Updates of Research in Waldenstrom Macroglobulinemia

Irene Ghobrial, MD
Associate Professor of Medicine
Harvard Medical School
Dana Farber Cancer Institute
Boston, MA
Waldenstrom Macroglobulinemia

- 1944, Jan Waldenstrom described 2 cases with LN, bleeding and anemia
- REAL/WHO: lymphoplasmacytic lymphoma
- Definition:
  - 1- IgM secretion
  - 2- LPL cells in the bone marrow
- 1500 new cases/year
- Asymptomatic and symptomatic
- MGUS, smoldering, symptomatic

Updates of research

- Tissue bank research studies
- CXCR4 regulation in WM
- Clinical trials with everolimus/bortezomib/dex and oprozomib study
- Future direction in IgM MGUS and smoldering WM
Development of an integrated tissue bank that is linked to clinical characteristics from patients with the different stages of WM.

- Goal of Tissue Banking Project:
- Consent 1000 WM patients to obtain clinical data along with samples and epidemiology survey.
- Collect patients’ epidemiology surveys.
- Collect patients’ samples.
- Collect patients’ clinical data.
- Consent a family and a non-family member for each of WM patient as control for their epidemiology survey.
- Collect participants’ epidemiology surveys.
- Collect participants’ samples (blood or saliva for the germline samples).
Development of an integrated tissue bank that is linked to clinical characteristics from patients with the different stages of WM.

<table>
<thead>
<tr>
<th></th>
<th>WM pts clinical database</th>
<th>pts consented on 09 233</th>
<th>pts Epis</th>
<th>Pts samples-BM</th>
<th>Pts samples-blood</th>
<th>Pts samples-saliva</th>
<th>Epis family/nonfamily</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2014</td>
<td>1182</td>
<td>565</td>
<td>420</td>
<td>151</td>
<td>631</td>
<td>153</td>
<td>106</td>
</tr>
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<td>April 2013</td>
<td>1061</td>
<td>445</td>
<td>345</td>
<td>90</td>
<td>230</td>
<td>90</td>
<td>50</td>
</tr>
</tbody>
</table>
Epidemiological survey

• 348 were diagnosed with LPL/WM and 48 with MGUS.
• The median age of patients at diagnosis was 67 years (range, 24-92 years).
• 245 (62%) patients were males.
• Caucasian race (N=305, 77%),
• Ashkenazi Jewish (45, 11%)
Family history of cancer

• Family history of several cancers in relatives: breast cancer (27%), prostate cancer (16%), colon cancer (14%), uterine cancer (14%) and lung cancer (17%).
• The most common hematological malignancies observed in relatives included leukemia (8%), WM (5%), other Non-Hodgkin’s lymphomas (5%).
Exposure to toxins

- Asbestos (11%), benzene and pesticides (9%), herbicides, fertilizers and gasoline or other solvents (7%), petroleum products, engine exhaust, and acrylic and oil based paints (6%).
- 5% or less of the patients reported prior exposure to Agent White, Agent Orange, and Metals.
MYD88 and CXCR4 in WM

Treon et al, NEJM 2012
• CXCR4/SDF1 plays a major role in modulating homing and trafficking of MM and to the bone marrow and extramedullary disease through “EMT” like transcriptional regulation

• CXCR4-related somatic mutation enhances tumor dissemination and drug resistance
CXCR4 somatic mutation occurs in WM patients

WHIM-like C1013G/CXCR4 variant

WHIM syndromes
inherited autosomal dominant mutation of the CXCR4 gene

↓

truncation of the C-terminal domain of the CXCR4

↓

impaired intracellular trafficking

↓

increased responsiveness to CXCL12

Treon et al. *Blood* 2014
Hernandez et al. *Nat Genetics*, 2003
Balabanian et al. *JCI*, 2008
# C1013G/CXCR4: status in WM and other B-cell malignancies

