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## ASH 2013 HIGHLIGHTS

BY JOHN PAASCH, IWMF RESEARCH COMMITTEE,  
GUY SHERWOOD, MD, IWMF VICE PRESIDENT FOR RESEARCH  
SUE HERMS, IWMF TRUSTEE, IWMF RESEARCH COMMITTEE

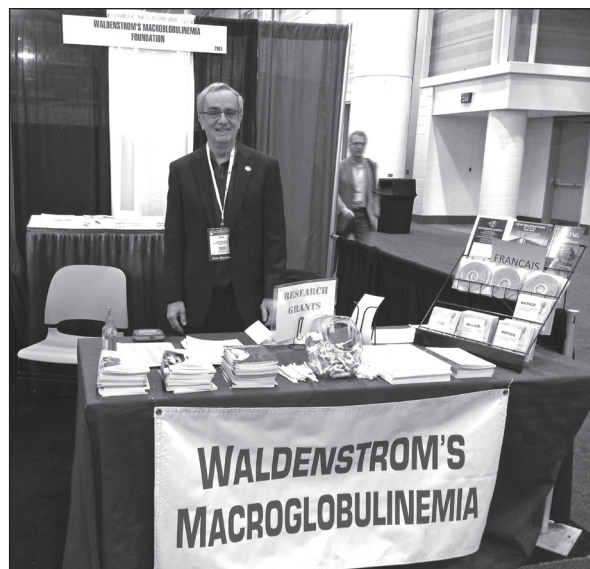
*The 55th Annual Meeting of the American Society of Hematology (ASH) was held on December 7-10, 2013, in New Orleans, LA. The IWMF staffs a booth each year at this conference which attracts hundreds of clinicians and researchers, as well as exhibitors from pharmaceutical companies, medical technology industries, and patient advocacy groups. The IWMF was represented by Dr. Robert Kyle, Trustee and Chair of the Scientific Advisory Committee (SAC), President Carl Harrington, and Sara McKinnie and Julie Jakicic from the Business Office.*

*This year a greater number of abstracts focused on WM than in previous years, and in fact six were chosen for oral presentations by the ASH Program Committee. The abstracts are organized here into the topics Basic Biology and Genetics of WM, Diagnosis and Prognosis, Familial WM, Newer Investigational Therapies, and Clinical Trials.*

*An important note on molecular nomenclature: names of biological molecules are often confusing and distracting, for example TAK1, IRAK, TRAF6. It may help the reader to pay less attention to these names and instead develop an awareness that they refer to molecules implicated in a series of chemical reactions, sometimes very long and complicated, leading to biological effects. Such reactions are referred to as cascades or pathways and can be visualized as comparable to falling dominoes.*

### BASIC BIOLOGY AND GENETICS OF WM

A few years ago the IWMF and the Leukemia & Lymphoma Society funded research to develop a cell line representative of WM that could be shared with others who wish to study the disease. Dr. Asher Chanan-Khan, now from Mayo Clinic, was successful; his cell line is identified as RPCI-WM1. A multicenter study presented by **Kasyapa S. Chitta, PhD, et al.** from Dr. Chanan-Khan's lab described how cells from this line were introduced subcutaneously into mice to create tumors that secreted the human form of IgM. Experiments evaluated the pharmacodynamics of a developmental drug labeled compound X and demonstrated that the drug was effective in reducing the size of WM tumors and the IgM level. Equally important was the observation that RPCI-WM1 cells can be used in mice to induce tumor growth which mimics the IgM-secreting clinical disease model, making this a valuable platform to perform preclinical evaluations and comparative analyses of different drugs in WM.



President Carl Harrington mans the IWMF booth at ASH 2013.

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*ASH 2013 Highlights, cont. from page 1*

The MYD88 L265P genetic mutation, noted in up to 90% of WM patients, was once again the subject of numerous oral presentations and posters at this year's ASH meeting. **Anne J. Novak, PhD, et al.** of Mayo Clinic described the activation of the TAK1 molecule, an important component of the pathway that activates NF- $\kappa$ B, which plays a key role in regulating the immune response to infection and other stressful stimuli. Using cell line models, she found that a complex is formed with MYD88 L265P and the molecules IRAK and TRAF6, resulting in activation of TAK1 and NF- $\kappa$ B. Dr. Novak introduced a selective TAK1 inhibitor and found that it was able to inhibit cell proliferation in cell lines expressing MYD88 L265P. The result was reduced cell growth and survival. This study suggests that targeting TAK1 may be an effective strategy for the treatment of WM cells that contain the MYD88 L265P mutation.

**Guang Yang, PhD, et al.** from Dana-Farber Cancer Institute (DFCI) investigated pathways directed by the MYD88 L265P mutation, in particular the Bruton's tyrosine kinase (BTK) signaling pathway that plays a crucial role in B-cell maturation and the PI3K/AKT pathway that regulates cell growth, survival, differentiation, motility, and intracellular trafficking. The BTK pathway is directed by MYD88. Dr. Yang was able to identify the pathways and signaling proteins affected by the MYD88 L265P mutation and tested inhibitors of this pathway, including the PI3K inhibitor CAL-101 (also known as idelalisib or GS-1101), to induce robust tumor cell killing. When CAL-101 was combined with the BTK inhibitor ibrutinib, synergistic killing of WM cells was demonstrated.

**Mariateresa Fulciniti, PhD, et al.** from DFCI described results of a multicenter study of the role of SP1 in WM. The SP1 protein, which can be an activator or a repressor of gene transcription, is involved in many cellular processes. Dr. Fulciniti reported that SP1 is a very active transcription factor, by 5.8-fold, in WM. Introduction of the inhibitor terameprocol (TMP) reduced the level of SP1 in WM cells and halted proliferation and viability of the cells, while also inhibiting IgM secretion. This study then looked at the effect of TMP on the NF- $\kappa$ B pathway, which is of special interest in WM. The activity of NF- $\kappa$ B increased over the nominal level after introduction of SP1 but then decreased below the nominal level when TMP was subsequently added. Given the present interest in the NF- $\kappa$ B pathway and the positive effects seen with ibrutinib, Dr. Fulciniti evaluated possible synergistic effects of treating the cells with TMP and either ibrutinib or other pathway inhibitors. For each combination of inhibitors and TMP, the proliferation of the WM cells was decreased in a dose-dependent fashion. These preclinical results suggest consideration for a clinical trial evaluation of TMP in combination with inhibitors of the MYD88 and NF- $\kappa$ B pathways.

**Aldo Roccaro, MD, PhD, et al.** from DFCI looked at the role of a mutated version of the CXCR4 gene in WM. CXCR4 is a receptor protein that normally resides on the

*ASH 2013 Highlights, cont. on page 3*



The IWMF *Torch* is a publication of:

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

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

surface of a cell and plays a role in its movement throughout the body. The CXCR4 mutation is yet another mutation discovered as a result of the whole genome sequencing effort at DFCI, partially funded by the IWFMF. This multi-center study determined that 28% of 131 WM patients carried the mutation, which was also present in IgM-MGUS at a similar rate, but was minimally or not at all present in the other forms of lymphoma evaluated. After injecting mice with WM cells that had the mutated and unmutated versions of the CXCR4 gene, Dr. Roccaro reported in both instances a significant dissemination of the injected WM cells to several locations in the mice. However, this effect was more pronounced with mice carrying the mutated version. Using WM cell cultures which included cells from the bone marrow microenvironment, Dr. Roccaro demonstrated that the cells with the mutated version of the CXCR4 gene exhibited increased adhesion and cell proliferation and that eliminating the CXCR4 gene consequently reduced both. A novel anti-CXCR4 monoclonal antibody exhibited anti-WM activity in cell cultures and in the injected mice. These results suggest that the mutated version of the gene for CXCR4 may be an “activating” mutation in WM. Dr. Roccaro was recently awarded an IWFMF research grant to further study the CXCR4 mutation in WM.

**Stephen Ansell, MD, PhD, et al.** of Mayo Clinic, in research also supported by the IWFMF, studied the interaction between PD-1 (programmed cell death protein 1) and its two ligands, PD-L1 and PD-L2. (A ligand is a protein molecule that binds specifically and reversibly to another molecule to form a larger complex.) This interaction plays a major role in immune responses and suppresses activated immune cells, especially T-cells. Dr. Ansell examined this interaction in the bone marrow of WM patients. Using bone marrow samples collected from six WM patients, he found that the level of PD-1 was comparable to non-WM bone marrow, but the presence of the two ligands PD-L1 and PD-L2 was much higher in the WM bone marrow. These ligands appeared not only in WM B-cells but also in dendritic cells, monocytes, and macrophages in the bone marrow environment. Dr. Ansell introduced these two ligands into a cell line that readily accepts genetic modification and co-cultured the modified cells with three WM cell lines as well as samples from WM patients. Dr. Ansell was able to show that PD-L1 and PD-L2, increased WM cell proliferation and viability and concluded that inhibition of PD-1 signaling may be a promising therapy in patients with WM.

**Barbara Muz, PhD, MSc, et al.** reported results of an IWFMF-funded grant to Dr. Kareem Azab at Washington University in St. Louis to investigate the role of hypoxia (reduced level of oxygen concentration) in WM. The bone marrow microenvironment is typically more hypoxic compared to the blood in the peripheral circulation. Dr. Muz showed that under hypoxic conditions the WM cells are not as proliferative, yet they do not die. Hypoxia also changed expression of certain proteins; in particular, CXCR4 was increased and E-cadherin was decreased. The former promotes increased cell movement while the latter reduces the adhesion of WM cells to the bone marrow stromal cells. The combination of

increased CXCR4 and reduced E-cadherin induced the WM cells to leave the bone marrow and disseminate.

**Matthew S. Neil, BS, et al.** presented research results on the role of the transcription factor GLI2 in bone marrow stromal cells. Transcription factors are molecules that enter the nucleus, attach to certain genes, and initiate the process to either make more or less of the proteins associated with those genes. The bone marrow microenvironment is required to support the existence of WM cells, and one of the microenvironment “signals” that supports the WM cells is the ligand for CD40, identified as CD40L. CD40 is on the surface of WM cells, and activating it with CD40L leads to cell proliferation. Mr. Neil was able to show that the production and release of CD40L into the microenvironment is influenced by GLI2 from stromal cells. Meanwhile, **Joel R. Dennison et al.** studied the role of GLI2 originating from WM cells. By controlling the amount of GLI2 within WM cells, he noted that the amount of IgM secretion could be altered. His research found that GLI2 affects the production of the surface receptor IL-6R, which is part of the IL-6 signaling cascade in WM cells that results in IgM production. Both researchers are members of Dr. Sherine Elsawa’s lab at Northern Illinois University. Dr. Elsawa, who previously worked in Dr. Stephen Ansell’s lab at Mayo Clinic, was awarded an IWFMF research grant in late 2013.

The DFCI Bing Center for WM continues to analyze the data collected from the whole genome sequencing of WM patients. **Zachary Hunter et al.** reviewed the common 6q chromosomal deletion found in WM. The “6q del,” a loss of a particular segment of the chromosome, results in correspondingly lost genes. Large-scale 6q deletions were found in 50% of the WM patients studied, but more frequent, smaller deletions were also discovered in this chromosome. The study identified a fourfold increase in the number of these smaller deletions, which are strongly associated with pathways commonly dysregulated in B-cell malignancies – the absence of these genes may lead to the development or progression of WM. Of interest was the finding of fewer deletions in patients who had the mutation in the gene for CXCR4 (believed to confer worse prognosis in WM patients). Many other genetic abnormalities and structural variants were found. The significance of each of these alone or in combination has yet to be determined.

**Bruno Paiva, PhD, Hospital Universitario de Salamanca, Salamanca, Spain, et al.** investigated phenotypic and molecular differences among clonal B-cells from IgM MGUS, smoldering WM (SWM), and symptomatic WM patients in order to discover the mechanisms of malignant transformation. This multi-center Spanish study found a complete overlap between the immunophenotypic expression profiles among clonal B-cells from the three groups. Clonal B-cells from IgM MGUS patients already showed some of the genetic features typically associated with more advanced stages of the disease. Dr. Paiva next looked at the molecular level, where preliminary analysis of gene expression profiles among clonal B-cells from IgM MGUS, SWM, and WM patients found little difference in deregulated genes. This





study also compared bone marrow cells from IgM MGUS, SWM, and WM patients to normal bone marrow cells. Comparing clonal cells to normal CD22<sup>+</sup>/CD25<sup>+</sup> B-cells, he found deregulation of 776 genes. Dr. Paiva also compared the clonal cells to a small subset of normal B-cells that present a CD22<sup>low</sup>/CD25<sup>+</sup> profile (typical of the WM phenotype), and discovered 185 genes deregulated in the clonal B cells. In summary, these results show that clonal B-cells from IgM MGUS patients already have a molecular profile that overlaps with those of WM and suggest that the WM clone may arise from normal CD22<sup>low</sup>/CD25<sup>+</sup> B-cells.

