

INMETORCH

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INTERNATIONAL WALDENSTROM'S MACROGLOBULINEMIA FOUNDATION

#### WHAT IS A BIOSIMILAR DRUG? BY SUE HERMS AND GLENN CANTOR. **INSIDE THIS** IWMF RESEARCH COMMITTEE MEMBERS ISSUE What is a biosimilar drug? How does it differ from a generic drug? Are there any biosimilars What Is a that can be used to treat WM? As WMers are hearing more about the approval of biosimilar Biosimilar Drug? ...... 1 drugs, these questions have been raised in posts on IWMF Connect. The following information is intended to help answer these questions and stimulate patient interest in the impact of biosimilars on the rapidly changing drug market. Chairman's Corner......5 A biosimilar is an almost identical copy of an original or reference biologic drug manufactured by a different company after the original drug's patent has expired. Examples of biologic drugs Medical News include vaccines, hormones, blood products, and monoclonal antibody therapies. Although the Roundup ..... 6 definition of a biosimilar sounds much like that of a generic drug, there are some important differences. Note in the definition that a biosimilar is The IWMF Celebrates Although the definition of a **biosimilar** sounds an "almost identical" copy of a Its History and the "biologic" product. Herein lie Educational Forum .. 12 much like that of a generic drug, there are some the basic differences between important differences. generics and biosimilars. IWMF Doc Star: Common brand name Dr. Christian Buske...18 small-molecule drugs are compounds in which the therapeutically active ingredients are composed of known chemicals synthesized (manufactured) by chemical reactions that can generally be copied. These small-WM: Flight/Fight/ molecule drugs can be easily and accurately reproduced as generics once their patents expire. Accept?.....19 Consequently, the generic forms of these drugs are considered to be identical to the original brand name drugs and yield the same therapeutic effect. In other words, they are the same in dosing, safety, strength, quality, the way they work, the way they are taken, and the way they A Tribute to should be used. It should be noted, however, that generic drugs do not have to contain the same Alice Swift Riginos... 20 inactive ingredients (fillers, dyes, preservatives, flavoring agents) as brand name products. Biologic drugs are larger, more complex molecules—typically proteins—that are synthesized From IWMF Connect: by living cells (hence the name "biologic"). The host cells are genetically altered so that they Spring 2020 ..... 22 produce the desired product-the drug. The host cells are supplied with nutrients (media) and grown in large-volume containers in a process called fermentation. Biologic drugs generally exhibit a great deal of molecular complexity and may be quite sensitive to changes in the Support fermentation process. The manufacturer of a biosimilar does not have access to an original Group News ...... 24 biologic drug's molecular clone or to its exact fermentation and purification process, thereby making it impossible for a biosimilar to be considered identical to the original. A good analogy to explain the difference between a biosimilar and a generic is to compare wine with soda pop. International Scene....27 It is unlikely that two bottles of chardonnay from two wineries are exactly the same—because of differences in soil, climate, year of grape harvest, storage, and aging-but it is very likely that two bottles of the same flavor of soda pop from two bottling plants are the same.

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### What Is a Biosimilar, cont. from page 1

Biosimilar drugs provide the opportunity for companies to compete and lower the prices of biologics. The difficulty, though, is producing a biosimilar that is sufficiently like the original reference drug. Although proteins are chains of amino acids, encoded by DNA, proteins produced in mammalian cells are never just straightforward strings of amino acids. The host cells produce sugars which attach to the outside of the protein. This process is called glycosylation. They aren't just simple sugars-they are branching chains of dozens of sugars, which vary in the type of sugar and how they branch. The problem is that the sugars that coat the proteins affect the biological properties of the proteins. Even for the original reference biologic drug, this is a problem. The glycosylation pattern can vary depending on many factors. The host cells which produce the protein are grown in huge stainless steel vats. The shape of the vat, the rate of stirring, the size of the vat, and the precise composition of the materials which are fed to the growing cells can all affect the glycosylation pattern. To make things more complicated, the host cells that produce the proteins are living organisms. As they reproduce, they never produce exact copies of themselves. They change, just like our children

# It can be challenging to **retain cells** which **produce proteins** in exactly the same way.

are not exact copies of ourselves. It can be challenging to retain cells which produce proteins in exactly the same way. So, it is impossible even for the original manufacturer to consistently manufacture identical proteins. For this reason, each manufacturer sets specifications, essentially a range within which the protein is considered acceptable, and sets control processes for manufacturing. The proteins must be within the specifications to be allowable. A whole science has developed around the biotechnology of optimizing the host cells, conditions for growth, conditions for fermentation, how to set specifications, and how to analyze the proteins to ensure that they are within specifications.

The biggest challenge for a company that manufactures a biosimilar is developing methods so that the host cells produce proteins similar enough to the original drug's specifications to cause a similar biological effect. This is not easy, but some companies have succeeded in manufacturing proteins that are similar enough to be acceptable. The biosimilar protein may not be identical to the reference drug, but it must be sufficiently similar that there is no clinically meaningful difference from the reference drug, in terms of safety and effectiveness in patients. Should **biosimilars** go through the same approval process as the **original biologic drugs** or could the process be shortened?

Once patents on several biologic drugs began to expire in the 2000s and biosimilars were being developed, a regulatory process had to be designed to approve biosimilars for human use. The questions then became: Should biosimilars go through the same approval process as the original biologic drugs or could the process be shortened? Is there a way to take advantage of prior knowledge obtained from developing the original drug and make the approval process faster and more efficient in order to reduce costs? The US Food and Drug Administration (FDA) decided to use a process referred to as an "abbreviated licensure pathway," created by the Biologics Price Competition and Innovation Act of 2009 and passed as a provision of the Affordable Care Act. This is now known as the 351(k) pathway. The European Medicines Agency (EMA) has a similar approval process in place for nations in the European Union.

The approval process for biosimilars still requires an extensive amount of data to be submitted with the application. This data is developed somewhat differently from the data used in original biologic drug applications. After pre-clinical testing in cell lines and animal models, an original biologic usually moves through three phases of clinical trial testing on its way to approval. Phase 1 is typically a safety study in a small number of people, and Phases 2 and 3 test the effectiveness and safety of the drug in a larger patient population. For biosimilars, the bulk of the data comes through analytical studies that support the structural similarity of the drug to the reference biologic. Cell studies are performed to show similar potency, as well as animal studies to assess toxicity. The clinical trial phase for a biosimilar can be abbreviated to start and end at Phase 3, during which time the biosimilar is compared to the reference drug. For a biosimilar drug to be approved, its Phase 3 clinical trial cannot show any clinically meaningful differences between it and the original biologic in terms of safety, effectiveness, or potency. It must have similar pharmacokinetics (the rate of distribution within the body and elimination from the body) and similar pharmacodynamics (cellular or molecular response to the drug). Regulators especially want to know if the biosimilar, which may have somewhat different sugars attached to the surface of the protein (glycosylation patterns) than the reference drug, causes similar immune reactions in patients. Testing must be more rigorous if the original biological is already known to cause immune reactions with adverse effects in some patients.

One advantage that a manufacturer of a biosimilar has is that it is not required to do a separate Phase 3 clinical trial for each specific disease (called an "indication") that the drug is used for. Once the biosimilar is approved for one indication, the company can go through a regulatory process called "extrapolation" to provide scientific data to the FDA to justify approval for other indications, while piggy-backing on the data from the original reference drug.

A higher bar for biosimilars to meet is the designation of "interchangeable," which indicates that it is not just similar to, but rather essentially identical to, the original. In the US, no biosimilars have been designated as interchangeable with their reference biologic drugs or with each other, meaning that if a healthcare provider wants to use a biosimilar instead of the reference drug, he or she must prescribe the biosimilar by name-a pharmacy cannot automatically substitute a biosimilar drug for a reference biologic or substitute one biosimilar for another without permission from the provider. However, the FDA does have a process in place to designate biosimilar interchangeability if a company should submit additional data to support the designation. In Europe, decisions on interchangeability are not made by the European Medicines Agency, but rather at the individual nation level; however, automatic substitution is not routinely practiced in Europe.

# The US has lagged behind **Europe** in the **acceptance** of biosimilars.

The US has lagged behind Europe in the acceptance of biosimilars. The European Medicines Agency approved the first biosimilar in 2006, and it was not until 2015 that the US Food and Drug Administration approved the first biosimilar for the US market. Several biosimilars for Neulasta, Neupogen, and Epogen/Procrit are now being marketed, as are biosimilars for the treatment of a variety of autoimmune diseases, diabetes, and certain cancers.

More recently, there are now approved biosimilars for rituximab (Rituxan or MabThera). Almost all WMers are familiar with Rituxan, which is a mainstay of most treatments for Waldenstrom's. The researchers who originated Rituxan determined that the CD20 antigen was the perfect target on human B-cells, as it was located on the surface of the B-cell, did not mutate, and did not move inside the cell or fall off during the life cycle of the cell. Then they developed a mouse antibody with high anti-CD20 activity and constructed a mixed mouse/human antibody by combining DNA from the mouse portion that binds to CD20 with DNA from the part of a human antibody that recruits one's own immune system to attack an antigen. In order to mass produce Rituxan, the antibody is now manufactured in cell cultures of Chinese hamster ovary cells. This was and is obviously a much more complex process than manufacturing a Tylenol tablet!

All biosimilars for **Rituxan** so far are given as **intravenous infusions** and cannot be administered subcutaneously.

The patents that Roche/Genentech held on Rituxan expired in Europe in 2013 and in the US in 2016. Naturally, as these patents expired, pharmaceutical companies were eager to share in a part of its sizeable market and so began the development of biosimilars for Rituxan. At press time, there are three approved for use in chronic lymphocytic leukemia and CD20 positive non-Hodgkin's lymphoma: Truxima (also marketed as Ritemvia, Rituzena, and Blitzima) is approved in Europe and the US (US approval date November 2018), Rixathon (also marketed as Riximyo) is approved in Europe, and Ruxience is approved in the US (approval date July 2019). More are awaiting approval. All biosimilars for Rituxan so far are given as intravenous infusions and cannot be administered subcutaneously. It should be noted that Rituxan biosimilars have similar side effects to Rituxan and carry a Boxed Warning, just like Rituxan, about the increased risk of fatal infusion-related reactions, severe skin and mouth reactions, hepatitis B reactivation, and progressive multifocal leukoencephalopathy, a rare brain infection.

There is concern about biosimilars that some modifications might occur during the manufacturing process that are undetectable and will lead to problems such as altered effectiveness, undesirable immune responses, or toxicity. This worry may turn out to be overblown, and the expectation is that manufacturers should be able to produce biosimilars in a way that is as consistent as the original biologic drugs, with predictable effects. Nevertheless, this concern and a general unfamiliarity with biosimilars by both clinicians and patients in the US may delay their acceptance here.