<table>
<thead>
<tr>
<th>Entity</th>
<th>N</th>
<th>CXCR4</th>
<th>C1013G</th>
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<tbody>
<tr>
<td><strong>Waldenström’s Macroglobulinemia</strong></td>
<td>131</td>
<td>37</td>
<td>(28%)</td>
</tr>
<tr>
<td><strong>IgM MGUS</strong></td>
<td>40</td>
<td>8</td>
<td>(20%)</td>
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<tr>
<td>Diffuse Large Cell Lymphoma</td>
<td>75</td>
<td>1</td>
<td>(1.3%)</td>
</tr>
<tr>
<td>Splenic Marginal Zone Lymphoma</td>
<td>14</td>
<td>1</td>
<td>(7%)</td>
</tr>
<tr>
<td>B-CLL (16 with monoclonal component)</td>
<td>37</td>
<td>0</td>
<td>(0%)</td>
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<tr>
<td>Hairy Cell Leukemia</td>
<td>35</td>
<td>0</td>
<td>(0%)</td>
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<tr>
<td>Multiple Myeloma (3 with IgM)</td>
<td>36</td>
<td>0</td>
<td>(0%)</td>
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<tr>
<td>IgA/IgG MGUS</td>
<td>22</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Lymphoplasmacytic Lymphoma (with no WM criteria)</td>
<td>13</td>
<td>0</td>
<td>(0%)</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>6</td>
<td>0</td>
<td>(0%)</td>
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<tr>
<td><strong>Total</strong></td>
<td>409</td>
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</table>

In collaboration with Jesus San Miguel and Ramon Garcia Sanz.
WM patients harboring the C1013G/CXCR4 variant present with higher surface CXCR4 expression vs controls.

Bone marrow-derived CD19+ cells
Waldenstrom Patients
Extra-medullary (lung; kidney) WM tissues present with **C1013G/CXCR4** variant

<table>
<thead>
<tr>
<th>Tissue</th>
<th>C1013G/CXCR4</th>
<th>Wild type/CXCR4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (n=3)</td>
<td>3/3</td>
<td>0</td>
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<tr>
<td>Kidney (n=1)</td>
<td>1/1</td>
<td>0</td>
</tr>
<tr>
<td>Small bowel (n=2)</td>
<td>0</td>
<td>2/2</td>
</tr>
<tr>
<td>Soft tissues (n=4)</td>
<td>0</td>
<td>4/4</td>
</tr>
</tbody>
</table>
C1013G/CXCR4: in vivo functional role in WM

CXCR4 → gain of function (CXCR4 ORF)
CXCR4 → loss of function (CXCR4 k.d.)
CXCR4 → C1013G/CXCR4 mutagenesis
Macroscopic involvement:
- Liver
- Kidney
- Lymph nodes
- Lung
- Bone marrow (limb paralysis)

Functional relevance of \textit{C1013G/CXCR4} variant in WM

\textit{In vivo} studies

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
C1013G Expression (qPCR, $2^{-\Delta\Delta Ct}$) & \multicolumn{1}{c|}{$P = 0.049$} \\
\hline
Parental cells & C1013G cells \\
\hline
\end{tabular}
\end{table}
Functional relevance of $C1013G/CXCR4$ variant in WM higher colonization vs parental cells

**H.E.**

**h-CXCR4**

**h-CD20**

**CXCR4 expression** (positive area; Log$_{10}$) vs Parental cells vs C1013G/CXCR4 cells

**CD20 expression** (positive area; Log$_{10}$) vs Parental cells vs C1013G/CXCR4 cells

$P < 0.01$
Functional relevance of \textit{C1013G/CXCR4} variant in WM higher colonization \textit{vs} parental cells

\begin{figure}
\centering
\begin{subfigure}{0.3\textwidth}
\caption{H.E.}
\includegraphics[width=\textwidth]{h-e.png}
\end{subfigure}
\begin{subfigure}{0.3\textwidth}
\caption{h-CXCR4}
\includegraphics[width=\textwidth]{h-cxcr4.png}
\end{subfigure}
\begin{subfigure}{0.3\textwidth}
\caption{h-CD20}
\includegraphics[width=\textwidth]{h-cd20.png}
\end{subfigure}
\caption{Liver (positive area; Log$_{10}$)}
\end{figure}