**Brian T. Gaudette from Emory University et al.** presented a complex international study on the heterogeneous expression of Bcl-2 proteins in WM and how they determine the response to inducers of intrinsic apoptosis (cell death). Bcl-2 and related proteins are key regulators of apoptosis. The researchers found that WM cell lines are not sensitive to Bcl-2 inhibition. They also showed that there are multiple and distinct differences in Bcl-2 family protein expression that lead to this insensitivity. These studies demonstrate that sensitivity to agents that kill through the intrinsic apoptotic pathway may vary within a disease that is characterized by a single activating mutation and suggest that additional diverse and distinct events regulate the expression of the Bcl-2 family of proteins.

As the result of a multi-center Italian study, **Alessandra Trojani, PhD, Niguarda Hospital in Milan, Italy, et al.** presented a poster on the characterization of genes and pathways of B-cells and plasma cells from the bone marrow of WM patients, compared to those from IgM-MGUS patients and from healthy subjects. The comparison of CD19<sup>+</sup> B-cells highlighted many differentially expressed genes. Genes involved in alternative splicing, cell cycle, protein phosphorylation, immune response, cell adhesion, and the negative regulation of transcription were progressively under-expressed in normal vs. IgM-MGUS vs. WM. The comparison among the CD138<sup>+</sup> plasma cells of the three groups demonstrated that 12 genes were under-expressed in WM. It was noted that IgM-MGUS plasma cells appear to be similar to the normal plasma cell counterpart.

**Yang Cao, MD, et al.** from DFCI reported on research efforts into the role of CXCR4 and the mutation in this gene that occurs in approximately 30% of WM patients. CXCR4 binds to the ligand CXCL12 present on cells within the bone marrow and plays a key role in the movement of WM cells within the body. The mutation identified in the gene results in decreased internalization and degradation of the CXCR4-CXCL12 complex, leading to promotion of WM cell survival and proliferation. Dr. Cao was also able to demonstrate that the positive response to ibrutinib therapy was diminished in patients who had this mutation in the CXCR4 gene. Knowing whether or not one has this CXCR4 mutation may help to determine the efficacy of certain treatments, including ibrutinib.

## DIAGNOSIS AND PROGNOSIS

Though the MYD88 L265P gene mutation appears in the great majority of WM patients, some do not carry this mutation. **Nikhil Patkar, MD, et al.** from the Tata Memorial

Centre, Mumbai, India, looked into the distinct clinical and biological features of those who do and do not exhibit this mutation. This retrospective study of 32 WM cases looked at somatic hypermutations (SHM) in the genes used for the production of IgM. These results showed that 96% of the cases demonstrated SHM, and the most common gene involved was IgHV3.7 (27.3%) followed by IgHV1-18 (18.2%). Twenty seven of the 32 patients (84.3%) studied had the MYD88 L265P mutation. Comparing these two groups, the unmutated group presented later in life with lower bone marrow infiltration and a more favorable ISSWM prognostic score. Dr. Patkar also performed a treatment response analysis on 23 of the 32 patients. Patients without the MYD88 mutation fared much better than those with the mutation. At the most recent follow up period, 44% of patients with the mutation had progressive disease, whereas patients without the mutation had no change from their initial post-treatment status.

**Efstathios Kastiris, MD, National and Kapodistrian University of Athens in Greece, et al.** presented a poster that showed a relationship between the serum levels of von Willebrand factor antigen (vWF-Ag) and the prognosis of patients with symptomatic WM. This factor is a normal constituent of the blood plasma, and its primary function is to promote platelet adhesion, prevent excessive bleeding, and lead to wound healing. It has been suggested that abnormally high levels of vWF-Ag are associated with adverse prognosis in patients with symptomatic WM, as vWF-Ag levels may reflect interactions between WM cells and other cells of their microenvironment. This Greek study analyzed the levels of vWF-Ag in 42 WM patients, who were symptomatic but had not received treatment. WM patients who were within the upper levels of vWF-Ag (defined as  $\geq 200$  U/dL) had a median progression free survival of 12 months vs. 63 months in patients with vWF-Ag  $< 200$  U/dL. It was noted that patients with elevated vWF-Ag also had elevated serum  $\beta$ -2 microglobulin levels. There was no correlation of vWF-Ag levels with IgM levels, with the extent of bone marrow infiltration, or with other disease manifestations. The study concluded that vWF-Ag levels may become an important prognostic marker in WM.

Since a bone marrow biopsy (BMB) can be an unpleasant and at times painful procedure, **Lian Xu et al.** at DFCI focused on determining whether the common MYD88 L265P mutation in WM patients can be found in WM cells that are circulating in the peripheral blood. This study was able to correlate the identification of the MYD88 L265P mutation in peripheral blood with the bone marrow in WM and IgM-MGUS patients using allele-specific polymerase chain reaction techniques (AS-PCR), particularly in untreated patients. The detection of MYD88 L265P by CD19-selected peripheral blood AS-PCR examination may provide a convenient and less invasive method to support the diagnosis of WM and IgM-MGUS.

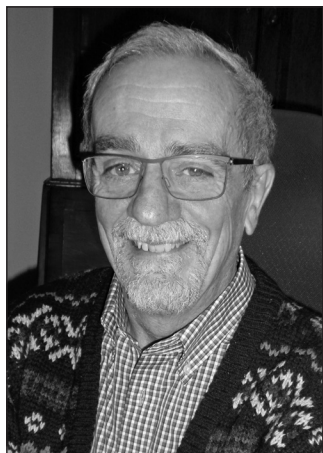
One of the requirements for a WM diagnosis is the presence of a monoclonal IgM component. In response to an antigen, normal IgM antibody is altered through a genetic process called somatic hypermutation (SHM). The normal B-cell



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## PRESIDENT'S CORNER

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Brrr! We had a nasty winter in Philadelphia and in the entire eastern part of the US in 2013-2014 (so nasty that I gave in to my wife's demand and grew back the goatee she claims to love).

Thank goodness, winter is over and spring is here! Spring is my favorite season, is it yours, too? It's not simply the beginning of warm weather – I love seeing the flowers and new growth spurting up everywhere.

New growth is everywhere at the IWMF, too. In fact, the theme of this year's IWMF Educational Forum in Tampa, Florida, is *Imagine a Cure: Seeds of Hope*. What do we mean by *Seeds of Hope*? We mean changes that will make life better for WMers everywhere as we move closer to our goal of finding a cure. Changes such as:

- All of the exciting progress reported at the convention of the American Society of Hematology last December. The article begins on page 1 of this issue and summarizes the many new research findings reported at the convention. We've never made so much progress in so short a time.
- The increasing number of WMers in the US who are on ibrutinib, the first cancer drug to win Breakthrough Therapy Designation for WM from the FDA (Food & Drug Administration). Don't miss the breakout session at the Ed Forum where WMers who have been treated with this new drug will share their experiences.
- Funding was just approved by the IWMF Board of Trustees for a new research study of the CXCR4 genetic mutation that affects 28% of WMers. It appears that the CXCR4 mutation may be involved in the more serious cases of WM. Dr. Aldo Roccaro from the Dana-Farber Cancer Institute will run this new investigation.
- A new IWMF website is in the works, one that will be even easier to use so you can find the information you need faster. Look for it by early summer.

- A new updated edition of our *Basic Immunology* booklet revised by Dr. Guy Sherwood. Look for this around the Ed Forum and stay current with the fast changing world of WM.

What seeds of change will you personally plant this spring to make the rest of 2014 and beyond better? How about:

- Asking your friends and family to support you and the IWMF by making donations to the IWMF? Since we're a rare disease, we need the help of everyone! My wife, our son, and several of our friends just donated to the IWMF in honor of my sixty-fourth birthday. Those were my favorite presents.
- Attending the IWMF Educational Forum in Tampa from May 16-18. If you haven't registered, there's still time. Come and hear the latest developments in WM. The array of speakers is our best ever. See the registration form on page 25 of this issue or go to [www.iwmf.com/services/ed-forum.aspx](http://www.iwmf.com/services/ed-forum.aspx) to register now.
- Attending the Fifth International IWMF Doctor-Patient Forum in London on August 17. The Forum will follow IWWM8, the eighth International Workshop on Waldenström's Macroglobulinemia that will bring together leading researchers from all over the world. Dr. Steven Treon and other researchers participating in IWWM8 will share the breaking news from the research world of WM. Roger Brown of the WMUK is coordinating the Forum, see page 19 of this issue. You can go to [www.wmuk.org.uk/shop/ticket](http://www.wmuk.org.uk/shop/ticket) to register now.
- Volunteering your skills and talents to help the IWMF, at your local support group or in your country. Whatever your special talents may be, let your support group leader or Sara McKinnie at the IWMF office know about them (941-927-4963).
- Thanking your caregivers more often. Where would we be without them?

Above all, let's work together in 2014 to plant the *Seeds of Hope* for WMers everywhere.

Stay well!

I hope to see you in Tampa or London,  
Carl



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## NEWS FROM THE IWMF BOARD

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Two changes of note occurred in the IWMF Board in the last half of 2013. Board member Elena Malunis became Vice President of Member Services over the summer, and in the fall Marlyn Friedlander joined the Board. Each brings special skills and experience to the IWMF in addition to a deep commitment to volunteerism.

**Marlyn Friedlander** joined the IWMF Board of Trustees as a member of the Fundraising Team in November of 2013, bringing with her considerable success in fundraising for organizations in the Seattle area, including Congregation Beth Shalom, the Seattle Symphony, the Seattle Academy, and the Seattle Biomedical Research Institute. As Marlyn herself comments, “I have been a community volunteer my whole life.”

For the Seattle Biomedical Research Institute, as member of the executive board and chair of the development committee, Marlyn was co-chair of their successful capital campaign to build a high containment tuberculosis laboratory. For Congregation Beth Shalom she served as co-chair of the capital campaign for new building, and for the Seattle Academy (an independent middle and high school) she directed the successful capital campaign to build a new gymnasium.

Born and raised in Montgomery, Alabama, Marlyn moved to Seattle in the mid-1970s to attend the University of Washington and has made her home there ever since. She is married to Gilbert Scherer, and they have three adult children.

From 1975-1980 Marlyn worked in the field of community health at a “free clinic” delivering care to low-income seniors and families. Her own interest lay in community outreach and hospice care. In later years she became an active participant in family marketing ventures, mainly in the area of human resources and benefits administration.

Among her hobbies Marlyn lists hiking, swimming, cooking, and travel.

To the IWMF’s *Imagine a Cure* Campaign, Marlyn brings her experience and enthusiasm – and a large amount of both.

**Elena Malunis** joined the IWMF Board of Trustees in 2012 and in 2013 became Vice President of Member Services. Elena brings to the IWMF experience drawn from a career of high achievement in the world of business and marketing, accompanied by a vision of expanding the outreach of the IWMF and improving its services to all members.

With a Bachelor of Science granted summa cum laude from Hunter College and a Master of Science in mathematics from the Courant Institute at NYU, Elena embarked on a career at IBM of more than thirty years, during which time she steadily advanced through marketing and management positions of increasing importance. When Elena retired from IBM she had held the position of Global Director of Wireless e-Business for two years. Retirement opened new opportunities for her as co-founder and managing partner of a small, privately held management consulting firm providing marketing and strategy assistance to multi-national technology companies. At present she is a busy independent consultant in marketing strategy and services to small and medium size companies in the US, Canada, and Europe.

When not traveling for business or pleasure, Elena and her husband reside in the picturesque Village of Sleepy Hollow in Westchester County, NY, where she is an active volunteer in her community. Elena is particularly committed to a local pre-school and after-school program established for non-English speaking youngsters.

For the IWMF, the new Vice President for Member Services is focused on “keeping all the wonderful services up-to-date and moving forward with changing technology and evolving needs.” Since joining the Board she has worked to realize the implementation of Google Translate for our website (in order to provide access for WM patients all over the world in their native language) and to promote a translation program of the IWMF booklet series into other languages in addition to English, starting with Spanish. And between now and the Ed Forum in May she will be involved in all aspects of the new website.

We are fortunate indeed that Elena has added the IWMF to her volunteer commitments, as we will all benefit from her experience, energy, and vision.





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# TREASURER'S REPORT AS OF DECEMBER 31, 2013

BY CYNTHIA RUHL, IWMF TREASURER AND SECRETARY

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The finances of the IWMF are accounted for through two separate funds. The Research Fund is used solely to provide research grants for projects that our Research Committee has reviewed and recommended. Our Member Services Fund provides for all of our outstanding services for members, including the Educational Forum, the website, and the *Torch*. Both funds are critically important to the work of the IWMF.

The following is a summary of the financial results for 2013. The amounts are rounded to the nearest thousand and have not yet been audited. However, I wanted to share with you where the IWMF stands financially through 2013.