The cost impact of biosimilars is not generally as dramatic as that of generic small-molecule drugs because the manufacture of biosimilars is much more difficult. The price of biosimilars is approximately 30-50% less than their reference biologics. With generics, by contrast, the price is usually at least 90-95% less than their associated brand name drugs. Nevertheless, the prevailing wisdom has been that biosimilars should have a positive impact on the access and cost of biologic drugs, which can be prohibitively expensive. This has been true in Europe where biosimilar use is encouraged and government is

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involved in setting drug prices. In the US healthcare system, the manufacturers of original biologic drugs have so far used a system of incentives, rebates, and discounts to encourage distributors and pharmacy benefit managers to favor their drugs, rather than biosimilars, in drug formularies. In the future, biosimilars may become more widely used, since a large number of biosimilars are currently in the development pipeline and are expected to reach the market in the next few years.

More information about biosimilars can be found on the FDA website at *https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars*.

## **CHAIRMAN'S CORNER**

BY CARL HARRINGTON



Carl Harrington and Newton Guerin

Great news! At the February IWMF Board of Trustees meeting we elected Newton Guerin as the full-time chief executive officer and president of the IWMF. Newton replaces Rick Smith, who left in November for personal reasons. Newton was previously the chief development officer for the IWMF. As you can tell from the picture above, Newton and I are delighted to be working together to support WMers worldwide.

As I explained in the October 2019 issue of the *Torch*, the IWMF Board of Trustees has been an operating board of all volunteers since its inception. That means that the Board not only directs the big picture strategy and policies of the IWMF, but is hands-on in executing everything we do, from writing, proofreading, and executing everything we produce, to selecting, contracting, and monitoring progress on all of our research projects. This structure means one or more IWMF Board members work with our staff and other volunteers in every single aspect of our work. As the IWMF has grown, our Board has been stretched far beyond what volunteers can be expected to do. In order to accomplish our ambitious goals, the IWMF Board decided to move from an operating board to

a governing board. This change will enable us to better serve our members and to intensify our search for a cure. We feel fortunate to have Newton as our new leader.

Newton has spent his entire career in non-profits and brings an incredible wealth of experience and expertise to the IWMF. His extensive non-profit experience includes:

- American Cancer Society
- Regional director at LLS (Leukemia & Lymphoma Society)
- Chief of staff at the National Multiple Sclerosis Foundation
- CEO and president at the American Liver Foundation
- Chief development officer and chief operating officer at the International Dyslexia Foundation

Since that's such an impressive background, why did Newton choose to join the IWMF?

"As the IWMF's new CEO, I am very excited about what lies ahead. I will work to foster a creative and innovative culture to help us take advantage of new opportunities as they arise. During my career, I have had the opportunity to serve in senior management positions with several mission-focused organizations. I've learned many important lessons along the way, none more critical than the need to share a common vision that provides organization-wide focus and direction. My goal for the IWMF is simple but not easy and is shared by volunteer and staff leaders throughout the organization. While we continue to aggressively search for a cure, the IWMF will be the GO TO source of information and support for all WM patients and caregivers.

"Since joining the staff in October as chief development officer, I have seen first-hand the huge impact the IWMF makes every day on the lives of the people we serve. These kinds of results don't happen by accident. They are made possible because of the commitment and dedication of the

Chairman's Corner, cont. on page 6

### Chairman's Corner, cont. from page 5

IWMF Board of Trustees and home office staff who work in partnership with hundreds of volunteer leaders throughout the organization to plan and carry out IWMF programs worldwide. Serving as the IWMF's CEO is an honor and privilege. There is nothing I would rather be doing."

While I am honored to have steered the IWMF for the past eight years, I look forward to a less all-consuming volunteer commitment, and I anticipate watching the IWMF grow under professional stewardship. As the chairman of the Board of the IWMF, I'll be helping Newton and the IWMF Board of Trustees achieve our vision of *a world without WM*.

In other good news, I want to make sure you know:

- We had a record year in terms of fund raising in 2019, raising over \$3,000,000 for the first time. This positions us well in the fight to find a cure. Thanks to each and everyone one of you who donated!
- We issued a new Request for Proposals for the IWMF-LLS Strategic Research Roadmap and received proposals from leading researchers from around the world, including applications from Dana-Farber Cancer Institute, Mayo Clinic, Memorial Sloan Kettering, and from institutions in Greece, Iceland, and Sweden. It is very rewarding to see the best researchers from around the world

competing for our grants. We will review all of the applications and decide which we can fund in June.

- We created new IWMF publications on two promising new treatments: venetoclax and acalabrutinib. See *https://www.iwmf.com/library/ iwmf-and-affiliate-publications*.
- We added new international affiliates in Israel, Chile, South Africa, and Portugal, bringing our affiliate total to 22! We're now on every continent except Antarctica and in 25 countries with nearly half of the world's population. In the fight against WM, you are definitely not alone.

We look forward to accelerating our search for a cure. And with Newton's leadership and your continued support, we will surely get there.

Stay well,

Carl



## **MEDICAL NEWS ROUNDUP**

### BY SUE HERMS, IWMF RESEARCH COMMITTEE MEMBER

Zanubrutinib Does Not Meet Endpoint in Phase 3 Trial Comparison with Ibrutinib in WM Patients -BeiGene announced that the Phase 3 study of its BTK inhibitor zanubrutinib (Brukinsa), comparing it to ibrutinib (Imbruvica) in WM patients, did not meet its endpoint of superiority in complete response (CR) and very good partial response (VGPR) rates. This trial, designated ASPEN, enrolled 229 WM patients, was conducted in 61 centers in Europe, Australia, and the US, and included two cohorts: 1) a randomized cohort consisting of 201 patients with a mutation in MYD88 who received either zanubrutinib or ibrutinib and 2) a non-randomized cohort in which 28 patients who had wild-type (unmutated) MYD88 received zanubrutinib. This announcement reported results from the first cohort, in which patients achieved a VGPR of 28.4% in the zanubrutinib arm and 19.2% in the ibrutinib arm - but the difference was not deemed statistically significant. There were no CRs in either arm. However, improvements in safety and tolerability were seen with zanubrutinib; serious adverse events were 58.4% for zanubrutinib and 63.3% for ibrutinib. Specifically, atrial

fibrillation of any grade was 2% for zanubrutinib and 15.3% for ibrutinib; minor bleeding was 48.5% for zanubrutinib and 59.2% for ibrutinib; major hemorrhage was 5.9% for zanubrutinib and 9.2% for ibrutinib; and diarrhea was 20.8% for zanubrutinib and 31.6% for ibrutinib. Neutropenia was higher in the zanubrutinib arm (29.7%) compared to ibrutinib (13.3%). BeiGene will discuss further steps with regulators, but analysts suggest it appears unlikely that the US Food and Drug Administration will approve zanubrutinib for WM based on the ASPEN data, although off-label use is anticipated.

**Phase 2 Trial Results Reported for Acalabrutinib in WM** – *Lancet Haematology* published the results of a Phase 2 trial of the BTK inhibitor acalabrutinib (Calquence) in both treatment naïve and relapsed/refractory WM. Patients received 100 mg oral acalabrutinib twice-daily in 28-day cycles until disease progression or unacceptable toxicity. The multi-center European and US trial enrolled 106 patients. With a median follow-up of 27.4 months, 93% of both treatment naïve and relapsed/refractory patients achieved a response. The most common serious adverse events were lower respiratory tract infection, pneumonia, fever, cellulitis, falls, and sepsis. Fifty percent of treatment naïve and 25% of relapsed refractory patients discontinued treatment on study.

The study concluded that **ASCT** for WM patients is a **safe** and **effective** treatment...

Mayo Study Discusses Use of Autologous Stem Cell **Transplant for WM in the Era of Novel Therapies** – An article by Mayo Clinic appearing in the journal Biology of Blood and Marrow Transplantation discussed the use of autologous stem cell transplant (ASCT) for WM in the era of novel therapies such as proteasome inhibitors and monoclonal antibodies. Records of all Mayo patients with WM who underwent ASCT between August 2005 and December 2017 were reviewed. The overall response rate to transplant was 100%; after a median follow-up of 58 months, the median progression-free survival after ASCT was 66 months, and the median overall survival was not reached. Treatment immediately prior to transplant, irrespective of rituximab (Rituxan) use, did not impact progression-free survival. Patients who had ASCT after more than two lines of therapy had an inferior progression-free survival compared to patients who had ASCT after two or fewer lines of therapy. Patients with diffuse large B-cell transformation at any point had inferior progression-free survival after transplant compared to those who did not transform. The median timeto-next-treatment was 49 months. The study concluded that ASCT for WM patients is a safe and effective treatment that provides patients a median treatment-free interval of four years, but that to obtain maximum progression-free survival benefit, ASCT should be performed earlier in the disease course, prior to receiving more than two lines of therapy.

**Retrospective Bing Center Study Demonstrates Deepening** of Treatment Response in Approximately 30% of WM Patients Who Complete Frontline Rituximab Regimens – A retrospective study from the Bing Center for WM at Dana-Farber Cancer Institute demonstrated that a deepening of response occurs in approximately 30% of WM patients who complete frontline rituximab (Rituxan)-containing treatment regimens. The study of 178 patients was conducted to better describe this occurrence. Deepening of response was defined as at least a 25% decrease in serum IgM achieved at a point in time later than when therapy was completed. Among the study participants, 116 received maintenance therapy and 62 were observed following initial treatment. Ultimately, 38% who received maintenance had at least a 25% decrease in serum IgM after completing maintenance; 31% who were observed had a similar decrease in serum IgM after completing frontline therapy. In both situations, the median time from end of treatment to lowest IgM level was 1.6 years. Deepening of response was found to be linked to better progressionfree survival. Characteristics associated with lower odds of deepening response included a baseline hemoglobin less than 11.5 g/dL, bone marrow involvement equal to or greater than 50%, the presence of CXCR4 mutations, and serum IgM equal to or greater than 4000 mg/dL.

**Bing Center Study Compares Features of WM to Non-IgM Secreting Lymphoplasmacytic Lymphoma (LPL)** – The Bing Center for WM performed a case control study comparing features, treatment, and outcomes between 93 patients with WM (which is lymphoplasmacytic lymphoma that secretes IgM) and 31 patients with non-IgM-secreting lymphoplasmacytic lymphoma. The frequency of MYD88 mutations was lower and median time-to-treatment was shorter in non-IgM LPL; also, extramedullary disease (outside the bone marrow) occurred more frequently, while neuropathy and hyperviscosity occurred less frequently, in these patients. Chemoimmunotherapy was more often used in non-IgM LPL, and proteasome inhibitors and BTK inhibitors were used less often than in WM. There were no significant differences in response and overall survival between the two groups.

... MYD88 wild type (unmutated) status alone was an independent **predictor** of transformation and was also associated with a shorter **time-to-transformation**.

