NEWSLETTER

Bing Center for WALDENSTRÖM'S MACROGLOBULINEMIA

Research • Treatment • Care

March 2015

Dear Patients & Friends-

Since our last Newsletter, there has been alot of activity with the Bing Center for WM. For those who are not aware, the FDA (Food & Drug Administration of the United States) has approved the use of ibrutinib (now known as *Imbruvica*) for patients with Waldenstrom's macroglobulinemia. Ibrutinib is the first therapy indicated specifically for WM and previously received Breakthrough Therapy designation for this use.

The new approval was based on data from a Phase II study performed between the Bing Center for WM, Stanford University, and Memorial Sloane under the direction of Drs Steven Treon, Ranjana Advani, and M Lia Palomba. More detailed information on the evolution of Ibrutinib with the Bing Center for WM can be found further into the Newsletter. Currently, the Imbruvica/ Ibrutinib Application for treatment of Waldenström's Macroglobulinemia (WM) has been accepted by the European Medicines Agency. This is the first step to Registration. If Registration is approved, IMBRUVICA would be the first label specifically authorized to treat WM.

Aside from our spotlight topic, constant updated information on our **9** dedicated website updates, forthcoming WM meetings and events have been included. Below Highlighted event[s] listed for the next couple of months. For further information regarding any of these events, please contact Chris Patterson at cpatterson1@partners.org or any of the referenced contacts listed after the announcements.

May (SAVE THE DATE[S])

30th of April to the 3rd of May The IWMF will be holding their annual Education forum in Dallas, Texas at the Hilton DFW Lakes Executive Center. It is a unique opportunity for patients and caregivers to learn from specialists in Waldenstrom's macroglobulinemia (WM) who are involved in many areas of clinical practice and research. Held in a different part of the United States each year, the "ED forum" offers something for everyone, no matter what your experience or level of knowledge. The agenda, additional information and to make hotel accommodations, please visit their website at http://www.iwmf.com/news-and-events/iwmf-educational-forum Presenting from our Center will be Drs Steven Treon and Zachary Hunter.

In order for many of our WMer's to see our Bing Center's updated lectures that have been performed around the world, current and past videos are posted on our You Tube site. Each video can be found by accessing the link below or by going to the (www.bingcenterforwm.org) website where you will find a YouTube link at the top of the webpage. The most current events is that of Dr Treon and the approval of ibrutinib. Many WM patients and caregivers have had questions about the pathway that led to the FDA approval of Imbruvica for WM. Please see this video of Dr. Treon's interview on this historic approval which we hope will answer many of your questions

Dr Treon: "***On the FDA Approval of Imbruvica for WM"*** **[NEW]**

https://www.youtube.com/watch?v=9rE1laXXP98

Dr Treon: "***Genomic and Treatment Advances in WM"***
NP Sandra Kanan: ***"Personal Survival Strategies***"
Zachary Hunter: "***Key Information About Your WM***"

http://www.youtube.com/user/BingCenterForWM?feature=plcp

NEW Publications List from 2014-2015

On behalf of the Bing Center for WM, the following publications have been published within the past twelve months. ***All publications*** are/will be found on the Bing Center Website at www.bingcenterforwm.org

1. ***The genomic landscape of Waldenstrom's macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis.*** (Blood publication, March 2014)

2. ***MYD88-independent growth and survival effects of Sp1 transactivation in Waldenstrom's macroglobulinemia.*** (Blood publication, April, 2014)

3. ***Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom's macroglobulinemia.*** (Blood publication, May, 2014)

4. ***Survival trends in Waldenström macroglobulinemia: an analysis of the Surveillance, Epidemiology and End Results database.*** (Blood publication, June, 2014)

5. ***The WHIM-like CXCR4 S338X somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenstrom's Macroglobulinemia.*** (Leukemia publication, June, 2014)

6. ***Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia.*** (Blood publication, July, 2014)

7. ***Detection of MYD88 L265P in peripheral blood of patients with Waldenström's Macroglobulinemia and IgM monoclonal gammopathy of undetermined significance.*** (Leukemia publication, August, 2014)

8. ***Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus.*** (Blood publication, August, 2014)

9. ***Transcriptional repression of plasma cell differentiation is orchestrated by aberrant over-expression of the ETS factor SPIB in Waldenström macroglobulinaemia.*** (BR. J. Hematology, publication, September, 2014)

10. ***Waldenström macroglobulinemia.*** *(*Hematol Oncol Clin North Am publication, October 2014*)*