	Research	Member Services	Total
Revenue	\$ 528,000	\$ 767,000	\$ 1,295,000
Expenditures	\$ 539,000	\$ 613,000	\$ 1,152,000
Net Income	\$ -11,000	\$ 154,000	\$ 143,000

We are so grateful for your generous support through the end of 2013. As a result, in 2014 we have been able to expand our member services with upcoming enhancements to the website, four issues of the *Torch* for 2014, and revisions of some of our literature. The Board also recently approved an important research grant.

At the end of December 2013, our cash reserves for the Research Fund are \$685,186 and for the Member Services Fund, \$356,811. We also received a generous contribution of land in 2013, which has not yet been sold.

As a Board member, I can assure you that we do our very best to make certain that every dollar given is wisely spent on serving you, our members, and keeping important research moving forward. Thank you for your continued support!

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## IWMF RESEARCH NEWS

BY GUY SHERWOOD, M.D., IWMF VICE PRESIDENT FOR RESEARCH

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At the most recent meeting of the IWMF Board of Trustees held in Tampa, Florida, on February 7-9, a new two-year research project was approved for funding by the IWMF Board of Trustees, consistent with our mission to help advance the cure for WM. Dr. Aldo Roccaro of the Dana-Farber Cancer Institute (and colleague at DFCI of Dr. Irene Ghobrial) was awarded a research grant for his project "Further genomic characterization of Waldenstrom's macroglobulinemia: unveiling the role of the CXCR4 somatic mutation, a crucial regulator of pathogenesis and important target for therapy."

Dr. Roccaro's proposal is based on the hypothesis that mutations in the CXCR4 gene, which codes for the Chemokine Receptor type 4 (CXCR4) that is implicated in the direction of hematopoietic precursor cells in the bone marrow, may lead to the spread of WM cells to distant organs (for example, the lymph nodes, liver, spleen) and to increased WM cell growth, resulting in worsening disease burden.

Dr. Roccaro's research project will study WM patients who have WM cells outside the bone marrow (extramedullary WM) and further characterize whether or not mutations of the CXCR4 gene occur in such patients. The aim is to identify new pathways of disease progression and newer, more powerful, targeted WM treatment(s).

The mutated CXCR4 gene has already been confirmed in up to 30% of WM patients. Confirmation seemingly confers a worse prognosis. Active research on the mutated CXCR4 gene

is currently conducted in WM, hypogammaglobulinemia, and in more than twenty-three other cancers, including breast and lung cancer.

Dr. Roccaro's research will provide much needed new insights into the biology and genetics of WM and will, most importantly, provide the necessary pre-clinical evidence for targeting CXCR4 mutated cells using new anti-CXCR4 drugs. It is hoped that his research will be quickly translated into clinical trials for the treatment of WM patients with anti-CXCR4-based drugs, used either alone or in combination with other conventional anti-WM therapies.

Donate and Participate!

*Guy Sherwood is a 13-year-plus survivor of WM. Diagnosed in early 2001 at age 40, Dr. Sherwood has considerable experience with many different treatments for WM, has participated in two clinical trials, and underwent an autologous bone marrow transplant in 2006. Guy quickly became involved in the IWMF after his diagnosis and has served on the Board of Trustees and on various committees for many years. Recently elected IWMF Vice President for Research in November 2013, he succeeds Tom Myers, Ph.D. Guy is the Medical Director of the busy Palliative Care Program at Indiana University Health Ball Memorial Hospital in Muncie, Indiana.*



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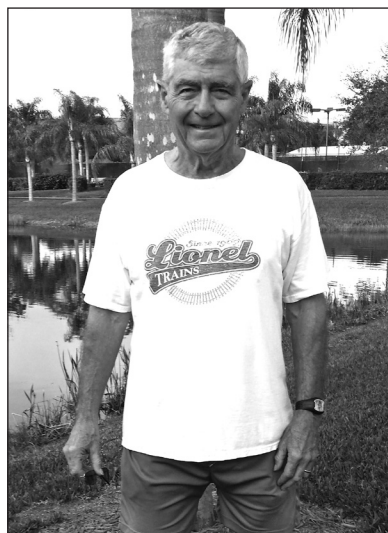
# MY WM STORY

BY BOB SHAFFREY, IWMF MEMBER

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*Diagnosed with symptomatic Waldenstrom's macroglobulinemia more than a decade before the introduction of Rituxan as an effective drug to treat WM, Bob Shaffrey elected to try a new "designer drug." After four rounds of 2CdA, treatment was halted when the side effects became life threatening. Gradually, however, his blood counts climbed back to a normal range, and ever since (for eighteen years) Bob Shaffrey has lived a full life free of cancer.*

I was diagnosed with Waldenstrom's macroglobulinemia in June of 1995 at the age of 56. In May I had tried to donate



*Bob Shaffrey, the very picture of good health, on vacation in Florida, February 2014.*

blood, as I had done many times during my life. When the drop of blood from the pinprick failed to sink in the test tube, I was told that I could not donate that day and was referred to my family doctor to check the iron level in my blood. My primary care physician in turn referred me to a hematologist who put me through a seemingly endless series of tests. When the results were in, the hematologist phoned me and told me that I

had either chronic lymphocytic leukemia (CLL), or multiple myeloma, or Waldenstrom's macroglobulinemia. In any event, I had some sort of cancer. What a surprise. I immediately felt I had been handed a death sentence! It's tough to put into words what you feel. From that phone call on, it was as if I had a cloud over me.

Later, still in early June as I recall, WM was confirmed with an IgM of 3000 and an abnormal paraprotein, I believe he said. I had a bone marrow biopsy to reconfirm the diagnosis. The hematologist believed the disease was caught early and suggested that I had it for eighteen months or so.

My symptoms included anemia, night sweats, peripheral neuropathy in my legs, nosebleeds, low energy, and fatigue –

a feeling as if I had low-grade flu all the time. I was an avid jogger, and before I was diagnosed I had noticed that my times were getting slow. I just figured it was part of growing old. My hemoglobin level at diagnosis was in the low 10's.

Once the diagnosis was made, my wife Mary Ann and I went to the University of Pittsburgh Medical School library to learn about WM. As this was before the Internet was available, the only source of information was a medical library. I remember that we looked in the Merck manual and saw that the average length of survival was 2–5 years. Again we learned some sad news!

At this point, still in June, the hematologist, Mary Ann, and I had a meeting to discuss options. The doctor gave me three. One: to do nothing, to watch and wait and see what developed. Two: to receive what was at that time, as I remember, the standard treatment of either chlorambucil or an alkylating agent of some kind. Three: to receive a "designer drug," as the doctor called it, the use of which had just been reported with excellent results by Dr. Meletios Dimopoulos at M.D. Anderson to treat hairy cell leukemia. The drug was reported to have produced durable remissions in some WM patients. I asked the doctor what he would do in my place, and he said that he would take the 2CdA (the "designer drug"). I replied, "OK! Let's do it!"

A battle with the insurance company followed. At first the company did not want to cover the cost because 2CdA was not FDA-approved for WM. Eventually coverage was granted, and by late June I had an operation to install a Hickman port in my left shoulder area and, as I remember, a procedure to stop the nosebleeds.

Still in late June, a nurse came to my house and installed the chemo bag, which I wore around my waist. This was a 24/7 infusion of 2CdA. I was still working at the time, and I did not want to show this bag to people at work so I wore a loose Hawaiian type shirt with the shirttail out. I had told my boss about my condition and was on a part time schedule at the time, as few as 8 hours a week, as I recall. But I did not want to expose the bag and did not want to share the diagnosis with others at work. The only people I told were immediate family and close relatives and friends. I remember that my Mom added my name to the prayer list at her church.

*My WM Story, cont. on page 9*

## 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 *Torch* editor Alice Riginos at [ariginos@me.com](mailto:ariginos@me.com)





From late June until October, I received four 7-day courses with three weeks off between them. Each treatment was followed by self-administered injections in the thigh of Neupogen to restore the WBC count. My blood was checked twice a week. Following the first three courses, my counts returned to “normal” by the end of the 3-week interval. Then, at the end of the fourth course, none of the counts rebounded. The condition was described as pancytopenia, “cells of all types low.”

From October until February, I was given twenty units of blood – packed red blood cells (RBCs) – to keep my energy up. During this time, I administered Procrit injections in my stomach, to stimulate RBC production, although I don’t think it worked for me. My red blood cells hit a low of 1.6, hemoglobin was 6.0, hematocrit was 17.9, and platelets were 12,000. The doctor told me not to do any work on my workbench out of concern that a cut would cause bleeding and be difficult to stop. A couple of times I was so weak that I could hardly walk half a block. I distinctly remember watching someone walk down the street and thinking enviously, “That person is taking that walk for granted, not even thinking about it. What a gift it is!”

If my counts had returned to “normal” after the fourth course, the plan was to give me as many as six or seven courses, the regimen that had been administered to CLL patients and others with similar diseases. My doctor certainly took a very aggressive approach to my treatment. He had lost his mother to cancer.

Finally, during an office visit in early February of 1996, my doctor said, “I think your counts are coming back.” In April 1996, 11 months after diagnosis, my IgM was in the normal range, and the other counts were steadily improving. I was in remission. Remembering back, I felt as if the disease had left me, and, for the first time in a long time, I felt unburdened from that “stuck in second gear” feeling and energy returned. There were lots of prayers from relatives and friends (and me!) that were answered. I thanked the Lord for answering all those prayers.

In July of 1997 my counts were: white blood cells 3.9, red blood cells 3.47, hemoglobin 12.8, hematocrit 39.1. After a few years of quarterly check ups with my counts remaining in the normal range, I was scheduled every six months, then annually. There was always the feeling that this wonderful bubble would pop at some point, and I would slip out of remission. At one visit a few years back, the doctor declared I was “cured” of WM. I asked how this could be so, since this is an incurable disease. He said he was aware of instances, where if one has an aggressive form of lymphoma and you hit it hard with chemo early on, you can sometimes cure it. I think he was theorizing that although WM is an indolent disease, I probably had an aggressive case of it. His theory worked for me. And at my last visit in April 2013, he said I did not need any further follow-up from him and recommended that I be followed on a routine basis by my family physician and cardiologist.

Since April 1996, for 18 years, I have maintained normal energy, allowing me to exercise daily and vigorously, getting my heart rate into the 140’s.

At the time of my April 2013 visit, I had a white blood cell count of 4.3, a hemoglobin level of 13.3, hematocrit of 38.0, and a platelet count of 173,000. Serum chemistry showed the potassium level as 4.1 and creatinine as 1.1. Liver function tests were normal. Quantitative immunoglobulins were normal with an IgG of 740, IgA 81 and IgM 113. And my absolute CD4 count has finally returned to normal at 524. I remember that Arnie Smokler, God rest his soul, advised me to get this test regularly. It took many years for this to return, because of the long-term suppression caused by the 2CdA.

I thank the Lord every day for this remarkable recovery. I regularly attend cancer support meetings to offer inspiration and hope to those with cancer. And for ten years I co-chaired with Shariann Hall the IWWMF support group known as the Western PA, Western MD, Eastern OH, and Northern WV group.

I’ve made many friends in these groups, some who are no longer with us. This is my way of giving back, and it has been very fulfilling.

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## FROM IWWMF-TALK

BY JACOB WEINTRAUB, M.D.

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While this has been an extremely cold winter in many parts of the country, the conversations on IWWMF-Talk have continued to be warm and cordial, with some heated discussions about topics both old and new. We have discussed such familiar topics as stem cell collection, fatigue, and Rituxan. Ibrutinib (now to be known as Imbruvica, its brand name) has continued to be a major focus of discussion, as has treatment with bendamustine. Ibrutinib was addressed in a separate article

in the January *Torch*, but I will add some complementary discussion and information.

### IMBRUVICA/IBRUTINIB

Discussion focused on reports of ongoing treatments and of experiences with insurance companies provided by IWWMF-Talk contributors. Those reporting treatment results up to now are all receiving Imbruvica in clinical trials. Only

*From IWWMF-Talk, cont. on page 10*

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very recently have a few other WMers commented on their experience in seeking insurance coverage for the high cost of this most promising drug.

**Mitch O** weighed in on his ongoing trial of ibrutinib. After 18 months of treatment, his most recent lab tests showed IgM continuing to be lower and other labs within normal range. Mitch is especially appreciative of being able to take pills instead of IV infusions. He now feels healthier than he has felt in 11 years since diagnosis.

One cautionary note came from **Michael L**. After an initial fall from 8000 to 6000, his IgM stabilized at around 5500 without any additional change, although his hemoglobin has improved. His bone marrow is still at 90% infiltration. Additionally, Michael has had some visual changes, and understandably this has worried him. In his most recent post Michael announced his intention to withdraw from the Imbruvica/ibrutinib trial and to begin another treatment following consultation with Dr. Ghobrial.

**John K** reported that ibrutinib treatment is not covered by Medicare Part A or B but is covered by Part D. Coverage by Part D involves the so-called “donut hole” which refers to increased patient payment up to a specified amount. Once a patient has paid the amount specified by Part D coverage, the insurance company covers the majority of the cost. Copay, however, can be very significant.