Joint Study Examines Risk Factors and Outcomes Associated **MYD88** Mutation with Status and Transformation in WM - Histological transformation in WM to a high-grade or more aggressive B-cell lymphoma is an uncommon complication. There is limited data regarding the impact of the MYD88 L265P mutation on transformation, and this joint study from Mayo Clinic and University Hospital of Reims, France, examined risk factors and outcomes associated with transformation in WM, highlighting the role of the mutation. Patients with WM seen at these institutions between January 1996 and December 2017 were included; of 1,147 patients, 50 (4.3%) transformed to a high-grade lymphoma, with a median time-to-transformation of 4.5 years. The MYD88 L265P mutation status was known in 38% of patients. Upon analysis, MYD88 wild-type (unmutated) status alone was an independent predictor of transformation and was also associated with a shorter time-to-transformation. Patients with transformation demonstrated a significant

increase in risk of death compared to patients who did not transform.

**Phase 1b Clinical Trial Announced for Mavorixafor and Ibrutinib in WM Patients with CXCR4 Mutations** – X4 Pharmaceuticals announced the initiation of a Phase 1b clinical trial of mavorixafor in combination with ibrutinib (Imbruvica) for the treatment of WM. Mavorixafor is a oncedaily oral inhibitor of CXCR4; mutations in CXCR4 are present in approximately 30-40% of WM patients, are known to play an important role in treatment resistance, and are associated with higher rates of disease burden. The clinical trial is expected to enroll 18 WM patients with CXCR4 mutations. The identifier number on *www.clinicaltrials.gov* is NCT04274738.

*CLR* 131 is a **small-molecule drug conjugate** designed to deliver radiation directly and selectively to **cancer cells** and is administered intravenously.

Novel Drug Granted Orphan Drug Designation for Lymphoplasmacytic Lymphoma – CLR 131 has been granted Orphan Drug Designation by the US Food and Drug Administration for the treatment of patients with lymphoplasmacytic lymphoma (LPL), a type of lymphoma which includes WM. The designation was granted based on results of the Phase 2 CLOVER-1 clinical trial of 20 patients with relapsed/refractory B-cell malignancies, during which a single dose of the drug showed an overall response rate of 30%. The most common adverse events observed were thrombocytopenia (low platelet count), anemia, neutropenia (low neutrophil count), and overall decreased white blood cell count. CLR 131 is a small-molecule drug conjugate designed to deliver radiation directly and selectively to cancer cells and is administered intravenously. Orphan Drug Designation allows a drug developer to receive seven years of market exclusivity, tax credits, and other incentives for therapies to treat rare diseases.

**FDA Warns of Potential Life-Threatening Breathing Difficulties in Certain Patients Who Use Gabapentin or Pregabalin** – The US Food and Drug Administration (FDA) has issued a warning that life-threatening breathing difficulties can occur in patients who use gabapentin (Neurontin, Gralise, Horizont) or pregabalin (Lyrica) along with opioids or other drugs that suppress the central nervous system or who are elderly or have a pre-existing respiratory impairment while on either drug. Gabapentin and pregabalin are used to treat symptoms of neuropathic pain, including peripheral neuropathy. Study Compares Bendamustine and Rituximab to Cyclophosphamide Regimens in Older Patients with Non-Hodgkin's Lymphoma – A study published in the American Journal of Hematology compared the combination of bendamustine and rituximab (BR) to cyclophosphamidebased regimens such as RCHOP or RCVP in older patients with follicular, mantle cell, and marginal zone/lymphoplasmacytic lymphoma who received these therapies in the first-line setting. Event-free survival was better with BR, yet overall survival did not differ between the two. Acute toxicity was lower with BR, including rates of hospitalizations, infections, cardiovascular events, and transfusions. There was no difference in the cumulative incidence of secondary cancers.

**Retrospective Study Reports on Long-Term Adverse** Effects of Bendamustine in CLL and NHL-A retrospective study from Georgetown University Hospital investigated the long-term adverse effects of bendamustine in patients with chronic lymphocytic leukemia (CLL) and B-cell non-Hodgkin's lymphoma (NHL). Of 194 charts reviewed, 54% had received treatment with bendamustine, typically in combination with rituximab (Rituxan). Patients who did not achieve a complete response or partial response with bendamustine did not respond well to subsequent treatments. Malignancies following bendamustine were diagnosed in 11% of patients and included squamous or basal cell skin cancers, prostate cancer, renal cancer, bladder cancer, melanoma, lung cancer, and histiocytic sarcoma. There were no occurrences of therapy-related myelodysplastic syndrome or acute myelogenous leukemia reported. Infections occurred in 63% of patients; however no deaths were attributable to bendamustine therapy. The study results were published in Clinical Lymphoma, Myeloma, and Leukemia.

**Preliminary Data Released for Phase 1 Trial of Novel IRAK4 Kinase Inhibitor to Treat Relapsed/Refractory** NHL – Curis Inc. announced updated preliminary data from its ongoing Phase 1 dose escalation study of CA-4948, an IRAK4 kinase inhibitor, for the treatment of patients with relapsed or refractory non-Hodgkin's lymphoma (NHL), including WM. Five of the six patients evaluable for anticancer activity at the two highest dose levels experienced reduced tumor burden. Patients are being treated in continuous 21-day cycles of the oral medication at different dose levels. Laboratory studies have indicated that CA-4948 activity is enhanced in combination with either BTK inhibitors or BCL2 inhibitors, and the company plans to explore these treatment combinations.

**Combination Treatment of Ublituximab and Umbralisib Evaluated in Phase 1 Trial of Relapsed/Refractory CLL and NHL** – The combination of ublituximab, a monoclonal antibody targeting CD20, and umbralisib, a PI3K inhibitor, was evaluated in a Phase 1/1b study in 22 patients with relapsed/refractory chronic lymphocytic lymphoma (CLL)

and 53 patients with relapsed/refractory non-Hodgkin's lymphoma (NHL). The dose escalation trial consisted of ublituximab given intravenously for 12 cycles plus umbralisib given orally once-daily until progression, toxicity, or study removal. The therapy, designated U2, exhibited low rates of the typical PI3K inhibitor symptoms such as diarrhea, colitis, pneumonia, and liver toxicity. Treatment discontinuation due to adverse events occurred in 13% of patients, and umbralisib dose reductions occurred in 15% of patients. The overall response rate for all patients was 46%, with 17% complete responses. The median duration of response was 20 months. The trial results were published in the journal *Blood*. Ublituximab is similar to rituximab but has been engineered to increase antibody-dependent cellular cytotoxicity, a method by which targeted B-cells are destroyed.

**Chinese Study Reports Results of CAR T-Cell Therapy** Targeting CD19 and CD22 in B-Cell Malignancies -Treatment relapse because of antigen escape has emerged as a major challenge for long-term disease control in CD19directed CAR T-cell therapy, meaning that the malignant B-cells have developed mechanisms to evade destruction by losing or altering their CD19 expression. Accordingly, a multi-center Chinese study was conducted in 89 patients with refractory/relapsed B-cell malignancies using dual targeting of CD19 and CD22 by sequential infusion of anti-CD19 and anti-CD22 engineered CAR T-cells. Among the 38 patients in the study with non-Hodgkin's lymphoma, the overall response rate was 72.2%, with a complete response rate of 50%. With a median follow-up of 14.4 months, the median progression-free survival was 9.9 months, and the median overall survival was 18 months. Antigen escape relapse occurred in one patient. High-grade cytokine release syndrome and neurotoxicity occurred in 22.4% and 1.1% of patients, respectively; all except one were reversible. This study was published in the journal Blood.

**Phase 1 Trial Combines Rituximab and Ipilimumab in Relapsed/Refractory B-Cell Lymphomas** – An article in *Clinical Cancer Research* discussed results of a Phase 1 trial of the combination of rituximab (Rituxan) and ipilimumab (Yervoy) in patients with relapsed/refractory B-cell lymphomas. Ipilimumab is a monoclonal antibody that boosts the immune response by activating the body's cytotoxic T-cells to attack the targeted cells, and researchers hypothesized that this action would improve the effectiveness of rituximab. Thirty three patients with relapsed/refractory CD20+ B-cell lymphomas received the therapy. Toxicity was manageable and effectiveness was modest, with a response rate of 24% and a median progression-free survival of 2.6 months.

**Phase 1 Trial Results Reported for Novel BTK Inhibitor That Targets C481S Mutation Associated with Resistance to Ibrutinib** – The investigational BTK inhibitor ARQ 531 demonstrated safety and clinical activity across a range of relapsed/refractory B-cell malignancies according to results from a Phase 1 trial presented during the 2019 ASH Annual Meeting. ARQ 531 targets the BTK-C481S mutation associated with resistance to ibrutinib (Imbruvica), and approximately 80-85% of patients who progress on BTK inhibitor therapy do so because of this mutation. Fourteen out of 47 patients achieved partial responses, and an additional ten patients had stable disease. The most common adverse events were hypertension, back pain, nausea, fatigue, rash, constipation, peripheral edema, fever, headache, diarrhea, upper respiratory tract infection, and cough. No atrial fibrillation or bleeding occurred. The recommended dosing for Phase 2 trials will be 65 mg once-daily.

The following are summaries of selected abstracts about basic research in WM presented at the 2019 ASH Annual Meeting on December 7-10, 2019, in Orlando, FL. Summaries of selected abstracts pertaining to clinical trials and survival trends previously appeared in the winter 2020 issue of the Torch. The abstracts are online at https://ash.confex.com/ ash/2019/webprogram/start.html. To read a specific abstract, type part or all of its title into the Search box; for a general search of all abstracts pertaining to or including WM, type "waldenstrom" into the Search box.

Resistance to the BTK inhibitor **ibrutinib** can be a result of **C481S mutations** in BTK, as well as **downstream mutations**.

A Novel HCK and BTK Dual Inhibitor KIN-8194 Shows Superior Activity over Ibrutinib and Overcomes BTK<sup>C481S</sup> Mediated Ibrutinib Resistance in Vitro and in Vivo in MYD88 Mutated B-Cell Lymphomas (Abstract 394) -This abstract from Dana-Farber Cancer Institute discussed the multiple pathways resulting from activating mutations in MYD88 that promote malignant cell growth and survival. HCK (a tyrosine kinase) is upregulated and activated by mutated MYD88 and in turn activates BTK, as well as ERK and AKT, which are also tyrosine kinases. Resistance to the BTK inhibitor ibrutinib can be a result of C481S mutations in BTK, as well as downstream mutations. The researchers therefore sought to develop potent and selective inhibitors that target HCK and have reported on a compound called KIN-8194, which is a dual inhibitor of both HCK and BTK. The new compound was tested in mice and in WM and ABCtype diffuse large B-cell lymphoma cells, showed selective killing of the MYD88-mutated cells, and overcame resistance in cells engineered to express mutated BTK C481S. The drug was well tolerated in mice. In addition, pharmacology studies

showed characteristics favorable to once-daily oral dosing of the compound.

...international study attempted to define the cellular origin of WM ...