11. ***The WHIM-like CXCR4(S338X) somatic mutation activates AKT and ERK, and promotes resistance to ibrutinib and other agents used in the treatment of Waldenström's macroglobulinemia***. (Leukemia, January 2015)

12. ***The BCL2 antagonist ABT-199 triggers apoptosis, and augements ibrutinib and idelalisib mediated cytoxity in CXCR4 Wild-type and CXCR4 WHIM mutated Waldenström macroglobulinemia cells***. (British Journal of Hematology, publication, January, 2015)

13. ***CXCR4 WHIM-like frameshift and nonsense mutations promote ibrutinib resistance but do not supplant MYD88(L265P)-directed survival signaling in Waldenström macroglobulinemia cells***. (British Journal of Haematology, March 2015)

14. ***Incidence of secondary malignancies among patients with Waldenström macroglobulinemia: An analysis of the SEER database*** (Cancer, March 2015)

A national online community provides support for individuals affected by Waldenström's Macroglobulinemia.

I'd like to invite you to join the Waldenström's Macroglobulinemia (WM) national community, brought to you by Dana-Farber Cancer Institute and Cancer Connect. This community connects you with many others from around the world affected by WM for support, guidance, and information about the disease and its related issues. You can share your experiences and knowledge, ask questions, and learn from others who are coping with WM. This community is moderated by Dana-Farber staff with extensive expertise in Waldenström's Macroglobulinemia.

Being the moderator of this online community room for over two years now, it is a very exciting and great way to assist and guide you with your questions, provide you with direction, and take this disease's progress to a new level.

Aside from the WM community room, there are other community rooms available at the same site for those who have secondary cancers or who are just inquisitive of other diseases. Looking forward to seeing you in the Community room!

If you would like to join this community, please follow these steps to register:

- ☐ Click here: http://cancerconnect.com/danafarber to access the Dana-Farber Welcome page, then click **Join now**.
- ☐ Enter your user name, e-mail address, and password, and click **Register**.
- ☐ Once you have registered, on the main Dana-Farber Cancer Connect Community page, you can access the Waldenström's community one of two ways, either:
  - o Scroll down the right side of the page, under **National group members**, and click **Waldenström's**, or
  - o Click this link after you have registered or logged in:

http://cancerconnect.com/group/Waldenstrom's-macroglobulinemia

Cancer Connect allows individuals to interact in a HIPPA-compliant, confidential, safe, and secure environment. As part of this program, members of the community can also participate in more than sixty disease-specific national communities. Cancer-specific groups are available, as well as groups focused on care giving, health and wellness, clinical trials, insurance, nutrition and survivorship, providing support for anyone affected by a diagnosis of cancer.

WM dedicated Websites:

Please go to any of the websites for current and updated information regarding WM

www.BingCenterforWM.org

We regularly update our Bing Center website in order to keep the content up to date.

- **Focus on Patients, Physicians/Researchers, and Caregivers**: Information that can be used "bench to bedside".
- **About the Bing Center**: Description of the Bing Center, clinic and staff.
- **News & Events**: Announcements for recent and upcoming conferences and support group meetings.
- **Clinical Trials**: Updates to current and pending clinical trials, and participating institutions.
- **Basic Research**: Updated with our most recent research projects and studies.
- **Publications**: Updated with our most recent abstracts and published papers (i.e. "How I Treat Waldenstrom's Macroglobulinemia" by Dr. Steven Treon).
- **Bing Center Spotlight:** Focus on topic of special interest to patients, physicians or caregivers.
- **Media Gallery:** Videos and photos from our conferences and special events.

www.stevenptreon.com

The official website of Dr. Steven Treon, its main focus is on Dr. Treon's research of WM.

- **Media**: Galleries of photos in several categories (Bing Center, Conferences, Support Groups).
- **Papers & Publications**: Papers which Dr. Treon has authored or co-authored, sorted by year of publication. Also includes "featured impact articles".
- **WM Info**: The complete description of Waldenstrom's Macroglobulinemia. Dr. Treon co-authored this paper with Dr. G. Merlini. A biography of Dr. Jan Gosta Waldenstrom's is also included.
- **Patient Resources**: Links to our partner groups and organizations.

www.wmworkshop.org

This website includes all the abstracts, agenda, photos, and other information from all the International Physician Workshops for WM held from 2000 to the present. The last Physician conference was held on August 14-17, 2014 in the city of London, UK. For additional updated information on the next Workshop in 2016 in Amsterdam, Netherlands, please go to www.wmworkshop.org

To research archival information from our previous eight workshops (London, 2014, Newport 2012, Venice 2010, Stockholm 2008, Kos 2007, Paris 2004, Athens 2002, and Washington DC 2000), please visit the website.

www.wmctg.org

UNDER RECONSTRUCTION!