**Billie E** commented that because the medication is a pill, another issue is whether or not the state in which a person lives is an “oral parity” state. If one lives in an oral parity state, Imbruvica/ibrutinib will be covered. For example, Texas and New York are oral parity states, and Medicare supplement insurance plans have covered ibrutinib for WM in those states. Some private insurance companies, including Group Health Cooperative in Washington State, also have covered Imbruvica/ibrutinib.

A “Patient Access” program, as reported by **Anita L**, is supported by Pharmacyclics, the company marketing ibrutinib. Initial enrollment is for a one year period and is handled through the patient’s own insurance. This program lowers the co-pay to \$25. Anita was enrolled in a matter of days following submission of her application.

**Scott K**, however, reported a problem with gaining insurance approval for treatment with Imbruvica. Approval was initially denied by his insurance company. The rejection letter indicated that the information submitted to the company did not show that other formulary alternatives had been tried and did not state whether they were effective. Scott has had multiple prior treatments for WM, but neither he nor his oncologist understood that it was necessary to document his treatment record in the application. Scott next contacted his oncologist’s office and the appropriate documents were submitted. His insurance company then gave approval.

## **IVIG (INTRAVENOUS GAMMA GLOBULIN)**

Although use of IVIG for our very compromised immune systems has been discussed multiple times, there continues to be useful information and discussion on IWMF-Talk.

**Pete DeNardis**, Board Trustee and our “List Dad,” reported his experience. Pete has low IgA and has often had significant reactions to the “standard” Baxter Gammagard Liquid 10% solution. After searching the literature, he found other formulations that are more tolerable for people with low IgG and IgA. His oncologist switched him to Gammagard S/D, which contains less IgA in the preparation. The doctor prescribed premedication similar to what had been previously used but in a more dilute preparation, causing slower infusion of med. With these changes Pete had absolutely no adverse reaction at all. He is currently scheduled to receive treatment every two months, so he is reserving judgment until at least the next infusion.

**Bonnie R** reported that she receives monthly IVIG. When she started WM treatment with Velcade, her IgM did not decrease. Her oncologist feels she was having an IgM flare from the IVIG that countered the Velcade treatment.

Others have also reported IgM flare with IVIG treatment. **Edward G** cited an article from Dana-Farber that reported IgM flares with IVIG treatment, especially in patients with low IgA. This flare is similar to a flare with Rituxan treatment.

## **CHEMICAL EXPOSURE**

One subject that crops up periodically is whether there are possible contributing factors to the development of WM in any particular patient.

**Leon** reported a career as a chemist, with exposure to chemicals and radioactive materials. He is not certain that chemicals can cause WM. His own review of obituaries of chemists and chemical engineers is notable for its absence of lymphomas in general and WM specifically.

However, **John K** is a retired chemist from the semiconductor industry who handled multiple chemicals of all types without much thought of preventing exposure. John now feels that his WM was related to this chemical exposure.

**Linda R** reported contact with many harsh chemicals over the last 15 years due to illegal dumping of chemicals into water and soil by a nearby company. Even a dog she was caring for has developed lymphoma.

**Dave B** indicated that speculation on the cause of WM really gets us “nowhere.” He needs to manage his WM and wants to focus on more currently important things such as medication costs. He also wants to focus on other areas such as improvement of life for WMers and better research.

**Julie D** expressed gratitude toward the WM researchers and their dedication to finding better treatments and a possible



cure. She feels their efforts will one day find a cure for future generations, and she spends little time contemplating the “who, what, when, and where” of her WM.

Former IWMF President **Judith May** suggested that everyone should be adding their chemical exposure to their data entered on the WM Patient Database. This will add to the overall data collection and help identify possible associations with various materials.

## REMISSION

There was some discussion of the meaning of “remission” in WM.

**Mitch O** offered the opinion that we tend to use the term to indicate a significant amount of relief from symptoms after treatment. We are aware that our “remissions” are partial and temporary, with considerable variance in the way we use those terms.

**Dr. Jacob Weintraub** suggested that complete remission is not a term correctly used in WM. For most cancers, “remission” is used to refer to the state of having no cancer detectable in a person. When a person is “in remission” for 5 years, it usually means that the person is “cured” of his or her cancer. In WM and other lymphomas, even when a treatment has produced a “complete response,” we generally acknowledge that WM is still present even if it is not detectable with the common testing we have available.

**Sue Herms**, Board Trustee, cited the Third International Workshop on WM. The recommendation from this group of physicians is that the preferred terminology is “response.” Remission usually implies an absence of disease markers, and this is very unusual in WM. The preferred terminology distinguishes between stable disease, minor response to treatment, partial response, and complete response. A complete response is characterized by the following: disappearance of serum and urine monoclonal IgM, absence of malignant cells in the bone marrow, resolution of enlarged lymph nodes seen on a CT scan, and no symptoms.

## SHINGLES

Finally, shingles (herpes zoster, often referred to simply as zoster) comes up for discussion on a regular basis in relation to diagnosis, treatment, and prevention.

**Hank S** reported that his wife developed a case of shingles and consulted with her family doctor, who made several recommendations concerning both the patient herself and her husband. The doctor recommended that Hank’s wife receive the shingles vaccine when she fully recovers. The physician also indicated that Hank would need to isolate himself completely from his wife for three full weeks after she receives the vaccine. Hank, he said, should not even be in the same house as his wife.

**Billie E** wondered why Hank would not simply take antiviral medication for the period of time after vaccination when his wife might be considered contagious. Billie questioned whether someone who had developed shingles might be immune from having shingles another time. She also questioned the efficacy of the shingles vaccine.

**Gerry W** reported that he has been taking acyclovir as a prophylactic measure for five years. Both Gerry’s local oncologist and Dr. Treon suggested stopping the med after a shorter time because the usual period for taking antivirals is only six months. However, given the potential seriousness of a shingles infection in an immunocompromised person (such as people with WM) both doctors have continued to prescribe acyclovir for Gerry.

**Hank** provided further information. He was already taking valcyclovir prophylactically after a course of Velcade. Hank’s dose of valcyclovir was lower than what would be prescribed for treatment. His local oncologist was again contacted for clarification, and he indicated that Hank was at higher risk from his wife’s current shingles outbreak than he would be if she had the vaccine. Transmission of zoster from the vaccine is a very rare event, and Hank’s oncologist cautioned that Hank would need to be in direct contact with any uncrusted lesions in order to develop a shingles rash.

Previous discussions have included cautions that patients with WM should not receive the shingles vaccine since it is a live virus vaccine.

There was much more detailed discussion about a variety of topics, with new and old members joining the conversations. Even those who are infrequent contributors voice their appreciation of the information and support from this group. Don’t hesitate to become a member.

## HOW TO JOIN IWMF-TALK

Here are two ways to join:

1. Send a blank e-mail to: [iwmf-talk-subscribe-request@lists.psu.edu](mailto:iwmf-talk-subscribe-request@lists.psu.edu)  
Make sure to enter the word “subscribe” as your subject, and do not sign or put anything in the message area (make sure you do not have any signature information in there). Also, do not put a “period” after “edu” or it will reject. Once approved you can post by sending e-mail to [iwmf-talk@lists.psu.edu](mailto:iwmf-talk@lists.psu.edu)
2. Contact Peter DeNardis at [pdenardis@comcast.net](mailto:pdenardis@comcast.net) and provide your full name





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# MEDICAL NEWS ROUNDUP

BY SUE HERMS, IWMF TRUSTEE

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**Imbruvica (Ibrutinib) Approved for Previously Treated CLL** – The US Food and Drug Administration has expanded the approved use of Imbruvica (ibrutinib) to chronic lymphocytic leukemia (CLL) patients who have received at least one previous therapy. The FDA completed its review of Imbruvica's new indication under the agency's accelerated approval process, which allows approval based on a surrogate or intermediate endpoint that is reasonably likely to predict clinical benefit. This type of approval is usually subject to confirmatory trials for verification. The approval was based on a clinical study of 48 previously treated CLL patients, of whom nearly 58% experienced tumor reduction from Imbruvica. The most common side effects included reduced platelets, diarrhea, bruising, anemia, neutropenia, upper respiratory tract infections, fatigue, muscle and bone pain, rash, fever, constipation, edema, joint pain, nausea, mouth sores, sinus infections, and dizziness.

**NCCN Guidelines Updated to Include Ibrutinib as Salvage Therapy for WM** – The National Comprehensive Cancer Network (NCCN) has updated its guidelines for WM to include the use of ibrutinib as salvage therapy in relapsed WM/LPL. Each recommendation in the NCCN Guidelines is identified with a category of evidence that reflects the quality of evidence available and the level of consensus. Ibrutinib was designated category 2A, which is evidence-based upon smaller randomized clinical trials, well-designed controlled trials without randomization, or well-designed cohort studies where there is uniform NCCN consensus that the intervention is appropriate. The NCCN is an alliance of 23 centers in the US, most of which are designated by the National Cancer Institute as comprehensive cancer centers. Its mission is the development and publication of practice guidelines for oncology care.

**New Trial Using IMO-8400 Opens for WM Patients** – Idera Pharmaceuticals announced that enrollment is open for a Phase I/II clinical trial of IMO-8400 in patients with WM, following acceptance of its Investigational New Drug application by the U.S. Food and Drug Administration. IMO-8400 is based on the presence of the MYD88 L265P mutation in approximately 90% of patients with WM and targets the Toll-like receptor (TLR) signaling pathway which is over-activated by the mutation. This trial will enroll approximately 30 patients with WM who have a history of relapse or failure to respond to one or more prior therapies and will assess the drug's safety, tolerability, and potential clinical activity.

**Idelalisib Will Be Reviewed for Use in NHL** – The US Food and Drug Administration has accepted for review a New Drug Application for idelalisib (CAL-101), a targeted oral inhibitor of PI3K delta, for the treatment of refractory non-Hodgkin's lymphoma (NHL). This follows a Phase II study

evaluating idelalisib in patients with indolent NHL that is not responsive to rituximab and to alkylating agent-containing chemotherapy. Idelalisib is manufactured by Gilead Sciences to block PI3K delta, which plays an important role in the growth, migration, and survival of B-cells.

**Phase III Study Combines Idelalisib and Rituximab in CLL** – Meanwhile, idelalisib and rituximab were combined in a multicenter Phase III study of relapsed CLL patients who have clinically significant coexisting medical conditions, making them less able to undergo standard chemotherapy. This combination was tested against rituximab plus placebo. The study enrolled 220 patients with decreased kidney function, previous therapy-induced bone marrow suppression, or other major coexisting illnesses. The median progression-free survival was 5.5 months in the placebo group and was not yet reached in the idelalisib group. Patients in the idelalisib group had improved rates of overall response compared to the placebo group (81% vs. 13%) and improved overall survival at 12 months (92% vs. 80%).

**Another PI3K Inhibitor Begins Phase I Trial for Indolent B-Cell Lymphoma** – Another PI3K inhibitor called BKM120, manufactured by Novartis, will be studied in combination with rituximab in a Phase I trial of patients with relapsed or refractory indolent B-cell lymphoma. The trial will be conducted at the Ohio State University Comprehensive Cancer Center.

**Novel Combination Therapy Begins Phase I Trial for CLL and NHL** – A potential new therapy on the horizon is the combination of TG-1101 and TGR-1202, which is entering a multi-center Phase I study for patients with relapsed/refractory CLL and NHL. Both drugs are manufactured by TG Therapeutics Inc. TG-1101 (also called ublituximab) is a novel engineered anti-CD20 antibody, and TGR-1202 is a PI3K delta inhibitor. MD Anderson Cancer Center will be the lead center for the trial. The company also hopes to combine TG-1101 with ibrutinib in the near future.

**Japanese Researchers Look at Possible Cancer-Initiating Cells in WM** – A group of researchers from the Osaka University Graduate School of Medicine in Osaka, Japan, has investigated the possibility of determining the cancer-initiating cells in WM, using the WM cell line MWCL-1, developed by the Mayo Clinic and funded through a grant from the IWMF and the Leukemia & Lymphoma Society. WM tumor cells typically express the B-cell and plasma cell markers CD20 and CD138, respectively. When stained with these antibody markers, the MWCL-1 cells were classified into three subpopulations: CD20-/CD138-, CD20+/CD138-, and CD20+/CD138+. When cultured, CD20-/CD138- cells yielded all three subpopulations, but the CD20+ cells

*Medical News Roundup, cont. on page 13*



did not yield CD20-/CD138- cells. The CD20-/CD138- subpopulation exhibited colony formation activities and was resistant to apoptosis (cell death) in the presence of anti-cancer drugs, in contrast to the other subpopulations, which were vulnerable to anti-cancer therapy. The data suggest that CD20-/CD138- cells might be a candidate for the cancer-initiating cells of WM.