Waldenström's Macroglobulinemia (WM) Is Preceded By Clonal Lymphopoiesis Including MYD88 L265P in Progenitor B Cells (Abstract 1527) - Although MYD88 L265P is very frequent in WM, by itself it is insufficient to explain disease progression since most cases of IgM MGUS also have mutated MYD88. Furthermore, a few WM patients have detectable MYD88 L265P in total bone marrow cells but not in CD19+ B-cells, raising the possibility that other blood cells may carry the MYD88 mutation. This multi-center international study attempted to define the cellular origin of WM by comparing the genetic landscape of WM cells to that of stem cells, B-cell precursors, and residual normal cells. Bone marrow aspirates from eight WM patients were sorted into subsets of precursor cells, and several test methods were used to determine whether the mutation was expressed in these other precursor cell subsets. All patients showed MYD88 L265P in their WM B-cells, and three also had mutated CXCR4. Notably, MYD88 L265P was also found in B-cell precursors in one patient and in residual normal B-cells in three patients; mutated CXCR4 was also found in B-cell precursors from one patient. A median of seven mutations occurred uniquely in WM B-cells. In some cases, mutations were found all the way from stem cell progenitors to WM B-cells and plasma cells. This study showed for the first time that WM patients can have mutations, including MYD88 L265P and CXCR4, at the B-cell progenitor level and suggests that, in some patients, MYD88 L265P is not the initiating event but that other mutations are required for disease progression.

**MLL1 Modulates IgM and Inflammatory Cytokines in Waldenstrom's Macroglobulinemia (Abstract 3966)** – A joint study from the University of New Hampshire and the Mayo Clinic found that the TLR (Toll-Like Receptor)-MYD88 pathway in WM cells with the MYD88 L265P mutation increases the expression of IL-6 and CCL2, two cytokines (cell signaling molecules) known to participate in the biology of several cancers. Furthermore, IL-6 has been shown to control IgM secretion and malignant B-cell growth in WM. An active ERK 1/2 pathway, which is elevated in WM patient samples, is required to maintain IL-6 and CCL2 expression in WM cell lines. Further analysis identified MLL1 as an important enzyme involved in TLR-MYD88 stimulation of WM cells. MLL1 and its binding partner, menin, were expressed at significantly higher levels in the CD19+CD138+ lymphoplasmacytic cells from WM patients compared to CD19+ cells from healthy donors. These results identify a novel role for menin-MLL1 in regulating inflammatory cytokines and IgM expression and secretion in WM and provide a rationale for targeting these molecules in WM patients.

Glutathione Metabolism Contributes to the Pathobiology of Waldenstrom's Macroglobulinemia (Abstract 3971) -Cancer cells have altered energy demand due to their increased proliferation. In WM, the bone marrow environment is disturbed due to the infiltration of the lymphoplasmacytic cells that continuously produce monoclonal IgM. An alteration in energy demand could skew the balance of certain metabolites (products of metabolism) and proteins towards a more favorable niche for WM tumor cell growth. The aim of this joint study by researchers at the Mayo Clinic and Zhengzhou University in China was to identify how changes in certain metabolites and proteins could contribute to understanding the WM disease process. WM patient samples numbering 101, which included bone marrow plasma, peripheral blood serum, and bone marrow cells, as well as 86 equivalent normal cell samples, were collected and used for metabolic and protein analysis. The data identified two distinct clusters for disease and normal samples, indicating that there are differentially expressed proteins and metabolites in WM versus normal samples. Furthermore, the majority of the altered metabolites were members of the glutathione (GSH) metabolism pathway, implying that GSH metabolism is key to the biology of WM. Moreover, stimulation of WM cell lines by IL-6 and IL-21, which are cytokines involving in inducing WM cell proliferation and IgM secretion, resulted in increased gene expression of transporters that control the uptake of substances required for GSH synthesis. The data suggest that there is a central role for GSH metabolism in WM and indicate that altering this metabolic process could be a potential treatment strategy for WM.

This **joint study** by the Mayo Clinic and Zhengzhou University in China looked at the **presence and activity** of MDSCs in WM.

Mass Cytometry Identifies a Novel Signature for Myeloid-Derived Suppressor-Cells in Waldenstrom's Macroglobulinemia (Abstract 3976) – Myeloid-derived suppressor cells (MDSCs) are a population of undifferentiated cells of myeloid blood cell lineage that are expanded and activated in certain pathological conditions, have the ability to suppress normal T-cell function, and consequently may

### Medical News Roundup, cont. from page 10

contribute to immunosuppression and tumor growth. This joint study by the Mayo Clinic and Zhengzhou University in China looked at the presence and activity of MDSCs in WM. Bone marrow aspirates from 17 WM patients were processed, and a population of MDSCs were identified. Cytometry data showed that the number of total MDSCs was higher in WM specimens than in normal control samples and that they expressed PD-L1 and Arginase 1. When MDSCs from WM patients were co-cultured with activated T-cells, the proliferation of activated T-cells in the presence of MDSCs from WM patients was impaired, compared to normal controls, thereby confirming the immunosuppressive role of MDSCs. Further analysis identified distinct MDSC populations in the bone marrow that were different when normal controls were compared to patients with smoldering WM or those with WM needing treatment. Specifically WM patients needing treatment had increased numbers of a distinct MDSC population that was highly positive for the surface markers CD163 and CD138. The study concluded that MDSCs in the bone marrow therefore present a therapeutic target that should be explored in WM patients.

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



### **2020 Educational Forum Cancelled**

*Out of concern for the health and safety of the worldwide community of WM patients, families, caregivers, and medical professionals because of COVID-19, the IWMF has cancelled the 2020 Educational Forum that was scheduled to take place in Renton, Washington, from June 5-7. The Renton location will now be used for the 2022 Ed Forum, to take place on June 24-26, 2022, at the Hyatt Regency Lake Washington.* 

This has been an incredibly difficult decision, as the Educational Forum has been a signature annual event for 25 years, and this will be the first time that we've had to cancel this unique opportunity to hear from and meet with leading researchers, clinicians, and fellow WMers from around the world.

The IWMF Ed Forum Planning Committee is exploring alternative ways to provide you with highlights of the information that was to be presented during the 2020 Ed Forum. We will continue to update you as plans come together.

In this time of global crisis, the IWMF wishes to extend its concern and support to everyone around the world who is affected by the coronavirus outbreak, and our hope continues to be for a speedy and effective resolution.

# THE IWMF CELEBRATES ITS HISTORY AND THE EDUCATIONAL FORUM

BY LAURIE RUDE-BETTS

Editor's note: The content of each Torch issue is planned months ahead of time, so occasionally a disconnect occurs with article relevance. COVID-19's disruption of our lives is also reflected in this issue's presentation of the IWMF's and the Educational Forum's history. With the Forum's Seattle meeting cancelled as we go to press, we feel people will still be interested in reading about the history of the IWMF and the Forum, as we look forward to a recovery.

Laurie Rude-Betts was the wife of Ben Rude, the second president of the IWMF, who served from 2000 until his death in 2005—with WM, not from it. She writes about her early recollections of the IWMF and the Educational Forum and has solicited memories from other members as well.

In 1997, the second annual conference of the Waldenstrom's Support Group (WMSG) wasn't called an Educational Forum. It was an event put on for the members of the fledgling national support group by the Smokler family: Arnie, the founder, and his family—Bernie and their two grown children. Arnie planned it, and his family helped him host it in Alexandria, VA. Ben and I were at this second gathering because Ben was diagnosed in late 1996, too late to attend the first. We were there to learn all we could about Waldenstrom's macroglobulinemia. The third annual support group meeting in 1998 in Atlanta was just before Arnie's application was approved to take the support group to a 501(c)(3) charitable foundation, which was named the International Waldenstrom's Macroglobulinemia Foundation by the first Board of Trustees. The IWMF was born in 1998.

These first years started us on a journey which turned out to be a heady, emotional, and wonderful time, filled with a feeling of accomplishment and dear new friends in our lives. I am still attending these great IWMF Educational Forums, as I feel as if you are all my family. I hope maybe you can relate to that feeling of being part of a family of WMers. The Educational Forums bring us together for those very meaningful face-to-face experiences, including meeting all of those healthy-looking WMers and learning all that the WM medical community has accomplished for us. Wow, what an occasion, don't you agree?

Judith May was a charter member of Arnie's original support group and became a member of the first Board in charge of research, but there was no IWMF research program so it had to be developed! She became president of the IWMF after Ben's death in 2005. She met her future WMer husband, Michael Luttrell, when he became a Board member; they fell in love and married! Michael said of their early experience: "We had no government or drug company support, no recognition, we were tiny and alone with a very rare disease with no known cause, no cure, and not even viable treatments. Arnie collected energy, and we were filled with a determination to find ways to create and organize and grow."

Mary Ughetta was also at the 1997 conference in Alexandria, VA. She remembers: "I have heard Dr. Frankel, Arnie's doctor, who was a regular at the early conferences, recount his astonishment at how he arrived at the conference expecting to speak to a dozen or so people and there were a couple hundred people there." We were desperate for information!

Mel Horowitz and Thad Raushi had already met when they both attended their first annual conference, also in 1997. Mel wrote that, as early as 1995, Arnie had started a newsletter. Thad wrote a many-paged article for that 1997 conference, which in 1999 was expanded and became the first IWMF



2002 Chicago Board meeting - Left to right: Jim Bunton, Ben Rude, Ron Payne, Lou Birenbaum, Judith May, Tom Myers, Tom Hoffmann, Peter Mitro, James Berg, Neil Massoth, Ron Draftz

IWMF Celebrates Its History, cont. on page 13

pamphlet, titled WM: What Is It?

Davell Hays and John Renshaw, both early Board members, remember good times. Davell, part of the team that put on the 2002 Forum in Las Vegas, wrote: "We were hopeful, joyful people determined to take the future into our own hands! And look at the result, even beyond our hopes and dreams." Another early member, Stan Eringis, remembers that Forums "...were very special. We



1998 RowBobRow fundraiser - Bob Lynch rowed from Key West to Miami; the boat was exhibited in the hotel at the Atlanta WM meeting.

became very, very close in such a short time."

Bob Lynch's wife, Sue, was an original Board member, although Bob is the WMer. Bob wanted to raise funds for this new, struggling foundation, so he decided to call attention to its cause by rowing alone for ten days from Key West to Miami! He called his endeavor RowBobRow. He sure did raise money and the attention of south Florida. At Arnie's suggestion, and with great difficulty, Bob then towed his boat to display it outside our conference room at the Atlanta support group conference in 1998! Bob wrote that good came out of his cancer: "The people we have met, the personal growth we have experienced, the strength we have discovered, and the hope we have been able to share with others are not anything either one of us would choose to change."

Jennifer Hoegerman was diagnosed in 1995 and found Arnie right away; like many of us, her mind was eased after talking with him. She attended her first Educational Forum of the newly formed IWMF in 1999 in San Francisco, and she remembers that back then everyone was anxious about their IgM. "Things certainly have changed!" The 2020 meeting in Renton would have been her 22nd Forum!

Sara McKinnie, for many years the only paid person in the IWMF office, was hired by Arnie in 1999. She reminded me of the Forum when the Board members entered the conference room, dressed in wigs, patient gowns, and medical coats and got an hilarious reaction.

