITAGE SOCIETY

The Ben Rude Heritage Society recognizes those who have made provisions for a future gift to the IWMF, such as a bequest, listing the IWMF as a beneficiary for a life insurance policy or qualified planned asset (such as 401k or IRA), or a life income agreement, such as a Charitable Remainder Trust. Legacy gifts represent an important component of the IWMF's financial future. There are many ways to support the IWMF through a planned gift, but a bequest is perhaps the easiest and most tangible way to leave a lasting impact. The following supporters are members of the Ben Rude Heritage Society:

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

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

- Aldo M Roccaro MD, PhD, Dana-Farber Cancer Institute, *Further genomic characterization of Waldenstrom's Macroglobulinemia: unveiling the role of the CXCR4 somatic mutation, a crucial regulator of pathogenesis and important targets for therapy,* 03/01/14 - 02/28/16
- Brad H Nelson PhD & Julie S Nielsen PhD, Deeley Research Centre, *Mutant MYD88: A target for adoptive T cell therapy of WM,* 10/01/14 - 09/30/16

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

- Dr. Marzia Varettoni, Fondazione Italiana Linfomi Onlus, *Non-invasive diagnostics and monitoring of MRD and clonal evolution in Waldenstrom's Macroglobulinemia,* 10/15/17 - 10/15/19
- Larry W Kwak, MD, PhD, Beckman Research Institute of the City of Hope, *Anti-tumor and immune microenvironment responses following a first in-human DNA fusion vaccine for asymptomatic WM,* 10/15/17 - 10/15/21
- Sherie L Morrison, PhD, The Regents of the University of California, *Novel antibody-targeted interferons in combinational therapies for Waldenstrom's Macroglobulinemia,* 10/15/17 - 10/15/20
- Shahrzad Jalali, PhD, Mayo Clinic, *Modulation of T-cell function by metabolomic signature of the bone marrow microenvironment in Waldenstrom's Macroglobulinemia,* 09/15/17 - 09/15/19
- Dr. Bruno Paiva & Dr. Jose Angel Martinez Climent, Clinica University of Navarra, *Single-cell next-generation flow and sequencing to unravel the pathogenesis of Waldenstrom's Macroglobulinemia and to design genetically driven human-like experimental models,* 09/15/17 - 09/15/19
- Dr. Gareth Morgan, New York University Grossman School of Medicine, *Using mutographs to define the molecular landscape and cell of origin of Waldenstrom's Macroglobulinemia,* 01/01/23 - 12/31/25

Hamberg Family Research Fund of the IWMF

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The Lynn M. Fischer Research Fund of the IWMF

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Leukaemia Foundation of Australia has supported the following research projects:

- Zachary Hunter, PhD, Dana-Farber Cancer Institute, *Multiomic analysis of DNA, RNA and epigenomic networks for prognostication and novel target identification in Waldenstrom's Macroglobulinemia,* 09/01/20 - 09/01/22
- Gareth J Morgan, PhD, New York University Grossman School of Medicine, *Using mutographs to define the molecular landscape and cell of the origin of Waldenstrom's Macroglobulinemia,* 09/30/22 - 09/26/24

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

- Dr. Morie Gertz, Mayo Clinic, *Biology to Treatment: Prognostic factors, Bone Marrow Microenvironment, Genomic and Proteomic Profile of Light Chain Amyloidosis in Waldenstrom's Macroglobulinemia,* 10/01/17 - 10/01/19

Carolyn K. Morris Research Fund of the IWMF

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

- Dr. Signy Chow, Sunnybrook Research Institute, *Characterization of Genomic Alterations in Treatment Naive Patients with Waldenstrom's Macroglobulinemia Through a Course of Targeted Treatment and Disease Progression,* 09/01/22 – 08/31/24

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

- Larry W Kwak, MD, PhD, Beckman Research Institute of the City of Hope, *Anti-tumor and immune microenvironment responses following a first in-human DNA fusion vaccine for asymptomatic WM,* 10/15/17 - 10/15/21

The Paul and Ronnie Siegel Family Research Fund of the IWMF

Waldenstrom's Macroglobulinemia Foundation of Canada has supported the following research projects:

- Zachary Hunter, PhD, Dana-Farber Cancer Institute, *Multiomic analysis of DNA, RNA and epigenomic networks for prognostication and novel target identification in Waldenstrom's Macroglobulinemia,* 09/01/20 - 09/01/22
- Dr. Signy Chow, Sunnybrook Research Institute, *Characterization of Genomic Alterations in Treatment Naive Patients with Waldenstrom's Macroglobulinemia Through a Course of Targeted Treatment and Disease Progression*, 09/30/22 - 09/29/24
- Zachary Hunter, PhD, Dana-Farber Cancer Institute, *Characterization of Isoform Usage, Novel Isoforms, and Tumor Evolution in WM,* 07/01/23 - 06/30/25
- Patrizia Mondello, M.D. PhD, Mayo Clinic, *Identifying the oncogenic cooperation between IRF4 and MYD88 L265P and their impact on the Tumor Microenvironment of Waldenstrom Macroglobulinemia*, 08/21/23 - 08/20/25

Robert and Nadeline White Family Research Fund of the IWMF has supported the following research project:

- Steven Treon, MD, PhD, Dana-Farber Cancer Institute, *Targeting MYD88 in Waldenstrom's Macroglobulinemia,* 09/01/18 - 08/31/20

Marcia Wierda Memorial Research Fund of the IWMF

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

- Steven Treon, MD, PhD, Dana-Farber Cancer Institute, *Targeting MYD88 in Waldenstrom's Macroglobulinemia,* 09/1/18 - 08/31/20
- Zachary Hunter, PhD, Dana-Farber Cancer Institute, *Multiomic analysis of DNA, RNA and epigenomic networks for prognostication and novel target identification in Waldenstrom's Macroglobulinemia,* 09/01/20 - 09/01/22

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

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If you have discretionary giving power and would like to help move our research program forward in a special way, we invite you to join those listed above. For more information about Research Partners and Named Gift Fund opportunities and potential gifting options that might make that possible, please contact Annette Preston, Director, Donor Engagement, *apreston@iwmf.com*.

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