**Rituximab May Interfere with Efficacy of Influenza Vaccination** – A Swedish study from the University of Skåne reported that rituximab treatment severely reduced antibody response to H1N1 influenza vaccination in patients with rheumatoid arthritis. While the study did not look for this effect in lymphoma patients, the authors of the study suggest that if it is practically possible, patients planning to start rituximab should get immunized against influenza before initiating treatment. In patients who have been taking rituximab, the probability of a protective immune response is best if vaccination is performed a few weeks before the next rituximab course.

**New BTK Inhibitor Tested for CLL** – Early data suggest that the second-generation oral BTK inhibitor ONO-4059 (in the same class of drug as ibrutinib) may be very effective in CLL. The response rate to ONO-4059 as single agent therapy was 89% overall in a Phase I clinical trial. Patients in this trial had already received a median of three prior therapies, including rituximab and fludarabine. All patients had improved hemoglobin and platelet counts after 3 months on ONO-4059 treatment and rapid reductions in lymph node size within the first cycle. Tumor burden was reduced by 50% for most patients. Ono Pharmaceutical is the developer of this drug.

**Enhanced T-Cell Therapy Research on the Rise in Hematologic Cancers** – Reports from several centers are indicating increasing research into the use of chimeric antigen-receptor modified T-cells (CAR-T) in hematologic cancers. When directed against the B-cell surface receptor CD19, such T-cells are known as CTL019. Both Kite Pharmaceuticals and Novartis are manufacturing these types of T-cells, and recently Fred Hutchinson Cancer Center, Memorial Sloan-Kettering Cancer Center, and Seattle Children's Research Institute have joined forces to launch Juno Therapeutics to develop these types of cells. Experts predict that CTL019 therapies may become commercially available sometime between 2016 and 2020. This therapeutic approach harnesses the power of the immune system by reprogramming a patient's own T-cells to recognize cancer cells for a precision attack. The patient's cells are extracted, engineered, and programmed to target the CD19 antigen. A virus is inserted to trigger the T-cells to expand and proliferate once they are reinfused. Side effects in pilot studies have included high fevers, muscle pain, low blood pressure, and breathing difficulties. The University of Pennsylvania has used the interleukin-6 inhibitor tocilizumab to tamp down these side effects.

**Retrospective Study Looks at Bendamustine in CLL and NHL** – A study from the Medical University of Lublin, Poland, looked at bendamustine as single-agent therapy and in a combination regimen for the treatment of CLL and NHL. This retrospective analysis included 92 patients. Bendamustine plus rituximab was used to treat 65.2% of patients, while 34.8% of patients received bendamustine alone. The overall response rate was 64.2%, and the median overall survival was 11.5 months. Beta2-microglobulin and hemoglobin levels significantly influenced survival. The overall survival was longer in patients who received less than 2 lines of previous therapy vs. more than 3 lines of previous therapy. Toxicities included neutropenia, thrombocytopenia, and anemia.

**Oral Cancer Drug Therapy Legislation Introduced in US Senate** – In December Senators Al Franken of Minnesota and Mark Kirk of Illinois introduced the Cancer Treatment Parity Act (S.1879) in the US Senate. The legislation is similar to a bill introduced previously in the US House of Representatives. Both bills seek to ensure that patients enrolled in certain federally regulated health plans have access to and insurance coverage for all anti-cancer regimens. The bills would require any health plan that provides coverage for cancer chemotherapy treatment to provide coverage for orally administered and self-injectable anti-cancer medications at a cost no less favorable than the cost of IV, port administered, or injected anti-cancer medications. A number of states have already passed oral parity legislation or are currently reviewing related legislation. Federal legislation will ensure a standard across all states.

**UK Epidemiology Study Investigates Common Infections and Subsequent Risk of LPL/WM** – An epidemiology study from Queen's University Belfast in the UK investigated the exposure to 14 common community-acquired infections and subsequent risk of LPL/WM in 693 LPL/WM cases vs. 200,000 controls. This report used the population-based Surveillance, Epidemiology End Results-Medicare database. Because emerging evidence supports the role of immune stimulation in the development of LPL/WM, the study looked at respiratory tract infections, bronchitis, pharyngitis, pneumonia, sinusitis, skin infection, and herpes zoster and found that all were significantly associated with a subsequent increased risk of LPL/WM. The researchers suggest that these findings may support a role for infections in the development of LPL/WM or could reflect an underlying immune disturbance that is present several years prior to diagnosis and thereby part of the natural history of disease progression.

*The author gratefully acknowledges the efforts of Peter DeNardis, Wanda Huskins, and John Paasch in disseminating news of interest to the IWmf-Talk community. The author can be contacted at [suenchas@bellsouth.net](mailto:suenchas@bellsouth.net) for questions or additional information.*



# MEMBER SERVICES: WHAT A GREAT DEAL!

The *Imagine a Cure* Campaign is designed to provide support for both member services and research. As you know, donations to the IWMF can be designated for either area. Many donors, however, choose not to designate a use or ask us to use the funds where they are needed most. In these cases, the gifts are placed in the Member Services Fund and are used later where the need is greatest. Every dollar designated for research is added to the Research Fund and is used to support a research project that has been approved by our Scientific Advisory Committee and the IWMF Research Committee.

In this issue of the *Torch* we highlight 10 member services that the IWMF provides at **no charge** to all of our members. The only exception is the Ed Forum, for which attendees are asked to pay a fee that covers less than fifty percent of the cost. Your gifts to Member Services make all ten of these services possible!

## 1. Booklets, Downloadable Publications, and Info Paks

Booklets, publications, and information packages (Info Paks) covering many aspects of WM are available online and in print. These publications provide answers to many of the questions that patients and their caregivers have. They explain how the immune system works, how to interpret the many medical and blood tests that are administered to those with WM, as well as explain available treatment options.

These publications can be downloaded directly from our website. Several of our more popular items are also included on CDs.

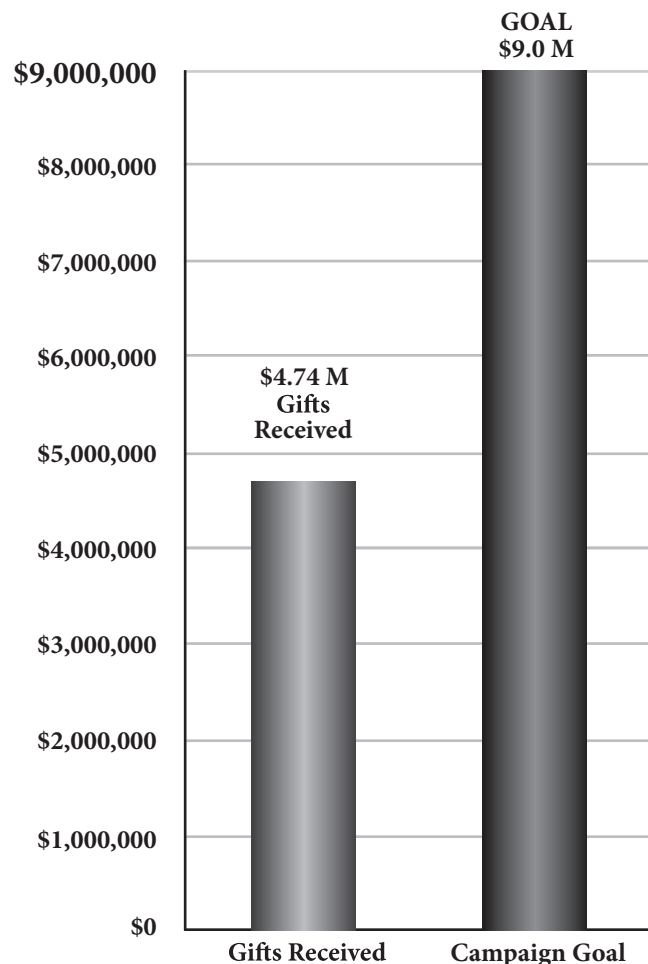
## 2. Caregiver Support

Caregivers play a special role in the lives of WM patients, providing both physical and emotional support. Special sessions for these members of the WM community are offered at the annual IWMF Ed Forum. Caregivers often participate in IWMF support groups, the Lifeline, and IWMF-Talk.

## 3. Educational Forum

Held each spring at a different US location, the Ed Forum features presentations by medical professionals who specialize in the study and research of WM. The presentations are directed specifically to the layperson. The Ed Forum also offers breakout discussion groups on specific topics of interest to both patients and caregivers. Many of the medical professionals remain for the duration of the Forum and are available to talk with attendees on an informal basis. Each Ed Forum concludes with the highly anticipated Ask the Doctor, a question and answer session moderated by Dr. Robert Kyle.

## Imagine a Cure Campaign Progress Report as of January 31, 2014



*The total amount for Gifts Received includes all gifts to the Member Services and Research Funds, pledges made over a five year period, and planned legacy gifts.*

Questions submitted by attendees and directed to a panel of WM experts provoke a lively exchange.

## 4. IWMF-Talk

This very popular e-mail talk list allows members of our WM community to share information about WM. Participants learn from each other, and the newly diagnosed benefit from the knowledge and wisdom of those who have significant experience with the disease. While IWMF-Talk is conducted in English, there is a separate list for those who speak Spanish and another for our Nordic members. IWMF members may also participate in e-mail discussion groups in French and German, as well as in groups based in the UK, Australia, and New Zealand.

*Member Services, cont. on page 15*





**5. IWMF Torch (4 issues a year)**

The many activities of the IWMF are reported in the *Torch*, including updates on research initiatives sponsored by the Foundation, fundraising, Ed Forum programs, support group meetings, and lively discussions on IWMF-Talk. The popular Doctor on Call feature addresses many aspects of WM, helping us gain a deeper understanding of our disease. Recent issues have included articles about disease transformation, the advisability of WM screening, complementary medicine, side effects in WM, and reports of advances in research about hematological malignancies in general and about WM in particular. The *Torch* is available both online and in print.

**6. IWMF Website ([iwmf.com](http://iwmf.com))**

The IWMF website is often the first point of contact that a newly diagnosed patient has with the IWMF. We strive to keep the website up to date so that all of our members, especially newly diagnosed patients and their caregivers, will be able to find all the information and services that they need, as well as learn how research supported by the IWMF is making strides towards better treatments and a cure.

**7. Lifeline**

The Lifeline is a list of patients and caregivers who volunteer to take phone calls and share their experiences regarding treatments, clinical trials, and other specialized areas pertaining to WM. These volunteers can help eliminate the mysteries of treatment options and help allay the fears of

those considering a new course of action. For those who feel more comfortable speaking in their native language, there are also Lifeline members fluent in languages other than English.

**8. Patient Database**

An online database that contains the active medical history of participating WM patients, the Patient Database will serve as an ever-growing, evolving, encyclopedic guide to the conditions and medical histories of WM patients.

**9. Telephone and E-mail Network List**

A list of IWMF members in your area, the Network is a means of putting patients and caregivers in touch with others living nearby.

**10. Support Groups**

The IWMF has support groups throughout the United States and in thirteen other countries. Typically, support group leaders are local volunteers who schedule and plan the meetings. A program might include the viewing of a video from a recent Educational Forum or a visit by a guest WM expert to discuss the disease and recent research developments. Participants benefit from an opportunity to share experiences, learn from each other, and provide mutual support.

How many of these IWMF member services have you used? Remember, your gifts to Member Services helps us keep offering and improving what we can do to support WMers everywhere.

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## FUNDRAISING IS A DAUNTING TASK: THAT'S WHAT FRIENDS ARE FOR

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It's hard to be a fundraiser and ask strangers to donate. We don't get a lot of WMers who volunteer for the Fundraising Committee. Yet there are creative ways you can help.

- An article in the April 2013 issue of the *Torch* described unique ways in which members of the IWMF have raised money to support member services and WM research.
- An article in the January 2013 issue described the many ways in which one family has supported the IWMF.

In 2013 the IWMF received gifts from over 2,000 individual donors, totaling approximately \$1,300,000. That's our second best year ever! Imagine what could be accomplished if, in addition to their own donations, each donor was able to raise funds from his or her family and friends in the amount of \$1,000 annually. With an additional \$2,000,000, the IWMF

would be able to support all research projects approved by our Scientific Advisory and Research Committees and enhance and expand our vital member services.

Raising \$1,000 may seem like a daunting task to many people, but if we all solicited 20 friends and family members, an average gift of \$50 would get us there. Because WM is such a rare disease, there are just too few of us to provide the funding necessary to accomplish our mission. And asking friends and family isn't like asking strangers . . . it's asking them to invest in you.

So, if each of us becomes an IWMF ambassador and spreads the word, we can greatly expand our donor base and make an enormous difference in the fight against WM. We hope we can count on you to join us. We're asking our friends and family to donate to the IWMF. Won't you join us?