Shariann Hall, diagnosed at 41, remembers being asked to play a "sexy" nurse in that skit. Her first conference was in 1997. She remembers Dr. Kyle and Dr. Bart Barlogie were there, and that, after the conference day was over, Dr. Kyle stood in the hotel lobby "listening to our stories until almost midnight!"

Marcia Klepac is part of a select group of familial WMers: her father also had WM. They were diagnosed when new patients were still calling Arnie for comfort and advice. "But what really resonated with me was his 'take control' approach to the disease." Marcia and her family took comfort also from

their first support group meeting and from joining the IWMF Talk List. Her first Forum was 2002 in Las Vegas. Although frustrated with the lack of knowledge at earlier Forums, she observes, "...Forums have been a real source of hope."

Don and Mary Brown have been the Chicago Support Group leaders since 2006. Their first Forum was in 2003 in Reston, VA, and they "... began to realize we were not alone." At that Forum she remembers the dinner cruise and watching Ben



2003 Reston, VA, Ed Forum - Ben Rude doing the limbo on a dinner cruise

and others doing the limbo. "Patients and caregivers can laugh and have fun!"

Bill Bass is the long-time leader of the Rocky Mountain Support Group, at one time along with Roy and Eileen Parker; later, Cindy Furst also became a leader. They formed this support group after meeting at the 2003 Forum. He mentions meeting Drs. Kyle, Treon, and Gertz at the meetings and how influential they were. Eileen remembers: "We attended every Forum for 12 years and watched the number of participants grow each year."

Cindy Furst adds, "Every Forum was always interesting and helpful. It was always fun to meet and share with the other WMers and doctors."

Guy Sherwood was a young MD who was one of the unlucky diagnosed with WM in their early 40s. Guy attended his first Ed Forum in 2003. He says that when he walked into the conference, he thought, "I must be at the wrong hotel; where's...all the sick people? A few days later I returned home from the conference with a sense of hope and clarity." Guy has served the Foundation in many ways and is a former long-time Board member.

I also reached out to those most important early members of our WM medical community: Dr. Robert Kyle, Dr. Morie Gertz, and Dr. Steven Treon. Where would we be without them and the involvement of their medical institutions? As Michael Luttrell observed, "Our enthusiasm was infectious, and it attracted the most talented of medical researchers at the best institutions, and they were swept along to join us..."

IWMF Celebrates Its History, cont. on page 14



2004 Lincolnshire, IL, Ed Forum - Tour of the City of Chicago

Dr. Robert Kyle's relationship with WM was intimate. He even had known Dr. Jan Waldenström, the Swedish physician who first described the disease in 1944. He says, "(Arnie) arranged a Waldenstrom's Macroglobulinemia Support Group (WMSG) conference in Arlington, VA, at a Holiday Inn in 1996. It was attended by 75 patients. I do not recall any formal lecture, but I did say a few words about WM and then answered questions from the attendees.

"In 1997, Arnie asked me to give a talk at the WMSG conference in Alexandria on the diagnosis and treatment of WM. I think that Dr. Donna Weber of MD Anderson also gave a presentation. After many questions from the patients and their relatives, the dining room closed, and we moved into the hallway. I was most impressed with the patients' interest in the disease.

I made a point to simply listen and then answer any questions they had of a medical nature."

Dr. Morie Gertz recalls that for years he and Ben had a custom

of running for half to one hour the first morning before the first lecture of the Forum. Ben certainly would be pleased that Dr. Gertz has memories of those runs!

Dr. Steven Treon writes that a cherished memory was the St. Louis Forum in 2000 because he was the only doctor who was able to make it. "...I had the opportunity to speak and then get to meet all the participants, perhaps 80 at the time. What ended up really impressing me was the spirit and optimism, and the sense of purpose...It was so upbeat. I realized what a wonderful family the IWMF had brought together to defeat WM. And I felt so fortunate to be a part of it."

The early days and early annual conferences were often difficult in that so little was known about this very rare cancer. But in recent years, the IWMF's funding of WM research has created new treatment choices, and expectations for long and healthy lives are high. We have come a very long way in the 25 years since Arnie put on the first conference, and we look forward to future Ed Forums, as we get closer and closer to "The Cure."



Early 2000s Ed Forum - Dr. Morie Gertz of Mayo Clinic receiving award from IWMF President Ben Rude



Left to right around the table: Barbara Bunton, Guy Sherwood, Stan Eringis, Laurie Rude-Betts, Grace Eringis, Jim Bunton, Sara McKinnie



### The Ben Rude Heritage Society for Legacy Gifts to the IWMF

The IWMF has a special club for those who name the IWMF as a beneficiary of their estate plan—the Ben Rude Heritage Society. No gift is too small for membership! If you have already made a provision for the IWMF in your will, trust, life insurance, or as a beneficiary of your IRA, please let us know, and we'll enroll you in the Ben Rude Heritage Society. You can remain anonymous if you prefer. Either way, we would like to say thank you and keep you in the loop with all things IWMF-related. For more information on estate gifts or to join the Ben Rude Heritage Society, contact Director of Development and Communications Jeremy Dictor at 941-927-4963 or *JDictor@IWMF.com*.

### **RESEARCH PARTNERS**

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

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

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

Targeting MYD88 Signaling in WM

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

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

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

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

Novel Antibody-Targeted Interferons in Combinatorial Therapies for WM

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

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

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

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

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

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

### The Yang Family Research Fund of the IWMF supports the following current research project:

Targeting MYD88 Signaling in WM

### NAMED GIFT FUNDS

For a commitment of \$10,000 per year for five years, or a lump sum of \$50,000 or more, you can establish a named fund at the IWMF in your own name or in the name of someone you wish to honor. This fund may support Member Services or Research or a combination of the two.

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

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

Ben Rude Heritage Society Roster			
*Deceased			
ANONYMOUS (4)	ARLENE HINCHCLIFFE	CYNTHIA RUHL	
JEAN-MARC AUDIBERT*	ELINOR HOWENSTINE*	ELMO R.* AND DOLORES SCHMID*	
BARBARA BACKER	WANDA L. HUSKINS AND	MICHAEL AND CAROL SESNOWITZ	
MARTIN BAER	JEFFREY A PRUPIS	ALLAN SHAW*	
C. EDWIN BAKER*	STANLEY KAUFMAN	DR. GUY SHERWOOD	
JACK BAKER	SHAN ELIZABETH KEARY	ELLEN SMITH	
JANE BAUSSER*	NANCY KERR*	RAY SOBOROWICZ*	
DAVE BENSON	THOMAS KEYS*	KEN AND LINDA SOLOW	
BEVERLY BLOSS	EVELYN KLIEN	CORDELIA AND PETER STEARNS	
VIVIAN AND ROBERT BOAS $\diamond$	MARCIA AND GLENN KLEPAC	JUDITH LEE STERLING AND LESLIE	
ELSA AND GARY BRADLEY	GEORGE KNIPELBERG*	CHARLES WILSON	
LESLEY MOORE BRADSTREET	CHARLES KOCH	JOHN AND DIANE TIPLADY	
ARLOU BRAHM*	DR. ROBERT A. AND CHARLENE M. KYLE	RUBEN TROSS*◊	
WILLIAM 0. BRESNICK AND ELLEN	ROY LANGHANS	TAMARA VINCENT	
KANER BRESNICK ◊	JANET LEVY*	PENNI WISNER	
RUTH L. BROWN*	MICHAEL E. LUTTRELL	JAMES P YEAGER*	
L. DON AND MARY BROWN	LENNY MARTIN	GREGORY FITZWATER AND	
PETER CARR	JUDITH A. MAY	MARILYN ZOLLNER-FITZWATER	
GERALD PRESTON CLANCEY*	KATHARINE E. MCCLEARY AND K.		
CHRISTINA CONLEY*	EDWARD JACOBI*		
IVY COOPER*◊	KATHLEEN MINER		
ROBERT* AND ANNE COULBOURN*	ANNE AND PETER MITRO $\diamond$		
JAN SOLOMON CRAMER*	ELEANOR MOORE*		
NORM CRANDALL	RIC MOORE		
TONY DYE*	MAYNARD MORRIS		
FREDERICK A. EBELING*	SAM AND GAIL MURDOUGH		
JEAN ELLIS*	BARRY NELSON		
RAYMOND* AND BETTE FISHMAN*	LINDA NELSON		
MARLYN FRIEDLANDER AND	BRANDT NORQUIST*		
GILBERT SCHERER	JIM AND BETTE ORTOLEVA		
CINDY L. FURST	ALAN PRESTELL*		
JEB GELBER	MARGUERITE C. REGAN, PHD*		
LESLIE C. GUTHRIE, JR.*	PAUL AND JANICE RIPPAS		
CARL HARRINGTON	ROGER AND BARBARA ROBINETTE		
JANE AND RALPH HENDRICKSON	MARGARET ROCKELMAN*		
JAN HERGESHEIMER	JOEL ROSENBLIT		
SUZANNE L. HERMS	LAURIE RUDE-BETTS ◊		



## **IWMF DOC STAR: DR. CHRISTIAN BUSKE**

AS TOLD TO RON TERNOWAY

Dr. Stephen Ansell, cochair of the IWMF Scientific Advisory Committee (SAC), is thrilled with the addition of Dr. Christian Buske to the team.

"We are delighted that Dr. Buske has joined the IWMF SAC, as he is an outstanding researcher and clinician in the field of Waldenström's macroglobulinemia (WM) and a strong advocate for WM patients. He has played a leading role in



Dr. Christian Buske

the development of new treatment strategies for this disease and other lymphoid malignancies. We are fortunate to have him as part of the SAC and look forward to his contributions."

Professor Christian Buske, MD, is medical director at the Comprehensive Cancer Centre and the Institute of Experimental Cancer Research at the University of Ulm, Germany, and an attending physician and professor of medicine at the University Hospital Ulm.

He has coordinated the use of large databases to generate a comprehensive understanding of WM across Europe, and he has led European efforts to develop consensus as to the optimal management of WM. In March many readers heard Dr. Buske and Dr. Steven Treon lead the CancerCare Connect webinar on "The Latest News in the Treatment of WM."

Prof. Buske has published over 100 peer-reviewed papers and acts as reviewer for journals such as the *New England Journal of Medicine*, *Science*, *Cancer Cell*, *Cell Stem Cell*, *Journal of Clinical Oncology*, and *Blood*. He is the principal investigator for a number of clinical trials, including a Phase 3 trial comparing DRC (dexamethasone, rituximab, and cyclophosphamide) to DRC + bortezomib, and a Phase 2 trial evaluating the efficacy of rituximab, ibrutinib, and bortezomib (B-RI) in treatment-naive WM patients.

Dr. Buske grew up in Westphalia, Germany, as the youngest of three children. "My parents were quite strict and I got a thorough education in high school with Latin as first language and piano lessons for many years. My parents were not involved in medicine, but I became interested in biology and medicine very early on. For me, cancer biology was the most fascinating field—it was a miracle and still is in some way—how cancer develops, why some people get cancer, and some do not." He received his medical training at the University of Münster, followed by a three-year research fellowship in Vancouver, Canada, which formed the basis for his subsequent research in leukemias. He returned to Germany and Munich under the tutelage of Wolfgang Hiddemann. "Hiddemann was the person who introduced me into the world of lymphoma and strongly supported me on my way to start clinical research in B-cell lymphomas including Waldenström's macroglobulinemia. He let me give talks instead of him, let me supervise clinical trials, and introduced me into the German Study Group for low-grade lymphomas."