We are now adding a seperate page for local WM specialists in your area (aside from those participating in Clinical trials)

This website is devoted to the Waldenström's Macroglobulinemia Clinical Trials Group. It is a resource for patients interested in the status of WM-related clinical trials, as well as links to general information about WM to a physician located close to home.

- **Physicians (USA)**: The list of USA-based physician members of the WMCTG and their locations are currently being updated.
- **Physicians (Int'l)**: The list of international-based physician members of the WMCTG and their locations are currently being updated.
- **Physician Pages**: Photos and biographies of each physician, as well as links to their corresponding institution websites (where available) and contact info. Each physician also has a link to the NIH website (ClinicalTrials.gov) showing their WM-related clinical trials (where applicable).
- **Contact Us**: An online form where comments or questions may be submitted for review by a WMCTG member.
- **Additional Resources**: Links to related websites.

www.iwmf.com

The IWMF, International Waldenstrom's macroglobulinemia Foundation, is a dedicated non-profit, all-volunteer organization, developed and financed solely by patients and their friends and families. It mission is to provide a means for those with Waldenstrom's macroglobulinemia , their family members, doctors, and others with an interest in the disease to find mutual support and encouragement, to provide information and educational programs that address patients' concerns, and to promote and support research leading to a cure.

For additional information, please contact

Sara McKinnie, IWMF Business Office, 6144 Clark Center Avenue, Sarasota FL 34238
Tel: (941)927-4963, Email: info@iwmf.com

http://wmfc.ca/

(NEWLY ADDED!) The purpose of WMFC is to provide support and information to the Canadian WM community. If you are a Canadian and have WM, or are a caregiver, friend, or relative of a WMer, or are an interested member of the Canadian medical community we would welcome you as a member of WMFC. Members of WMFC automatically become members as well of the International Waldenstrom's Macroglobulinemia Foundation (IWMF).

SAVE THE DATE!

WMFC Educational Forum

Saturday, September 26th, 2015
Courtyard Marriott, Calgary Airport
Calgary, Alberta

For further information about meetings, lectures, etc., please contact the WMFC president, ***Arlene Hinchcliffe*** at ahinchcliffe@wmfc.ca or by telephone at 905-337-2450

www.ewmnetwork.eu & www.Waldenstrom's.info

The (EWM network) are members of the European Cancer Patient Coalition, (ECPC) and European Organization for Rare Diseases (EURORDIS). Their aim is to collectively represent all WM patients' interests at a European level. This way, WM patients are given a voice at European health institutions and in European health politics. Hence their motto "Patients for Patients". EWM network is an umbrella organization for European WM patient support groups or patient support organizations.

EWM network was initiated in 2008 by the Dutch MM&WM Patient Association (CMWP), The Netherlands and is registered as a not-for-profit organization under Dutch Law. EWM network aims to represent the interests of WM patients on a European level. It is an organization run by patients and their relatives for patients ("Patients for Patients").

http://portail.Waldenstrom'sfrance.org/

The Waldenstrom's France associate was officially established in 2009. Their website has just been released in hopes to benefit all French-speaking patients, caregivers, physicians, and medical specialists and to guide them properly in the knowledge of WM on a clinical, research, and patient-support direction. Currently, the association has a very active Talk list for all Francophone members (more than 153) from Canada, Belgium, Brazil, Switzerland, North Africa and France. Please visit their website for more information http://portail.Waldenstrom'sfrance.org, become a community member or contact the president of the association of WM France, ***Patrice Ostermann*** at contact@Waldenstrom'sfrance.org with any questions.

http://www.wmuk.org.uk/

The Waldenstrom's Macroglobulinemia (WM) United Kingdom (UK) Support Group was officially established in 2000. They are a non-profit organization created to support those suffering from WM as well as their family and friends in UK and Eire. A specific UK support group chat line is available. For more information, contact ***Roger Brown*** at info@wmuk.org.uk or telephone 0117 3735 733.

The next WMUK Patient forum is being held on April 11th, 2015 at the iconic Birmingham library. For more details to register, please visit their website.

What's Around the Corner?

For more information about the clinical trials at the Bing Center for WM, please contact our Clinical research coordinator, Kirsten Meid at kirsten_meid@dfci.harvard.edu or 617.632.5598 or https://clinicaltrials.gov/

There are a few new trials that will begin shortly under the direction of Drs Castillo and Treon, and NP Sandra Kanan.