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# INTERNATIONAL SCENE

EDITED BY ANNETTE ABURDENE

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## AUSTRALIA

### WMozzies: THE AUSTRALIAN SUPPORT GROUP

Colin Perrott has successfully passed to Andrew Warden the role of IWMF patient support liaison for Australia, WMozzies. In 2014 the Australian Support Group will be working with the Leukaemia Foundation of Australia on advocacy issues confronting WMozzies. Principal focus is on initiatives to enhance Australian WM best patient treatment and funding. Other areas being addressed by the group include:

- Organization of suitable meetings and forums for WM patients and carers;
- WM patient support activities and the website;
- Identification of WM specialist haematologists and hospitals experienced in treating our orphan disease (IWMF has already published an Australian specialist list);
- Facilitating financial donations to support WM research scholarships and fellowships;
- Reviewing treatment options available to identify any shortfalls from WM world-best practice;
- Active advocacy to assist initiatives to widen PBS (pharmaceutical benefits scheme, funded by the government) coverage to provide funding of world-best WM treatments in Australia.

The initial members of the group are: Andrew Warden (WMozzies liaison), Peter Carr (Qld), Peter Marfleet (Vic), Peter Smallwood (Qld), David Young (NSW), Janelle Sullivan (NSW), and Andrew Warden (NSW). Intentions are to broaden the group membership to include other states and territories as well as other WMozzies with a keen interest.

**Andrew Warden, WMozzies reporting.**

## BELGIUM

### JANUARY SYMPOSIUM

On January 30 a group of more than 260 enthusiastic patients, partners, relatives, and friends met on the beautiful grounds of the International Convention Center, Ghent, where the Belgian Hematological Society was holding its annual conference. CMP Vlaanderen (Contactgroep Myeloom en Waldenström Patienten Vlandereen; our contact group for WM and multiple myeloma patients in Flanders) was invited to organize the concluding anniversary symposium.

We eagerly seized this opportunity, especially since we were allowed to plan the program ourselves. This explains why, three months after the successful October 2013 WM symposium in Antwerp, we were able to invite our group members back to another patients' day.

We put our heads together to create our part of the program. Since CMP Vlaanderen supports both multiple myeloma and Waldenström patients, the program had to be attractive and suitable to both diseases. In the morning two distinct programs for MM and WM were scheduled.

Nearly sixty attendees were present at the presentations for WM by hematologists Dr. Schauvliege, Dr. Trullemans and Dr. Van Hende, three physicians whose presentations at earlier symposia were very interesting. And this time it was no different. Dr. Liesbeth Schauvliege of the hospitals AZ Delta Campus Stedelijk Ziekenhuis Roeselare and Sint Jozefkliniek Izegem, gave a presentation in which she expertly explained the disorder, the diagnosis, symptoms and complaints. Then it was the turn of Dr. Fabienne Trullemans of the University Hospital, Universitair Ziekenhuis (UZ) Brussels, who gave a clear explanation of the standard treatments of WM. Finally, Dr. Vanessa Van Hende of UZ Ghent introduced us to the latest developments in the treatment of WM. Dr. Van Hende made it clear that novel drugs, such as bortezomib and bendamustine, that have primarily been tested for other lymphomas and are currently used to treat multiple myeloma, could in the future play an important role in the treatment of WM. Other agents, including alemtuzumab, thalidomide, and lenalidomide, are not recommended because there is still relatively little experience with such drugs or because of their side effects. Nevertheless this presentation brought a message of hope.

We chose to put the Ask the Doctor session at the end of the morning program. The three doctors formed a select panel that answered the many questions from the audience.

After lunch, for the first time, the participants were offered the opportunity to opt for one of five workshops, each studying in depth one subject concerning both MM and WM:

- Neuropathy, pain, bone problems: diagnosis and treatment (Dr. Koen Van Eyghen, AZ Groeninge Kortrijk);
- Medical imaging examination: X-ray, MRI, CT scan, PET, ultrasound: why and when they are prescribed (Prof. Dr. Koenraad Verstraete, UZ Gent and U Ghent);
- Autologous versus allogeneic stem cell transplantation, transplantation of stem cells from umbilical cord blood (Dr. Koen Theunissen, Jessa Hospital Hasselt);
- Immunotherapy (Prof. Dr. Rik Schots, UZ Brussel);
- Major MM and WM laboratory values and their significance (Dr. Ronald Malfait, UZ Antwerpen).

*International Scene, cont. on page 17*



These workshops were all interesting, instructive, enriching, but unfortunately focused mainly on MM.

A short coffee break strengthened us to complete the final program offering. Two eminent professors, Dr. J.-J. Cassiman, President of the Flemish League against Cancer, and Dr. René Westhovens, President of the College of Physicians for Orphan Drugs at the National Institute for Health and Disability Insurance (RIZIV in Dutch, INAMI in French), gave an explanation of a topic that in our country is currently a hot subject, namely the accessibility of orphan drugs and the reimbursement of innovative medicines. A subject very difficult to digest: so many rules, so many proposals, so many bodies involved!

Afterwards everyone was ready for a refreshing drink and a chat with fellow sufferers. Everyone went home, tired but hopeful, and looking forward to the next meeting.

**Joanna Van Reyn, CMP Flanders, reporting.**

## **CANADA**

### **ED FORUM IN VANCOUVER**

On April 5 the WMFC will host an educational forum in Vancouver B.C. This will be an informative day with the participation of leading specialists in WM who are involved in many areas of clinical practice and research.

**Arlene Hinchcliff, WMFC, reporting.**

### **CALGARY, ALBERTA, SUPPORT GROUP**

The Calgary, Alberta, Canada, WM Support Group tries to meet three to four times per year. We currently have approximately 14 patients as members, with our meetings consisting of 16 to 22 folks. We draw from a very wide area comprising the southern half of the province and even one couple from Edmonton. We hold very informal get-togethers in the basement of one of our members where coffee and treats and fellowship are the order of the day. Typically we bring in a speaker for our group on topics as far ranging as presentations by hematologists to travel insurance experts. At the September 2013 meeting, our speaker was a WM patient who just recently completed a stem cell transplant. Our goal is to offer support for our members as well as education and a format to talk openly with other WMers who understand the treatments and frustrations involved. To this end, at least half of each meeting is dedicated to updating each member's health, symptoms, changes in treatments, and discussions with their doctors.

Our last meeting was held on January 21 and was devoted solely to an update of the medical status of each of our members and reactions to various treatments. Sixteen people, both patients and caregivers, attended. Probably the most common response to this meeting was how unbelievably diverse are the symptoms and reactions to the various treatments that we all experience. No wonder the doctors find treatment for this rare disease so challenging.

Two of our group will be attending the Tampa Bay Educational Forum in May and two or three may be attending the Vancouver Education Forum in April. Consequently our group will meet next in early June and discuss the information received from both of these forums.

**Cameron Fraser, Calgary, Alberta, Support Group reporting.**

## **UNITED KINGDOM**

### **WMUK UPDATE**

Things at WMUK have been hectic with the launch of several initiatives, particularly the online *UK patient survey* and the *WM UK doctor survey of treatment*, both of which will help us build up a clearer picture of WM in the UK. The other main operation was the successful launch of the new website in January which uses cutting-edge "adaptive technology" to reformat the site depending on the device used to view it, greater use of video, and capacity for editing in-house to cut down costs. It aims to draw the UK community, doctors, patients, and carers together and has attracted a lot of interest.

Following the merging of the UK support group with WMUK in January, leaving a single UK point of contact, we have done extensive work merging the UK databases of both doctors and patients, which should benefit all sufferers and carers. Another milestone was the first reclaim payment under the UK government's Gift Aid scheme, allowing us to increase donations from UK taxpayers by 25%. Plans for a new high profile patron and clinical data registry are advancing.

As usual, we have received much support and encouragement from the IWFM and hope to financially assist with a research programme application from University College Hospital, London, to the IWFM, if approved by the IWFM review process.

**Roger Brown, WMUK, reporting.**





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# COOKS' HAPPY HOUR

BY PENNI WISNER

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I spent the first few months of 2014 as a shut-in. Not because of WM, let me hasten to say, but because of bunion and hammer toe surgery. The experience reminded me of how our tastes change according to our life circumstances. (At least mine do.) I still vividly recall that first bite of raw apple after a week of feeling nauseous following chemotherapy. A friend gave me a cookbook – was it vegan? macrobiotic? – meant to help me eat my way to health. But I discovered I could not stomach miso, a primary ingredient in the recipes. After that, I decided to listen to what my belly said.

Early on in my convalescence this winter, a generous pal offered to bring supper over. But what, she wanted to know, should she bring? I said I felt flat and lifeless, and not just my hair. I wanted bright flavors. Believe it or not, she got the recipe just right: baked salmon on melted leeks and fennel and a salad of little gem lettuce; shaved, raw fennel; and grapefruit and orange segments. The dressing combined the citrus juices with a splash of good olive oil and salt and pepper. After that supper, I felt happy and special, not the “poor-me” character of just an hour before.

When you read this, it will be April, a season for bright, fresh flavors: young lettuces, asparagus, fresh crop potatoes. And nettles. Have you caught the nettle bug? By that I mean, are you cooking nettles? (Not looking for any bugs on the foraged nettles.) Their intense, blue-green color practically screams “Spring tonic! Right here!” In order not to go overboard on the health kick, all these foods taste great on pizza. Yes, pizza. A pizza I still dream about emerged from the oven covered with melting pools of creamy, fresh goat cheese and nettle puree. If you are inclined to feel guilty about eating pizza, add whole-wheat flour to your dough. Roll it extra thin. Savor it slowly.

To wash nettles, wear your longest rubber gloves. Discard any thick stems and then dunk them in boiling, salted water. The sting disappears immediately. Blanch the nettles very briefly, just until they wilt. Drain and refresh in ice water. Drain again and squeeze out the water with your hands. Chop the mass roughly and puree it in a food processor with garlic (a stalk of spring garlic if you have access to it), lemon zest, salt, pepper, and some olive oil. Now dollop that on your pizza dough

under some thinly sliced potatoes. Or team it with spoonfuls of a light, fresh cheese such as chevre or ricotta. Of course, if you want to stay away from pizza, you can transform the idea into a finger food: boil whole, small, new crop potatoes until tender, scoop out a little of their flesh (and eat that as a ‘cook’s snack’). Stuff the potatoes with a spoonful of puree and top with a crumble of fresh goat cheese and a drizzle of new crop olive oil.

Nettles make wonderful soup, too. Use your basic soup-making method: In your soup pot, sauté aromatics (onion and garlic, maybe a leek, parsley stems, some chopped thyme) in olive oil or butter or ghee. (Ghee is my newest discovery. The production process removes most or all of the milk proteins leaving just the fat and the butter flavor. Without the milk solids, ghee is appropriate for sautéing at higher heat.) Add really good stock to your pot. It isn’t important whether it be vegetable broth or chicken stock. And add a large, cubed, peeled potato with a generous bagful of washed nettles. Simmer until the potato is soft, about 10 or 15 minutes. Let the soup cool until it can be safely blended until smooth. Return the soup to the pot to reheat gently and season to taste with salt, freshly ground pepper, and a little lemon if you like. Serve with a swirl of crème fraîche or Greek-style yogurt and sliced, toasted almonds. And, for color, add another harbinger of spring, a vibrant, snappy flavored nasturtium flower. And while we are on nasturtiums, don’t forget to pick young, round leaves as well as the flowers to add to your salad.

It would interest me to hear what you could stomach – or not – during your treatment. Cancer treatment frequently causes changes to our palates as does pregnancy – so taste changes are more about physical changes than about disease or a lack of interest in eating. And some foods (such as raw foods) might be forbidden to some people. To perk up flagging appetites, Rebecca Katz, the author of wonderful cookbooks including *The Cancer-Fighting Kitchen*, recommends careful seasoning adjustments when cooking, often by adjusting the sweet/tart balance with lemon and maple syrup, just a tiny bit at a time until the flavors of a dish pop.

***Our motto: Eat Well to Stay Well***



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## IN THE TORCHLIGHT: BERL HOWELL

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Stepping into the Torchlight for this issue is Berl Howell, jazz musician extraordinaire and leader of the Yosemite Jazz Band in the mountain community of Oakhurst in northern California near Yosemite National Park. In 1993 Berl formed the band soon after he and his wife moved into the Yosemite area. Blending Dixieland, early swing, gospel, and traditional jazz, Berl and the guys play gigs up and down the state of California at dances, county and state fairs, local jazz festivals, weddings, funerals, and grand openings. When not on the road, the band can be found performing at the Oakhurst Pizza Factory.

Berl proclaims making music to be “the joy of my life” – a sentiment written across his face in the accompanying photograph (see the “guy holding the trumpet”). His radiant smile belies the fact that for many years he has suffered severe back pain, well before receiving the shocking diagnosis of Waldenström’s macroglobulinemia in 2010. Stunned to hear the words “cancer, rare, not curable,” Berl turned to the Internet, did an online search, and found the IWMF website and IWMF-Talk. He is ever so grateful for the information he has received about WM through the website and for contacts with many others “who have been through what I am about to go through.”

Berl is a patient at the California Cancer Center in Fresno and is doing well following treatment. His caregivers? Berl names



*The Yosemite Jazz Band – Berl is the “guy holding the trumpet” in the lower left.*

the fun-loving guys in his band who “watch and take care of me” and who share their leader’s joy in making music.