Dr. Buske moved to Ulm ten years ago. "It was a major step for me as medical director at the Comprehensive Cancer Center Ulm, with my own group and responsibilities. Ulm has a major focus on hematology/oncology, and it is the ideal place to do clinical and translational research in lymphoma and leukemia."

There are about 5000 WM patients in Germany. Ulm is a center of excellence for WM in Germany, providing advice and direction to hematologists throughout the country. Buske typically sees about 100 WM patients annually. His advice to the newly diagnosed: "Seek information, contact us, contact patient advocacy groups. Information is so, so important to understand that there is a life with this disease. Very often the quality of life stays the same—we have highly efficient treatments available, and we are making progress, rapid progress, in managing this disease."

Dr. Buske was a co-founder and is now president of one of the largest lymphoma study groups in Europe, the German Lymphoma Alliance (GLA).

His commitment to WM patients extends far beyond the borders of Germany. In 2009 he was one of the founders and is now coordinator of the European Consortium for Waldenström's Macroglobulinemia, a group of clinicians and researchers whose aim is to optimize the clinical management of WM patients in Europe and Australia. "The major goal is to achieve this as a group—to collaborate, to communicate, to do clinical trials together, as well as basic and translational research."

Dr. Buske is married with three "wonderful" children, who are most important for his work-life balance. "I love classical music, cultural events—I love to go into the opera, for instance. My favorite leisure activity is travelling around, to meet people, to learn about their way to live."

Christian Buske has never lost his early fascination with biology, medicine, and cancer, nor his compassion for others. "I love my work! To be involved in moving the field forward and to help patients with WM is a great joy every day."

# WM: FLIGHT/FIGHT/ACCEPT?

BY HARVEY BARTZ

I've often thought about how I used the word "battle" to refer to our grandson Zac's ten-year fight to defeat neurofibromatosis that morphed into cancer before he died at age 11. As I sat with him through countless chemo infusions, radiation treatments, and surgeries, I wished I could trade places with him. I was nearing the end of my life. His was just beginning. While that was not to be, his motto "I'll never give up" always warms my heart and envisions his smile.

> My view is **grounded** in my **understanding** of the incredible healing power of **nature**.

My experiences with Zac helped prepare me for a surprise of my own when I was diagnosed with Waldenstrom's macroglobulinemia (WM) five years ago. WM is a non-Hodgkin's lymphoma—a rare blood cancer affecting only three people in a million. The bone marrow produces too many of the abnormal lymphoplasmacytic lymphoma cells of WM that crowd out healthy cells, producing a protein that accumulates in the blood, impairs circulation, and causes complications.

Interestingly, I never felt compelled to describe my pending journey as a "battle." A battle begins when I feel attacked and respond by attacking back, a sure recipe for inflaming the conflict. Instead, I found myself asking the question, "What is happening here?" This helped me focus on trying to understand WM rather than wasting energy in denial or feeling angry or scared or sorry for myself.

I came to see my cancer not as an outside enemy, but as part of me. If I ignore it—take flight—it will demand my attention. If I fight it, I'm fighting myself, which escalates the conflict. I'm reminded of a quote from Abraham Lincoln: "The best way to destroy an enemy is to make him a friend." Better to accept than reject; to be a healer than a fighter; to be a selflover than to hate a part of me.

My view is grounded in my understanding of the incredible healing power of nature. When a tree loses a branch, the broken stub heals over. Marshes and waterways have selfpurifying qualities that mitigate our polluting habits. Our bodies also have self-healing capacities. When I cut myself, my blood mobilizes to cleanse the cut, stop the bleeding, and begin a healing process.

Current medical research is finding new ways to harness the body's internal resources to heal itself (e.g., immunotherapy). Recent discoveries offer hope that there may be better ways to address cancer than "battling" it by cutting off the offending parts, "nuking" with radiation, or dousing with toxic chemicals, all of which have damaging side effects. By accepting that my cancer is part of me, my energy is freed to explore ways to work with my body toward greater health. Emerging therapies offer exciting promises. In the meantime, I seek out and utilize the best available treatment. And I practice self-care: nutritious meals, exercise, sleep, loving relationships, pleasurable activities, and meaningful missions.

A few months before Zac died, I took him to church and we all had a dialog about his journey. My last question: "Zac, how have you survived all the chemo and radiation and surgeries and pain?" He looked at the congregation and said, "You have to have a positive attitude." That "brought down the house!"

> There is much about WM that I cannot **control**. But I can **take charge** of my own attitude.

There is much about WM that I cannot control. But I can take charge of my own attitude. Rather than fight it as an enemy, I accept it as a new part of me with which I am learning to get along. Zac's "positive attitude," or, as I say, "hope always," is a healing power that supports me on my journey.

### **Have Your Say**

The *Torch* welcomes letters, articles, or suggestions for articles. If you have something you'd like to share with your fellow WMers, please contact *IWMF Torch* editor Shirley Ganse at <u>shirleyganse@hotmail.com</u>

# **A TRIBUTE TO ALICE SWIFT RIGINOS**

BY SUE HERMS

"...I am sorry to hear about the loss of Alice. She was a very selfless woman who went through life helping others and above all, a gentle soul. Alice always set a high standard in her work and charity which continues to be measured."

"What a privilege it has been to have known Alice. Her wit, charm, and brilliance of spirit will always



Reading the Torch in front of Riginos's house on the Greek island of Samos

be remembered. A life well-lived I think we can all agree."

"So sorry to hear this sad news. Alice's contributions of time and effort to the Torch, and the IWMF, enriched all our lives. My heart goes out to her family in their loss. She will be greatly missed." The passing of any member of the "IWMF Family" is difficult, but the recent loss of retired *IWMF Torch* Editor Alice Riginos has been particularly so, as evidenced by these and many other expressions of sympathy received from members of the IWMF.

Most of us knew Alice through her work as editor of the *Torch*, which she led from 2008 to 2018, and from her attendance at Ed Forums. Alice stepped forward as guest editor at a difficult time in 2007 to help then-Editor Don Lindemann who was quite ill. When Don passed away in 2008, Alice graciously agreed to become the new editor. During her tenure, Alice was constantly focused on ways to improve the *Torch*, including updating its appearance with modern graphics, glossy paper, and a redesigned masthead; adding regular columns such as Cooks' Happy Hour, International Scene, Doc Star, and In the Torchlight; adding a Best of the Torch feature to the IWMF website; and using her creativity to constantly look for new ideas for articles. Little known to most of us was her interesting life before the *Torch*.

Alice was born in 1941. Her father was an archaeologist who excavated in Greece and Turkey, and as a teen-ager, Alice helped her father to catalog artifacts. After graduating from the University of Chicago Lab School (a high school), she

A Tribute to Alice, cont. on page 21



### A Tribute to Alice, cont. from page 20

enrolled at Stanford University as a pre-med student but decided to leave after the first year and return to the University of Chicago, from which she graduated with a BA in Ancient History and MA in Classical Archaeology. During this time she participated in a summer excavation at Kenchreai, which was the east harbor of the ancient city of Corinth, Greece.

In 1964 Alice was awarded a traveling fellowship to the

American School of Classical Studies in Athens and traveled on the ocean liner Queen Frederica, sailing from New York to Piraeus, Greece. It was during this trip that she met her future husband Vasilis Riginos, and the two had a shipboard romance that continued through the summer. The plan for the 1966 excavation season at Kenchreai was to expand the land work to



underwater excavation. To that end, Alice took diving lessons in Chicago and then joined the excavation as a diver/archaeologist, during which time she typically made at least two dives every day, handling an air compressor hose to suck up debris and objects from the sand and mud on the sea bottom.

After a long courtship, Alice and Vasilis were married in Athens, where they lived during the Greek military dictatorship until the spring of 1968, when Vasilis was released from mandatory service in the Greek army. At the end of that year's excavation season, Alice and Vasilis moved to New York City to pursue their doctorates, with Alice earning her PhD in Classics at Columbia University and Vasilis obtaining his PhD in Electrophysics from Stevens Institute of Technology. During this time, their daughter Cynthia was born. The busy couple split child care duties, with Vasilis taking care of the baby during the day so that Alice could do her library research and Alice taking over in the evenings while Vasilis worked in his laboratory on his own research.

In 1974 they moved to Washington DC. Alice wrote a book called *Platonica: The Anecdotes Concerning the Life and Writings of Plato*, published in 1976 and based on her doctorate dissertation. The book is viewed as a very influential and important work by classical scholars. In 1975 she was asked to be a lecturer by Howard University, and in 1978 second daughter Corinna was born. At Howard, Alice taught classical Greek and Latin and a popular course in classical mythology, eventually becoming an associate professor and remaining at Howard until her retirement

in 2004. During this period, Alice published an article in the Journal of Hellenic Studies entitled "The Wounding of Philip II of Macedon: Fact and Fabrication," which was the result of many years of research and chronicled the evidence supporting and disputing claims that a rich tomb discovered in 1997 belonged to King Philip. For several years, Alice served as



president of the local DC chapter of the American Institute of Archaeology (AIA), eventually becoming a life member of the national AIA, its ombudsperson in 2001, and a national trustee from 1995-2005. Alice was a member of several other professional societies, including the American Philological Association, the Institute of Nautical Archaeology, the Hellenic Institute of Marine Archaeology, the Classical Association of the Atlantic States, the Washington Classical Society, and Eta Sigma Phi.

In the fall of 2002 during a routine medical checkup, her internist discovered that Alice was slightly anemic and subsequently referred her to a hematologist-oncologist, who performed a bone marrow biopsy and diagnosed her with WM. She eventually consulted with Dr. Morie Gertz at Mayo Clinic for treatments. During the next 16 years, her typical pattern would be treatment followed by twothree years of remission followed by another treatment; during remissions she traveled to Greece, Australia, and India, and often edited *Torch* issues from a summer home in Greece. Eventually, Alice's immune system became severely compromised by the disease and by multiple treatments for it, and she developed a series of infections, the last of which was caused by the common JC virus and affected her brain, ultimately leading to her death in December 2019.

Alice will be remembered for her adventurous spirit by her husband Vasilis and their family. She was devoted to a number of causes and served as a mentor to her Howard University students. She was a woman of warmth, wisdom, and wit, an outstanding writer and editor, and had a truly generous heart. Her decade-long stewardship of the *Torch* remains her unique and lasting legacy to its readers and to the IWMF.

The IWMF Torch expresses its appreciation to Vasilis Riginos for supplying much of the biographical information contained in this article and extends its deepest sympathies to Alice's family.