(1) A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination With Rituximab in Subjects with Previously Treated Waldenstrom's Macroglobulinemia
Open and accruing for previously treated

(2) Phase II Trial of ixazomib, dexamethasone and rituximab in patients with untreated Waldenstrom's Macroglobulinemia Untreated. **Estimated opening April 2015**. **Ixazomib** is in the same class of drugs as Velcade® (bortezomib) and is made by the same company, Millennium: The Takeda Oncology Company. Ixazomib is considered to be a second-generation proteasome inhibitor because it has improved characteristics and activity over Velcade. In addition, ixazomib is available as a pill whereas Velcade is only available as an injection (subcutaneous or intravenous).

(3) Phase II Study of Phosphatidylinositol-3-kinase (PI3K) Inhibitor Idelalisib (GS-1101) in Waldenström Macroglobulinemia previously treated. **Estimated opening May 2015**. US Brand name of Idelalisib is Zydelig. Idelalisib is an investigational, targeted, highly selective oral inhibitor of phosphoinositide 3-kinase (PI3K) delta, a molecular target that is critical for the activation, proliferation and survival of B lymphocytes. PI3K delta signaling is hyperactive in many B-cell leukemias and lymphomas and drives proliferation, survival and trafficking to lymphoid tissue. - See more at: http://www.gilead.com/news/press-releases/2013/6/gilead-announces-interim-phase-2-data-for-idelalisib-showing-response-in-refractory-indolent-nonhodgkins-lymphoma#sthash.uIn7Wy8a.dpuf

(4) Phase I trial of ARGX-110, a CD70 monoclonal antibody for relapsed/refractory WM patients to determine the safety and efficacy. **Estimated opening May 2015.** ARGX-110 is a CD70-specific SIMPLE Antibody™ that potently modulates both known functions of CD70: tumor cell proliferation and survival, and tumor immune escape. ARGX-110 has been equipped with POTELLIGENT® to enhance its ability to destroy CD70-positive tumor cells. This cytokine, CD70, is also reported to play a role in regulating B-cell activation, cytotoxic function of natural killer cells, and immunoglobulin sythesis. [provided by RefSeq, Jul 2008]

Ibrutinib...PART 2

Yesterday...Today...Tomorrow....

Yesterday

For WM patients, Ibrutinib is generally well tolerated. The dose for WM is 420 mg (3 pills) daily and should be taken approximately the same time each day. It should be taken with 8 ounces of water and can be taken with or without food, according to the package insert. Avoid grapefruit, star fruit, Seville oranges and the juices from these fruits as this can affect the metabolism of ibrutinib. There can be some gastrointestinal symptoms from ibrutinib, which include diarrhea, nausea, heart burn or acid reflux. You may take Imodium which is an over the counter medication if needed to help with the diarrhea or obtain a prescription for anti-nausea medication if needed. Switching to night time administration may help if you continue to have diarrhea. Ibrutinib can affect platelet aggregation (platelets are the blood component that helps stop bleeding).

Labs should be monitored closely to make sure platelet counts are within an acceptable range. Let your doctor know if you are having any bleeding such as nosebleeds. You should avoid or minimize medications that can thin the blood such as aspirin, NSAIDs (ibuprofen, Aleve, etc) and fish oil supplements while on ibrutinib. Ibrutinib will need to be held for a few days if you are going to have an invasive procedure (usually 3 days before, the day of and 3 days after the procedure). There are drug interactions with ibrutinib and medications that are strong CYP3A4/5 inhibitors, inducers or substrates. Taking one of these medications can either increase the ibrutinib levels in your blood or decrease the levels. This can either cause more side effects/make you feel sick or cause ibrutinib drug concentration levels to be too low to be effective.

Check with your doctor prior to starting any new medications, including antibiotics and over the counter medications. Other possible side effects include minor skin rash, mouth sores or sensitivity, scalp tenderness, joint pains, bruising more easily and minor cuts that take longer to heal. There have been some reports of atrial fibrillation especially in patients with a prior history of this condition. If this occurs, it should be managed between a cardiologist and your oncologist especially if new medications are recommended to make sure they are safe to take while on ibrutinib. Utilize your resources if you have any questions or concerns about taking ibrutinib.

Overall, it is a great drug that has been a tremendous impact and helped a lot of WM patients. The response rate is approximately 80% and the onset of response is around four weeks. The duration to be on ibrutinib is long term, as long as it is working and you are tolerating it well.