*In the Torchlight is a column for sharing the personal stories of Wallies of all ages to illustrate spirit and strength in the face of adversity. Our pages are full of stories of awards, accomplishments, successful treatments, new adventures, strength of character. Won’t you share yours with the Torch? Let us hear from you at: [ariginos@me.com](mailto:ariginos@me.com)*

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## FIFTH INTERNATIONAL IWMF DOCTOR-PATIENT FORUM LONDON: SUNDAY AUGUST 17

BY ROGER BROWN, WMUK, AND GUY SHERWOOD, MD, IWMF TRUSTEE

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The Fifth International Doctor Patient Forum, which will take place on Sunday, August 17 following the conclusion of IWWM8, the doctors’ workshop ([www.wmworkshop.org](http://www.wmworkshop.org)), is jointly organised and supported by the IWMF and WMUK. It is now taking shape very quickly with worldwide interest. Sixty bookings were taken even before the final programme was ready! The highlight is sure to be Dr. Steven Treon’s team summarising the latest from trials, treatment, and research discussed at IWWM8 over the days immediately before the Forum. The old favourites such as Ask the Doctor will be there as well.

Bookings in £, \$ or € or via Paypal can be taken directly on the WMUK site at [www.wmuk.org.uk](http://www.wmuk.org.uk) where you can also download a programme and other details such as hotels.

Please contact Roger at WMUK if you want to book in other currencies. Apart from encouraging UK doctors to attend IWWM8, WMUK has also happily pledged to support financially the Young WM Investigator Program in the UK to allow younger researchers to attend and present at IWWM8.

Finally, another limited edition Forum mug is being designed for August!



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# SUPPORT GROUP NEWS

EDITED BY PENNI WISNER

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## CALIFORNIA

*Sacramento and Bay Area*

By now members of the group know to come with an appetite to the “finger food potluck” meetings. At the March meeting, after watching a DVD entitled “How Chemo Works” – a talk delivered by Dr. Joseph Mikhail of the Mayo Clinic in Phoenix – the generous potluck offerings fueled conversation as WMers who have participated in clinical trials shared their experiences. The lively, two-hour discussion took place at the Kaiser Permanente in Vallejo.

## COLORADO

In February Lisa Wingrove, an oncology nutritionist from the University of Colorado Cancer Center, led a lively presentation and discussion: “Fighting Cancer with a Fork.” She sorted fact from fiction in relation to nutrition, organics, and supplements. And she described how to use nutrition to live the best life possible, even with cancer. The twenty-plus highly motivated members responded enthusiastically. The Denver chapter of the Leukemia & Lymphoma Society (LLS) provided the food and drink (naturally, these were in accordance with all of Ms. Wingrove’s recommendations). The next gathering is planned for Saturday April 12, during the LLS Rocky Mountain Blood Cancer Patient Education Conference. Dr. Ed Libby of the University of Washington in Seattle will lead the WM breakout session.

## IDAHO

The advantage of a very small support group is that it is able to use the “kitchen table approach” as the preferred method of communication. The group consists of two patients, two spouse-caregivers and one surviving widow of a past member. In 2001 they began meeting as a support group, and since then they truly have become a family. Members also provide information about WM to all the doctors in the area who might identify other patients as well, and they also reach out to patients and caregivers in the nearby states of Wyoming, northern Utah, and Montana. Our members get together quarterly, either at a home or, as the photo of our winter meeting indicates, “out” to lunch. Alas, the male members decided that work saved them from this “hen” party. Several hours at table allowed the



*Members of the Eastern Idaho Support Group out for lunch at Jaliscos Fantastic Mexican Food. From left to right, Janet Corson-Stanton, Barbara Britschgi, and Marsha Stanger.*

ladies to delve deeply into global issues as well as personal issues of health, education, families, joys and sorrows. While not always agreeing, members do listen and give each other a nonjudgmental space in which to vent when necessary. WM has given them the opportunity and gift of friendship that can be difficult for others to understand.

## ILLINOIS

*Chicago Area/SE Wisconsin*

On Saturday April 26 the group will hold its first 2014 meeting. The gathering begins at 12:30 pm at the Johnson Auditorium of the Advocate Lutheran General Hospital in Park Ridge, Illinois. Dr. Shou Ma has agreed to present an update on WM treatments. She is a great doctor from Northwestern University and has spoken at several Lymphoma Research Foundation workshops on Waldenstrom’s. Dr. Ma also has some experience with the new drug ibrutinib.

## NEW YORK

*Eastern New York/Western New England*

By March the group REALLY needed to GET OUT and beat the WINTER BLAAHS! One of the most popular events is the Annual Luncheon celebrating the end (???) of winter and the approach (hopefully) of spring. It’s a time to eat, drink, and be merry. (Not an original line but heartfelt.) A dozen members gathered for lunch in a private room at the Capital Buffet. They talked and ate and talked and ate. The “Chinese” buffet has many types of cuisine including American, Italian, Japanese, and more. Some participants traveled almost three hours to get to the event. Among topics discussed were the May IWMF Ed Forum, the recently announced IWMF advocacy alerts, the new LLS online video (“Making NHL and CLL Treatment Decisions”), and the several very hopeful announcements of progress and studies on WM treatments. On a sad note, member **Dave Hare** from Vermont passed away. And **Tom** and **Kay Zolezzi**, who are moving to Florida, bid the group *au revoir*. A speaker program is planned for May.

## OREGON/SOUTHWEST WASHINGTON

Who says it always rains in Oregon? On a bright, cool, sunny January day, about thirty members – including three new people – gathered for the first meeting of 2014. Dr. Stephen Spurgeon, researcher, staff physician, and professor at the Oregon Health Sciences University Knight Cancer Institute presented: “News You Can Use: an Update on Waldenstrom’s from the Latest ASH Conference.” In an energetic and easy to understand manner, Dr. Spurgeon outlined the newer knowledge about WM made possible through the genomic study of healthy and diseased cells in WM patients. He reviewed the discovery that in about 90% of WM cases

*Support Group News, cont. on page 21*





the patients have a mutation of the MYD88 gene, and he explained how the inhibition of this mutation affects the NF-κB pathway. Apparently this mutation triggers the activation of Bruton's tyrosine kinase (BTK) in WM cells, which stimulates the reproduction of WM cells. Dr. Spurgeon went on to explain that this BTK activity has become the focus of a new treatment approach with the drug ibrutinib. Most exciting is the fact that this new drug, along with other BTK inhibitors under development, targets and attacks a gene signaling pathway and not cellular DNA (as do such drugs as fludarabine and Cytosan). As a result, not only is this drug well tolerated but is also much less destructive to the patient's immune system in the long run. Dr. Spurgeon spent a good amount of time answering questions and hearing comments. The Oregon/SW Washington IWMF support group meets quarterly on the fourth Saturday of the first month in that quarter. Meetings are held at the Fairfield Inn and Suites, 6100 SW Meadows Road, Lake Oswego, Oregon. Meetings are from 12 noon to 2 pm, and lunch is provided through a partnership with the local LLS. The IWMF group provides ongoing connection, information, and support for patients and their caregivers and families.

#### **PENNSYLVANIA**

##### *Philadelphia*

Due to an unexpectedly severe early snowstorm, the December meeting of the Philadelphia Group had to be cancelled at the last minute after members had already started out and then had to turn around and return home. The plan for that meeting, to show the Ask the Doctor DVD from the 2013 Ed Forum, was moved forward to the March meeting.

#### **SOUTH CAROLINA**

The South Carolina support group held an informal "sharing-and-caring" meeting last November in Columbia. Both veteran WMers and newly diagnosed WMers attended. The next meeting is planned for the late spring and will be held in Charleston.



*Members of the Washington DC area support group at their January meeting.*

#### **WASHINGTON D.C./METROPOLITAN AREA**

The Washington D.C. metropolitan area group turned out in force on the weekend after Thanksgiving for an informal discussion. Future meetings in 2014 are scheduled for 2:30 pm at Holy Cross Hospital on the following Sunday afternoons: June 1, September 14, and November 30.

### **Support Group Leader Workshop**

**Thursday, May 15, 12 noon to 6:00 pm, Tampa, Florida**

IWMF support group leaders will gather for a leadership workshop on the afternoon of May 15, the day prior to the Ed Forum, which will be held May 16-18. Plans are well underway and feature networking opportunities and presentations that will provide essential tools to assist leaders in planning and facilitating meetings. Guest speakers will address key topics of effective group facilitation and LLS collaboration. Leaders will share their unique success stories so all can benefit from new ideas. Hope you will join us for a fun, interactive, and informative workshop!

Marcia Klepac, Support Group Leader Coordinator  
[marciaklep@hotmail.com](mailto:marciaklep@hotmail.com)  
412-421-2437



will then undergo class switch recombination (CSR) in order to change from IgM to IgG or IgA. WM cells are seemingly able to undergo SHM but not CSR. **Marie-Christine Kyrtsolis, MD, et al.** from the National and Kapodistrian University of Athens, Greece, performed a detailed analysis of somatic hypermutation in 36 WM patients and focused on the heavy chain gene variable regions, called IgVH, looking for common rearrangements in the IgM antibody in these patients. Of the seven IgVH families, Dr. Kyrtsolis reported that the IgVH3 family displayed mutations in 73% of the WM patients. The high rate of mutation points to a derivation of WM cells from post-germinal center memory B-cells. The germinal centers are the secondary lymphoid organs, such as the lymph nodes and spleen, where most B-cells acquire the somatic mutations that will enable them to target antigens more specifically. The prevailing theory is that WM develops from B-cells after they have acquired these mutations, so-called post-germinal center B-cells. Three of the patients with unmutated IgVH genes were found to be negative for the MYD88 L265P mutation, leading to the hypothesis that a subgroup of WM may not arise from post-germinal center B-cells.

**Richard Lemal, MD, et al.** from the Université d'Auvergne, Clermont-Ferrand, France, explored the expression and role of the TCL1 proto-oncogene and protein in WM. TCL1 is normally only expressed in the early phases of lymphocyte development. Chronic lymphocytic leukemia (CLL) patients with overexpressed TCL1, as well as mouse models with overexpressed TCL1, develop an aggressive form of the disease with a poor outcome. This multi-center French study compared the gene expression of TCL1 in WM patients with CLL and multiple myeloma patients. Preliminary data showed TCL1 expression in approximately 80% of WM patients and suggested that these patients may have a poor outcome. Further studies are required to validate these findings.

Another poster presented by **Efstathios Kastritis, MD, et al.** analyzed the survival history of 408 symptomatic WM patients who received treatment within the centers of the Greek Myeloma Group. The objective of the multi-center study was to see if there was any difference in survival statistics for those who were older than 75 when they died vs. those who were younger. During the follow up, 52% of patients had died. Deaths were classified into two categories: 1) WM-related (due to disease itself, treatment toxicity, or myelodysplasia/transformation) and 2) WM-unrelated, i.e., those from other causes. The median survival for those older than 75 years was 5.3 years vs. 9.7 years for patients 75 years and younger. For both age groups the WM-specific death rates were similar at slightly more than 20%. In the older patients, more than 40% of the deaths were unrelated to WM. The data from this study shows that among patients of advanced age twice as many die of causes unrelated to WM than of causes related to the disease. Dr. Kastritis concludes that this is an important consideration in determining treatment strategies for older patients and in designing clinical trials.

**Sydney Nelson et al.** studied Surveillance, Epidemiology, and End Results (SEER) data and the changing epidemiology

and improved survival in patients with WM. Nelson, who is a high school student and summer intern, performed the analysis in cooperation with Emory University. The SEER registry includes data from 1973-2010 from 18 geographic areas, representing 28% of the US population. The SEER data of 4,304 patients (1244 patients diagnosed before 2000 and 3060 patients after 2000) were used to evaluate the changes in incidence and survival patterns in a time when modern therapeutic agents such as rituximab, immunomodulatory drugs, and proteasome inhibitors are now available to WM patients. The incidence rate of WM increased with age. Median survival for all WM patients was 74 months. Nelson's study showed significant survival improvement in the current era (84 months after year 2000 vs. 64 months prior to year 2000); these results may be due to newer drugs used to treat WM. However, younger patients (< 50) and African American patients did not see survival benefit. Over the last decade the trend of incidence rates in WM has been steadily decreasing across all age groups for reasons that are unclear.

The presence of extramedullary involvement in WM has not usually been a subject of intense scrutiny. Extramedullary disease (EMD) is defined as disease outside the bone marrow, excluding involvement with the lymph nodes, spleen, and amyloid deposits. **Ranjit Banwait, MA, et al.** from DFCI performed a retrospective analysis of 985 cases of WM; 50 of the 985 patients had biopsies that confirmed EMD involvement, 38 of whom developed EMD after therapy. The male/female split in these 50 cases was 56%/44%, and the median age was approximately 58 years. The EMD biopsy sites used in this analysis included lungs, soft tissue, cerebrospinal fluid, kidney, bone, peripheral blood, neck mass, skin, breast, eye, liver, gall bladder, small bowel, prostate and colon – all more prevalent in those who presented with EMD post-therapy. The median time to EMD presentation from diagnosis was 75.7 months. Prior to EMD presentation, 31 of the 38 patients who developed EMD after therapy had a rituximab-based regimen, 15 had a cyclophosphamide-based regimen, 12 had a fludarabine/cladribine-based regimen, and 11 had a bortezomib-based regimen. At the time of data collection, 32 were alive, 10 were lost to follow-up, and 8 had died from progressive disease.