# **FROM IWMF CONNECT: SPRING 2020**

BY JACOB WEINTRAUB, MD

Winter is now over, and our thoughts turn to pursuits of spring and warmer weather. However, in spite of good weather, avoidance of COVID-19 has many of us self-isolating, so we cannot attend support group meetings. But we know we can still rely on supporting each other through IWMF Connect. This online forum allows members to share information, links to scholarly articles, and human interest articles. They can also share personal experiences and recommendations for various remedies that have helped alleviate some WM and treatment side effects. Someone has even found a rock band named "Waldenstrom's"!

# Members share **information**, links to scholarly **articles**, and **human interest** articles.

**IWMF Connect Manager and IWMF Trustee Peter DeNardis** posted links to several items. Some were scientific and clinical studies, and some were links to human interest stories, which resonate with the WM community and involve issues we deal with on a regular basis.

Peter posted a link to a clip from a movie titled 50/50, which is a humorous look at dealing with the enormity of cancer. One line involves a scene we can relate to when we try to tell someone that we have Waldenstrom's macroglobulinemia. The line in the movie concerning the character's complicatednamed cancer is "Tough break. The more syllables, the worse it is." (It was said tongue-in-cheek.) https://youtu.be/5PudpLbRsuM

Peter also posted a link to an article titled "Qi Gong and Tai Chi improve the lives of cancer survivors." This was published on a Nevada news website. Although Pete did not attempt to validate or locate the studies mentioned in the article, it does provide some encouragement for those who might consider tai chi or qi gong to help improve their quality of life. Here is the link: *https://www.theunion.com/news/qi-gong-and-tai-chi-improve-the-lives-of-cancer-survivors/* 

**Bonnie B** added that she has practiced and studied tai chi for 20 years. She believes in the restorative effects of practicing it.

**Kenneth K** also added that he practices a type of qi gong from Taiwan a couple of times a day. It is easy and has no space or timing restrictions. He posted a website for those who are interested in learning more. This site is primarily in Chinese, but translation is available. *www.meimen.org/* 

**Suzanne R** posted a link to an opinion piece in the *Washington Post* about living with chronic illness. It is all about balancing

the fear with the love.

www.washingtonpost.com/opinions/living-a-chronic-life-ina-fix-it-now-world/2019/06/17/628d53ac-8ebe-11e9-adf3f70f78c156e8\_story.html

**Ron T** posted an article from a cancer survivor giving advice for those who don't understand how to respond when someone tells you they have cancer. The response is simpler than you think.

https://www.theglobeandmail.com/life/first-person/articlewhen-someone-tells-you-they-have-cancer-the-response-issimpler-than/

Finally, in his never-ending quest for useful or informative information, Peter happened upon a Facebook page for a rock music cover band based in Brazil that calls itself "Waldenstrom's." The Facebook page is *https://facebook.com/waldenstrom1906/*. He noted that 1906 was the year Jan Gösta Waldenström was born. After some further investigation, he found that the band consists of three hematologists, one infectologist, and a plastic surgeon. They love to play classic rock, and their patients know of the band and love it. They play for fun, with only rare presentations, though one IWMF Connect member posted a note that it would be great if the band could play at the next Ed Forum, or at least send a video for us to watch.

### MENTAL HEALTH

This is a topic that comes up periodically. Questions are posed regarding effects of various treatments on our ability to think, and how WM itself can affect us.

**Larry S** posted that he has had WM for seven years. His first treatments were with Rituxan and bendamustine, then Rituxan maintenance. Now he has been taking ibrutinib (Imbruvica) for two years. His job has required multitasking and addressing multiple issues, and he has been good at this. However, for the last 8 to 12 months, he has had difficulty putting thoughts into words and explaining what is going on mentally. Now he finds himself focusing on one thing and getting irritated very easily. He was wondering if this could be his age, WM, treatments, stress, or other factors. Have others had any mental/thinking issues while taking Imbruvica?

**Tina Ann** echoed Larry's questions. She notes that since this is "hardly immediately life threatening," it has been difficult to get her oncologist to help her think about the issue.

**Roy P** posted that he has been taking Imbruvica for the past two years and has experienced these same symptoms. They came on gradually. Now he has difficulty finding the right word and remembering names. He did mention this to his oncologist, but she did not appear to be too concerned. The issue was magnified over the holiday period when he had to speak to more people than usual and had significant difficulty with one particular word that he commonly uses, but couldn't find.

### She has been taking **ibrutinib** for over a year, and it is **working very well** for her WM.

**Suzanne R** also thanked Larry for raising the issue. She is only 54 years old but has trouble finding words and seems to be more emotionally "wobbly." She has been taking ibrutinib for over a year, and it is working very well for her WM. She often says words that she is reading or looking at instead of the word she meant to say. She feels her multitasking skills are impaired. She always has been great at this. She had not thought about it being related to her ibrutinib, but is grateful for this discussion and finding that others are having the same difficulty while taking the same treatment.

**Ed G** added that he has a very straightforward oncologist whom he respects for her wisdom. She had given him some very pragmatic advice and has included the observation that "no matter what the drug companies say, Imbruvica is a chemical designed to treat cancer, and, therefore, is chemo. With that said, chemo brain is a logical side effect." He added he definitely has the problem, and that some days he needs a name tag to remember who he is.

**Ginger H** posted a note that echoed a prior discussion here about the general topic of chemo brain. She was treated with fludarabine, ending treatment five years ago. She feels she never completely recovered her executive functions such as organizational skills, following instructions, and remembering what she needs to do. She is better than she was two years ago, so she feels she is continuing to recover but still has deficits. She went to a workshop on chemo brain last fall and was given some good checklists for helping recall.

# NEULASTA AND IVIG (INTRAVENOUS IMMUNE GLOBULIN)

These topics recur, and IVIG has had extensive discussions in the past. Neulasta is a product that stimulates the immune system to produce neutrophils to help fight infection.

Linda A asked about people's experience with Neulasta. She was in treatment with Rituxan and bendamustine and will start to use a Neulasta patch.

**Ron T** reported that he self-injected Neupogen for 18 months with no untoward side effects. Neupogen is a product similar to Neulasta. Ron did comment that some people have experienced bone pain as a side effect.

**Megan D** posted that her husband had the Neulasta shots, and that may be different from the patch. He did experience bone pain, which the infusion nurses said was common and likely due to the increasing bone marrow production of neutrophils. The nurses recommended doubling the dose of premeds Claritin and Aleve, and that helped a lot. Megan thinks that helped more than the other prescription pain meds he had taken.

**Patty** added that she had Neulasta after each bendamustine treatment. She had no problems at all, and she did not have to go back to her doctor to get the shot.

**Gata H** posted that she has had both the shots and the patch. She lived close enough that going to get the injection was much preferred. She found the patch to be a nuisance and worrisome. However, if she lived far away, it would be a godsend. She felt she felt "out of sorts" for a day or two after the shot.

**Nancy** N posted that her husband had four rounds of bendamustine and Rituxan. He had the Neulasta patch each time for low white count. It was a nonevent. It beeps to let you know when it is starting to be administered, and then beeps when done, and you can see on the device that it is empty. Then you just pull it off. He was told to take an allergy medication to avoid possible bone pain, but he had no side effects at all. He put the patch on his abdomen.

There were a few postings about another immune system product, IVIG, which is intravenous immune globulin, providing ready-made antibodies to help fight infection.

**Erin S** started the discussion by saying that she will be starting IVIG infusions, and she was a little nervous. She asked for people to share experiences, both short-term around the time of infusion, and also any long-term effects, benefits, and adverse effects. She had been having recurring chest and sinus infections, needing multiple courses of antibiotics, steroids, and other meds.

**Paul L** said that the day after IVIG, generally he has mild flulike symptoms with congestion and sluggishness, but those clear by the next day.

Sue Herms, retired IWMF Trustee and LIFELINE volunteer, suggested Erin read the IWMF Fact Sheet on IVIG at *https://www.iwmf.com/system/files/IVIG\_FactSheet-English.pdf*. This gives a lot of background information about what to expect. IVIG can be given subcutaneously or intramuscularly, in case it is difficult to tolerate intravenously.

Marilyn S added that her husband gets monthly IVIG, and it's a lifesaver. He does get colds, but has not had any more severe sinus or chest infections. He gets Benadryl, Tylenol, and a steroid before each infusion, and he mostly sleeps through the slow drip. He drinks a lot of water the day before and gets a liter of saline right after. The hydration is important. They *From IWMF Connect, cont. on page 24*  are now able to travel again and spend time with their little grandchildren.

**Joseph V** posted that he has received subcutaneous Ig (HyQvia) every four weeks for the last three years. He has not had any issues. He has read information that indicates the rate the Ig enters your system is a big factor in the body's reactions. A subcutaneous injection into the belly or thigh fat causes the globulin to be released into the system over several days. Initially he has had a fewminor headaches the day after the injection, but these have gone away.

### **IN MEMORIAM**

The IWMF Connect community learned of four members who died recently. **Alice Riginos**, previous editor of the *IWMF Torch*, was a long-time contributor and friend to many of us. A separate tribute to her is published in this issue of the *Torch*. **Eunice Johnson** was a long-time survivor of WM and died unexpectedly from a cause likely not related to her WM. She was a frequent contributor to this forum. This group will miss her advice and suggestions. **Gerry Wergland** also died recently. He, too, was a frequently contributor, and his contributions will be missed. Finally, **Carl E. Graf** also passed away. He was a long time WMer, over 25 years, and periodically posted to the online forum.

Everyone is welcome to **join** and **participate**, or just benefit from the **support** and **information**.

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

### **SUPPORT GROUP NEWS**

EDITED BY PENNI WISNER



South Florida Support Group January meeting

### PLEASE NOTE

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

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

### FLORIDA

South Florida

On December 7, 2019, the South Florida Support Group held its holiday meeting at Memorial Hospital West. Over 25 persons attended. Members engaged in a roundtable discussion among themselves as well as a Q&A session with Dr. Daren Grosman of Memorial. Bob Lynch, a WM patient for more than 25 years, spoke about how he has lived with WM, including his "RowBobRow" activities, such as rowing from the Keys to Miami. Lunch was provided courtesy of the Leukemia & Lymphoma Society (LLS).

Support Group News, cont. on page 25



South Florida Support Group at the February LLS conference



Dr. Steven Treon at the WM breakout session of the South FL LLS conference

LLS has organized annual blood conference educational seminars for the past few years in the South Florida area, including special WM sessions with Dr. Steven Treon of Dana-Farber Cancer Institute. The conference was held this year on Saturday, February 29. The main and breakout sessions were informative, and once again Dr. Treon was here for the WM breakout session. To enable patients with similar diagnoses to find each other, lunch tables were labeled for specific blood cancers. Every year, the number of tables for WM patients has increased. The group likes to think that this is not an indication of increased incidence of WM, but rather that more WMers are coming to this wonderful event, which typically serves as the winter support group meeting. The next meeting is planned for April 25.