Today

In January 2015, Waldenstrom's became the fourth cancer for which ibrutinib has been approved by the U.S. Food and Drug Administration(FDA). In 2013 and 2014 the drug was successively approved for patients with mantel cell lymphoma who have been treated with one previous therapy; for patients with chronic lymphocytic leukemia (CLL) who have received at least one previous therapy; and for patients whose CLL tumor cells have lost a specific section of chromosome. The common thread is that all four conditions are malignancies of B cells, white blood cells that make antibodies to fight infections. Ibrutinib works by stifling a protein called BTK in malignant B cells. BTK enables B cells to reproduce and survive and carry out two critical functions- adhering to neighboring cells and traveling in and out of lymph tissue. By blocking BTK, ibrutinib essentially prevents cancerous B cells from carrying out the activities they need to survive.

Approximately 3,500 patients have received IMBRUVICA in clinical trials conducted in 35 countries, by more than 800 investigators around the world. As of June 30, 2014, 12 Phase III trials have been initiated with IMBRUVICA and approximately 50 trials are registered on www.clinicaltrials.gov. The overall clinical development program in CLL currently includes seven Phase III trials and covers all lines of therapy and various combinations of treatments.

Tomorrow

Currently, the European Commission (EC) has granted marketing authorization for IMBRUVICA™ (ibrutinib) throughout the 28 member states of the European Union (EU). IMBRUVICA, a first-in-class, oral, once-daily, non-chemotherapy treatment, is now approved to be marketed for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL), adult patients with chronic lymphocytic leukaemia (CLL) who have received at least one prior therapy, or in first-line in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemo-immunotherapy. Acceptance of a Type II variation application for IMBRUVICA® (ibrutinib) by the European Medicines Agency (EMA) for Waldenstrom's macroglobulinemia occurred in December 2014, and currently is being reviewed and evaluated for WM. Anticipated outcome should be sometime late summer/ early fall. If approved, IMBRUVICA would be the first label specifically authorized to treat WM.

Forthcoming, the Bing Center for WM is forward thinking and engaging in combination therapies with Ibrutinib. Discovery of its genomic mechanisms and ability to partner with other therapeutics can help us understand WM better, and also guide us towards an even better treatment for WM.

For a comprehensive list of affordability programs, please visit www.youandiacess.com.

Additional information on IMBRUVICA, go to www.imbruvica.com or call 1.877.877.3536

As Spring is here, so are all the wonderful things that come with it; cherry blossoms, outdoor sports, a BIG good-bye to snow!, and, of course, our Nurse practitioner, Sandra Kanan, at the Bing Center for WM running the Boston marathon in April for charity! Again! She LOVES the WMer's so much, that she is raising money again for us. Her last marathon in November 2014 raised close to $13,500.00, and we thank each and every one of you who had participated in any way they could have done.

http://www.rundanafarber.org/2015/skanan

Sandra is running on behalf of the Bing Center for WM, Dana Farber Cancer Institute, and all proceeds she raises are given explicitly to the Bing Center's research under the guise of Dr Steven Treon and his lab team. It is a truly a thoughtful activity and hope that you would be able to add to Sandra's goal and the strides in battling WM with our research. If you have the capacity, below is the link to her donation page. Her goal for the Boston Marathon is $20,000.00, and currently she is at $3,175.00.

IN the UK,

Virgin money LONDON MARATHON 2015

We have another marathon runner, Louise Millard, who will be running the London Marathon on April 26th, 2015, on behalf of her step-father with all proceeds going to the Bing Center for WM. Another dedicated mercenary towards WM, Louise has been an exemplary team player for the Bing Center and her family battling WM. With Imbruvica on a direct path into Europe this year, the research being discovered and developed at the Bing Center for WM can only add more to the unraveling of the genomics and interpretation of this disease. For more information and willingness to contribute, please go to Louise's donation page. Her goal for the London Marathon is $10,000.00, and currently she is at $245.00 http://www.rundanafarber.org/2015/louisemillard

The Bing Center for Waldenstrom's macroglobulinemia would like to thank all the Wmer's, caregivers, families, and friends who have done great achievements for their loved ones in 2014.

Throughout last year we received many contributions towards our research for WM, that it would not have been possible for us to have had achieved such great strides in our work and discoveries.

A VERY BIG thank you to the Kelliher/Davis family! Andrea's brother, Stephen, participated in a 100 mile bike fundraiser in September for Waldenstrom's with all proceeds going to the Bing Center for WM!

See you in August

This newsletter is being sent as a courtesy to patients of the Bing Center for Waldenström's Macroglobulinemia. To be removed from this mailing list, or to change your contact information, please visit http://www.wmprogram.org/Contact.asp provide your name and email address, and specify your request in the message box.