#### FAMILIAL WM

**Yosra Aljawai, MS, et al.** from DFCI reported the most recent epidemiological analysis of surveys completed by almost 400 WM patient and 100 family and non-family member controls for Dr. Irene M. Ghobrial's Tissue Bank project. While it is important to obtain this information from patients, it is equally important to have a control group for identification of risk factors leading to WM. The median age at diagnosis was 67, and 62% were male. The findings also indicate that 77% of the survey patients are Caucasian and that 94% have a college degree or some college education. WM patients most frequently reported a history of osteoporosis/osteopenia (20%), followed by lymph node enlargement (13%), thyroid disorder (11%), and other autoimmune disease (10%). Patients reported a family history of several cancers, including breast cancer (27%), prostate cancer (16%), colon cancer (14%), uterine cancer (14%) and lung cancer (17%).



The most common hematological malignancies observed in relatives were leukemia (8%), WM (5%), other forms of non-Hodgkin's lymphomas (5%), and multiple myeloma. Finally, in terms of environmental exposure, the top three were asbestos at 11%; benzene and pesticides at 9%; and herbicides, fertilizers, and gasoline or other solvents at 7%. This study has the potential to identify important risk factors that have not been studied in WM. The IWMF grant supporting this effort continues through late 2016.

### NEWER INVESTIGATIONAL THERAPIES

One of the drugs frequently used in the treatment of WM is bortezomib (Velcade), which is a proteasome inhibitor. A proteasome is a protein complex within the cell that degrades unneeded or damaged proteins into small pieces that can be recycled to build new proteins. When the proteasome mechanism is inhibited, these proteins accumulate and eventually cause cell death. Many patients with WM become refractory to bortezomib; therefore, **Kasyapa S. Chitta, PhD, Mayo Clinic, et al.** used the proteasomal inhibitor b-AP15 to target a part of the proteasome complex (the cap of the proteasome called 19S) which is different from that targeted by bortezomib. This international study showed that treating with b-AP15 at the same time as bortezomib or the newer carfilzomib did not interfere with the activity of either. When using b-AP15 as solo treatment, increasing the dose levels of b-AP15 resulted in apoptosis (death) of the WM cells.

**Aneel Paulus, MD, MS, Mayo Clinic, et al.** developed bortezomib-resistant cells for each of the three commonly used WM cell lines to mimic the emergence of resistance frequently seen with the persistent use of bortezomib in WM patients. The resistant cell lines were treated with single agent bortezomib, carfilzomib, and the novel agent b-AP15 (discussed above). This international research study determined that the bortezomib-resistant cell lines remained sensitive to b-AP15: MWCL-1 cells were the most sensitive, compared to BCWM-1 and RPCI-WM1 cells. The study also attempted to gain further insight into the genetic processes that regulate cellular response to b-AP15 and discovered a common cluster of 38 genes associated with cell division and proliferation that were differentially expressed in the cell lines treated with b-AP15.

### CLINICAL TRIALS

**Steven P. Treon, MD, MA, PhD, et al.** at DFCI presented interim results from a multi-center study of ibrutinib, a Bruton's tyrosine kinase (BTK) inhibitor, in 63 patients with relapsed or refractory WM. The MYD88 L265P mutation supports malignant growth via signaling involving BTK. Ibrutinib, a daily pill, inhibits BTK and induces apoptosis of WM cell lines bearing MYD88 L265P. Additionally, mutations in the CXCR4 gene induce BTK activity and confer decreased sensitivity to ibrutinib. Forty of 43 (93%) patients tested had the MYD88 L265P mutation, and 10 of 40 (25%) had CXCR4 mutations. At best response, the median serum IgM level fell from 3,610 mg/dL to 1,340 mg/dL, and hematocrit rose from 30.8% to 38.1%. At six months, assessment of 34 patients showed a reduction in bone marrow infiltration from 70% to 45%. The best overall response rate was 81% with a median time to response of four

weeks. Thrombocytopenia (14.3%) and neutropenia (19.1%) were the top Grade 2 or greater toxicities. Only four patients discontinued the study. Of note, the major response rate was 77% for those without the CXCR4 mutations and 30% for those with the CXCR4 mutations.

**Dr. Steven P. Treon et al.** also presented results from a study of the combination therapy carfilzomib, rituximab, and dexamethasone (CaRD) in 31 WM patients. Carfilzomib is, like Velcade, a proteasome inhibitor. Dr. Treon found that CaRD is highly active and offers a neuropathy-sparing approach for proteasome-inhibitor based therapy. Therapy consisted of six induction cycles, followed by maintenance CaRD for 8 cycles beginning 8 weeks after induction. Median hematocrit rose from 32.2% to 40.9%, and hemoglobin rose from 10.7 g/dL to 13.7 g/dL. A total of 30 patients concluded induction therapy with bone marrow involvement reduced from a median of 60% to 7.5%. With a median follow-up of 8 cycles, 22 patients remain in the study, including 20 currently on maintenance therapy. Median time to response was 2.1 months. There was no Grade 2 or greater peripheral neuropathy.

**Dr. Steven P. Treon et al.** reported multi-center trial results for the mTOR inhibitor everolimus (RAD001) as primary therapy for WM patients. Everolimus acts on mTORC1, which is part of a pathway that regulates growth and survival of WM cells. The 33 patients accrued for this study were symptomatic but with adequate organ function and no symptomatic hyperviscosity. Patients received oral everolimus daily and were treated until progression or unacceptable toxicity. If toxicities occurred, dose reduction was allowed. The use of an oral dexamethasone mouthwash was encouraged to prevent oral ulcerations. The results showed a median increase in hemoglobin from 10.8 g/dL to 11.8 g/dL, a median reduction in serum IgM from 4,440 mg/dL to 1360 mg/dL, and a median reduction in bone marrow involvement from 70% to 40%. The most frequent side effects were anemia, oral ulcerations, thrombocytopenia, hyperglycemia, and neutropenia. At a median follow-up of nine months, 6 of 33 patients remain on therapy without progression. Of note was the commonly observed discordance between serum IgM levels and bone marrow disease burden; thus, serial bone marrow assessments should be used for more accurate response monitoring when using everolimus.

In order to investigate the addition of high dose dexamethasone to a protocol of bortezomib, **Véronique Leblond, Hôpital de la Pitié-Salpêtrière, Paris, France, et al.** led a French Phase II trial of 34 patients with advanced WM. All patients started with bortezomib for two cycles; those who had minor or partial response continued with bortezomib, while for those who presented with stable or progressive disease, dexamethasone was added. Both groups then continued for four more cycles on their respective protocols, either bortezomib alone or combination therapy. Two of the objectives monitored were response and safety. At the end of six cycles, the overall response rate for the bortezomib only group was 50%, while for the combination group it improved to 75%. Median overall survival was 41.3 months,





and median progression free survival was 16.8 months. Most Grade 3/4 adverse events were hematological; peripheral neuropathy of Grade 2 or less was seen in 11 cases and of Grade 3/4 was seen in 3 cases.

**Irene M. Ghobrial, MD, et al.** at DFCI presented results of a Phase I/II multi-center clinical trial evaluating everolimus (RAD001) and rituximab, or everolimus and both rituximab and bortezomib in 46 relapsed or relapsed/refractory WM patients. The treatment plan included six cycles followed by everolimus as maintenance for two years. Groups of three patients tried different combinations and dose levels. In the Phase II part, the 16 patients evaluable for response included 13% with a complete response, 68% with a partial response, and 6% with minimal response, for an overall response rate of 88%. No grade 3/4 neuropathy was seen.

Another multi-center study reported by **Irene M. Ghobrial et al.** presented updated results of single-agent oprozomib. This Phase Ib/II study included 42 patients, 12 of whom had WM. Oprozomib is an oral, second-generation proteasome inhibitor that selectively and irreversibly binds to its target. Preliminary findings from Phase Ib show acceptable safety and tolerability and promising antitumor activity in patients with hematologic malignancies. The clinical benefit response rate for WM was 80%. Dose escalation studies are ongoing and the Phase II part will begin once the maximum tolerated dose is reached and the safety profile analyzed.

**Allison C. Rosenthal, DO, et al.** from Mayo Clinic presented a Phase II international study that evaluated the combination of lenalidomide, rituximab, cyclophosphamide, and dexamethasone (LR-CD) in 15 untreated WM patients. Anemia has been noted as a problem in previous trials with lenalidomide, and prior to initiation of treatment, 40% of the patients had either a Grade 2 or Grade 3 anemia. After 12 therapy cycles, the best overall response rate was 80%. The most common Grade 3 or 4 adverse events were anemia, neutropenia, and leukopenia. The median overall survival was 86%, the median progression free survival was 25 months, and one patient died because of disease progression. At the time of this presentation, four patients were still receiving treatment. Based on results from this study, a randomized trial is suggested.

**Sheeba K. Thomas, MD, et al.** from M.D. Anderson Cancer Center conducted a Phase II clinical trial that included induction therapy and autologous stem cell harvest, followed by one cycle of consolidation chemotherapy, for 38 symptomatic untreated patients. As has been previously reported, nucleoside analogue (NA)-based combinations provide excellent responses and survival but may hinder adequate stem cell harvest. To take advantage of the response to NAs, the trial performed stem cell harvest prior to using one cycle of consolidation therapy with the nucleoside analogue 2CdA (cladribine)-cyclophosphamide-rituximab. The induction regimen consisted of rituximab and bortezomib to spare the stem cells. Of the 37 patients treated with this induction regimen, 21 responded. Those who were non-responsive received rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone (R-CVAD). Twenty six patients proceeded to harvest, and 25 of the 26

underwent a successful harvest followed by the 2CdA-containing consolidation therapy; 52% of these patients had a partial response and 48% a very good partial response. At 48 months, 92% of the patients remained alive, and median time to next therapy was 65.5 months. Dr. Thomas concluded that rituximab and bortezomib is a well-tolerated, effective frontline treatment which will still allow for successful stem cell harvest and that one cycle of 2CdA-containing consolidation therapy was sufficient to improve the degree of response.

**Christine I. Chen, MD, Princess Margaret Cancer Centre, Toronto, Canada, et al.** presented results from a Phase I multi-center study of the oral drug Selinexor, which inhibits the activity of the transporter protein XPO1. A total of 29 patients participated in the trial, 26 with multiple myeloma (MM) and 3 with WM. XPO1 plays a key role in transporting tumor suppressor proteins out of the nucleus and leading to their inactivation. Inhibition of XPO1 by Selinexor results in nuclear retention and reactivation of the tumor suppressor proteins, causing the death of multiple myeloma and WM cells while sparing normal B-cells. One of the tumor suppressor proteins affected resulted in inhibition of the NF- $\kappa$ B pathway – a major pathway implicated in WM and noted to be upregulated by the MYD88 L265P mutation. The major adverse events were nausea, anorexia, and fatigue as well as thrombocytopenia, neutropenia, and anemia. All three of the WM patients who participated in this study showed a minor response.

**Ajay Gopal, MD, the University of Washington in Seattle, et al.** reported results of an international Phase II Study of the oral PI3K-delta inhibitor idelalisib with indolent B-cell lymphoma patients who were refractory to both rituximab and an alkylating agent (e.g. bendamustine). Idelalisib was taken continuously until disease progression or intolerance. A total of 125 patients enrolled in the study, 10 of whom had LPL/WM. The overall response rate for the LPL/WM group was 80%. Idelalisib was well tolerated, had an acceptable safety profile, and was highly effective in this study population. This response rate was consistent across all subgroups, regardless of disease histology, number of prior regimens, refractoriness to bendamustine, or tumor bulk. With continued administration of idelalisib, responses were durable beyond one year, substantially exceeding the median duration of response for the last prior therapy.

**Matthew S. Davids, MD, et al.** at DFCI presented data from an ongoing international Phase I study of the Bcl-2 inhibitor ABT-199 (GDC-0199) in patients with relapsed/refractory non-Hodgkin's lymphoma (NHL). Dysregulation of the anti-apoptotic protein Bcl-2 is a hallmark of NHL pathogenesis and contributes to chemotherapy resistance. ABT-199 is an oral, selective, and potent small molecule Bcl-2 inhibitor that is a promising agent for the treatment of patients with NHL. While only 3 of the 32 patients had WM, one of the three had a complete response and the other two had partial responses.

*If you have questions about ASH 2013 or would like to have an electronic file of ASH 2013 abstracts on WM, please contact [john3474@comcast.net](mailto:john3474@comcast.net).*



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