### **NEW MEXICO**

#### Santa Fe/Northern New Mexico

The IWMF Santa Fe and Northern New Mexico WMers had a meeting on Saturday, February 8, that included vegetarian pizza, lots of raw veggies, shrimp, tea, coffee, cookies, and a spot of pinot grigio. Members spent much-appreciated time getting to know one another better, discussing WM experiences, and making plans for the next meetings. It was decided that each would independently listen to, or connect online to, the upcoming educational seminar being given by the Lymphoma Research Foundation and the IWMF on Thursday, March 19. Members would then bring their thoughts, ideas, and questions provoked by the conference to the next meeting. The ensuing discussion would be enriched by the various points of view and experiences of the group's members. For another meeting, Karen Gano, an oncology social worker with Christus St. Vincent Cancer Center, will be the speaker. Dates in late March and early May for these two meetings have yet to be finalized. The February gathering was small, due to members' illnesses, care-taking of an ill friend, and such.



Santa Fe/Northern New Mexico Support Group attendees in February

### NEW YORK

### Eastern NY/Western New England

The next program, to be held at the ACS Hope Club located at 1 Penny Lane, Latham, NY, on Saturday, April 25, will feature three presenters. They are Pete Skinner, Ken Dales, and Mel Horowitz. All were at the annual IWMF Educational Forum in Philadelphia this past July. They will discuss the reports of

Support Group News, cont. on page 26

progress and hope from the presenters. As a bonus we'll also tell you about some new IWMF initiatives given a big assist from Pete (the use of ZOOM). The main program is planned for 11:00am to 12:30pm followed by lunch. Afterward, those interested can share their progress and questions. Discussion will also include ideas and dates for 2020 programs and the IWMF Ed Forum in Renton, WA, June 5-7.

### EASTERN OHIO/WESTERN PENNSYLVANIA/ WEST VIRGINIA

The Hilton Garden Inn, Akron, OH, was a lovely venue for the early December, pre-holiday meeting and lunch. A large group of patients and caregivers enthusiastically gathered to begin the afternoon with a delicious lunch of sandwiches, salads, holiday cookies, and desserts. The program began by warmly welcoming George Schatz, MD, staff physician at the Center for Functional Medicine, Cleveland Clinic. In a very engaging style, Dr. Schatz presented the topic of "Functional Medicine/Nutrition in the Cancer Setting." Members gained insight into the concept of functional medicine, a systems biology approach to health that addresses the root cause of disease with the key component of retelling the patient's story. Functional medicine is a fairly new field. The Cleveland Clinic started the Center in 2014 and it is booming. Dr. Schatz, who completed a fellowship at the Arizona Center for Integrative Medicine, focused most of his talk on recommended nutrition guidelines related to cancer, definitely a hot topic with an abundance of questions! Those who wished to discuss their WM-related concerns and experiences in a group sharing circle participated in this opportunity following the presentation. The group will take a winter break and reconvene in early spring.



Oregon/SW Washington Support Group members

### **OREGON/SOUTHWEST WASHINGTON**

In January, the group welcomed Dr. David Knox from the American Cannabinoid Clinics for a fascinating presentation: an overview of the human endocannabinoid system (ECS) and the benefits of cannabis therapeutics. The ECS was discovered overseas in the 1990s, and the therapeutics

are viewed as a natural-based approach to disease. Topics included the utility of cannabinoids in dealing with WM symptoms and the side effects of treatments. The group had many questions for Dr. Knox, who stayed after the Q&A to learn more about WM, as members shared disease histories and current health conditions. As always, the support offered to everyone was gracious and appreciated. The next meeting is scheduled for April, when the topic will be an update of current medications used for both an initial WM diagnosis as well as for cases of relapse.

Leukemia & Lymphoma Society...[has] many **resources** and **tools** for patients. These include four **financial assistance** programs available to WM patients.

### TEXAS

### Dallas/Northern Texas

The first meeting of 2020 took place on February 15 at the Baylor Scott & White Charles A. Sammons Cancer Center-Cvetko Patient Resource Center in downtown Dallas. The meeting featured two guest speakers, Dawn Guerrero, patient access manager from the Leukemia & Lymphoma Society (LLS), and Ashley Jones, Board-certified art therapist for Baylor Scott & White. Dawn told the group about the LLS's many resources and tools for patients. These include four financial assistance programs available to WM patients. LLS has professionals who consult over the telephone about nutritional needs and help patients develop smart and intelligent choices in their daily diet. Plus, the LLS has a new LLS Health Manager App. This phone app tracks side effects, medications, food and hydration, questions for your doctor, grocery lists, and more. Additionally, many other support services are in the Dallas area, including YMCA partner LIVESTRONG, which sponsors a cardiac health program.

Ashley Jones gave an overview of the importance of managing one's total health. She led the group in a discussion about the mental challenges of "watch and wait," and methods of coping with the stress of not taking action despite a cancer diagnosis. Taking one day at a time and doing simple things like art therapy or some other hobby or activity helps sift the focus to something other than "I have cancer." Discussion included how the traditional response to the word "cancer" elicits thoughts of "treatment to eliminate" or "time left to live" and the desire to take action against it. Coping mechanisms, in addition to staying active, include being mindful of one's activities and keeping a journal or log. Being able to look back at how one has been feeling from one day to the next

Support Group News, cont. on page 27

### Support Group News, cont. from page 26

WASHINGTON

Olympic Peninsula

over the past several months can lower the anxiety level that might occur leading up to the next doctor visit. Yoga, meditation, and other mindful exercises can also keep you on an even keel. Ashley reminded the group that no matter how expert a doctor or other medical professional is, no one knows a patient's body better than him- or herself. Paying attention can help correlate a new symptom with something one has done or changed recently to determine if it is WM related or just "life" related. During the session with Ashley, members incorporated some sharing time, hearing emailed news from those who could not attend and updates from those in attendance. Following the meeting, the Cvetko Center provided a chicken and fish buffet lunch topped off with apple pie and cheesecake, which fueled much socialization.

### The first meeting of the Olympic and Kitsap Peninsulas IWMF Support Group met February 8 in Poulsbo, WA. This kickoff meeting featured sharing and a roundtable discussion of topics and formats for future meetings. The next expected meeting will be in the June through August time frame.

### **INTERNATIONAL SCENE**

EDITED BY ANNETTE ABURDENE



China – CEEPO meeting participants, with Group Leader Roger Yao in center holding sign over his head

### CHINA

# Chinese WM Support Group attends second CEEPO meeting in Beijing, China

On November 27 and 28, 2019, the second Chinese Experience Exchange of Patient Organization (CEEPO) meeting was held in Beijing. CEEPO, sponsored by Roche, offers a platform for different patient organizations in China to get together annually and discuss topics of common interest, share experiences, seek cooperation, and support each other. Roger Yao, as the representative of the Chinese WM Support Group (CWMSG), attended CEEPO, along with seventy other representatives of patient organizations. Lectures in the meeting included "From Molecule to Clinical Application," "Empowering Patient Organization: International Patient Organization View," "Government Policy Advocacy," "Patient Organization Involvement and Medicine Development," and

"Big Data and Its Value." Case practice discussions were held after the lecture section. Roger Yao participated in the discussion group "Fund-raising and Sustainable Income Management" and held a presentation titled "4P Marketing Strategy Implementation in Non-Profit Organizations."

# Online consultation during novel coronavirus outbreak in China

The novel coronavirus outbreak in China, starting in January 2020, has drawn great attention from all over the world. According to the Chinese government's official reporting, 44,722 patients have been diagnosed and 1,114 deaths have occurred in the country as of Feb 12. In order to reduce the risk of new coronavirus infections in public places, the Chinese government mandated that people to stay indoors and avoid public events and traveling. Most public transportation services were closed, and cross-city travel became almost impossible, which made it difficult for patients to visit their doctors for regular check-ups or treatment. For patients travelling to doctor appointments, exposure to crowds is not safe.

Worry and anxiety spread among people, especially those who have weak immune systems with WM. How to meet their doctor, get an opinion, have a regular check-up, and continue their scheduled treatment became challenges with the coronavirus outbreak. Hematologists and doctors in China were looking for solutions for this emergency. Dr. Yi Shuhua from Blood Disease Hospital and Institute of Hematology in Tianjin, versed in WM, launched online consultation programs for WM patients who were unable to travel long distances. Supported by Johnson Pharmaceutical, Dr. Yi held

International Scene, cont. on page 28



China – Dr. Yi Shuhua, Blood Disease Hospital and Institute of Hematology, Tianjin

his first on-line lecture about WM on January 17, 2020. One week later, and right before the Chinese New Year holiday, the coronavirus situation got more serious. Dr. Yi sacrificed his rest time to hold an online question and answer session in our WM We Chat discussion group and offered personal consultations to patients.

For WM patients who are participating in clinical trials, regular on-site blood check is compulsory in normal times. In the coronavirus infection area, it is currently impossible for WM patients to visit their hospitals. Considering these real difficulties, Dr. Yi coordinated the clinical trial initiators and the allied hospitals close to the patients to work out a special plan to simplify the process so that patients can easily have their blood checked at hospitals close to where they live. Subsequently, Dr. Yi reviews the examination results online. This arrangement has greatly helped WM patients in this difficult time. Confronted with such an epidemic outbreak, we need innovative thinking, and to reach final success, we need to work together. IT technicians make online work possible. But more important is the involvement of people like Dr. Yi, whose care and dedication make it possible to continue to help patients.

#### Roger Yao, WM China, reporting

### INDIA

WM India kicked off 2020 by conducting its first support group meeting in the vibrant city of Mumbai. Among the members to attend was Jennifer Talwalkar, an 82-year-old English woman who has lived in India for the better part of 50 years. Listening to her recount her journey of not just living with WM but also living in India soon after its independence was insightful and fascinating. For those of you wondering, Jennifer is healthy and doing well, with WM firmly in the rearview mirror.



Co-leaders Saurabh Seroo and Rajini Seroo (Saurabh's mother and a WM patient of 10 years); Jennifer Talkwalkar, center, an English woman with WM, who has lived in India for almost 50 years

### UNITED KINGDOM

It's been heads down for the WMUK team since the last edition of the *Torch*, with lots of work taking place behind the scenes. Our newly designed website has the same address: *www.wmuk.org.uk* but features an easy-to-navigate layout and regular updates on WM activity in the UK through our news feed.

#### Ibrutinib with rituximab in Scotland

Currently, ibrutinib is not available through the National Health Service (NHS) for WM patients in Scotland. Scotland has a different system for assessing whether new treatments can be funded and made available to patients, led by the Scottish Medicines Consortium (SMC). The SMC is currently considering whether to fund a combination treatment of ibrutinib and rituximab for WM patients in Scotland, and WMUK is working hard to make a good case to make this combination treatment available north of the border.

#### Lindsey Bennister, WMUK, reporting

#### CANADA

WM support groups are across Canada in Atlantic Canada, Ottawa, Montreal, Toronto, Oakville, Calgary, and Vancouver. Check the *www.wmfc.ca* website for times and locations. If someone outside of these areas would like to start a support group, please contact Betty McPhee at *betty.mcphee@wmfc.ca*.

#### Betty McPhee, WM Canada, reporting

#### Saurabh Seroo, WM India, reporting

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