\begin{figure}
\centering
\begin{subfigure}{0.5\textwidth}
\caption{CXCR4 expression – Liver (positive area; Log$_{10}$)}
\includegraphics[width=\textwidth]{cxcr4.png}
\end{subfigure}
\begin{subfigure}{0.5\textwidth}
\caption{CD20 expression – Liver (positive area; Log$_{10}$)}
\includegraphics[width=\textwidth]{cd20.png}
\end{subfigure}
\caption{P<0.01}
\end{figure}
Functional relevance of \textit{C1013G/CXCR4} variant in WM: higher colonization vs parental cells

\begin{itemize}
\item Positive area – Lymph nodes (Log_{10})
\item Positive area – Lung (Log_{10})
\end{itemize}

\begin{itemize}
\item Parental cells
\item C1013G (CXCR4)
\item C1013G (CD20)
\end{itemize}

\begin{itemize}
\item \textit{P}<0.001
\item \textit{P}=0.007
\end{itemize}
Functional relevance of \textit{C1013G/CXCR4} variant in WM

Reduced survival vs parental cells

\begin{figure}
\centering
\includegraphics[width=\textwidth]{graph.png}
\caption{Comparison of survival rates between parental and \textit{C1013G/CXCR4} cells.}
\end{figure}

\begin{equation}
P = 0.003
\end{equation}
Development of CXCR4-overexpressing WM cells
CXCR4-gain of function studies
*In vivo* sequelae: bone marrow

**CXCR4 expression** – Femur (positive area; Log_{10})

**CD20 expression** – Femur (positive area; Log_{10})

*Control* vs. CXCR4 over-expressing cells

*P* < 0.01
CXCR4-gain of function studies:
Detection of higher serum IgM and reduced survival

![Graph showing detection of higher serum IgM and reduced survival](chart)

- Human IgM [ng/µg total protein]
  - Uninjected
  - Scramble #1
  - #2
  - #3
  - #4
  - CXCR4 K.I.

- Percent survival
  - Scramble
  - CXCR4+

- P < 0.004
- P = 0.02

![Graph showing survival analysis](chart)
C1013G/CXCR4 WM cells differ at mRNA level from the parental cells
C1013G/CXCR4 variant and drug resistance

CXCR4 mutation predicts resistance to Ibrutinib, RAD001 and CAL101 but not to Carfilzomib or bortezomib
Anti-CXCR4 monoclonal Ab in C1013G/CXCR4 harboring mice

WM mutated cells

Control Ab

anti-CXCR4 Ab
BMS936564/MDX1338

Macroscopic involvement:
Liver
Kidney
Lymph nodes
Lung
Bone marrow (limb paralysis)
MDX1338-dependent inhibition of C1013G/CXCR4 cell colonization in vivo
MDX1338-dependent inhibition of *C1013G/CXCR4* cell colonization *in vivo*
Consensus recommendations of the 4th International WM meeting

• **First Line therapy:**
  – Combination therapy
    • (RCD or CPR; Cytoxan+nucleoside analogues+R; R-CHOP, R-CVP)
  – Rituximab single agent
  – Nucleoside analogues
  – Alkylators

• **Salvage therapy:**
  – Re-use therapies
  – Bortezomib
  – Thalidomide+steroids
  – Alemtuzumab
  – AHSCT

*Dimopoulos, JCO 2009, Treon et al Clin Lymph and Myeloma 2009*
Everolimus and bortezomib and rituximab in WM

% of specific lysis

E:T Ratio

BMSC + 0 10 20 40

Rituximab
RAD001+Rituximab
Bortezomib+Rituximab
RAD001+Bortezomib+Rituximab
RAD001+Rituximab
Bortezomib+Rituximab
RAD001+Bortezomib+Rituximab
Phase I/II Study of Everolimus, Bortezomib and/or Rituximab in Relapsed/Refractory WM

Study Design

Registration

Phase I study
Everolimus/rituximab
Everolimus/bortezomib/rituximab

Determine maximum tolerated dose (MTD)

Phase II study ongoing with 3 drug combination
Baseline demographics

• 46 patients have been enrolled in this phase I/II clinical trial
• The median age is 65 (range, 47–84) yrs
• The median lines of prior therapy is 5 (range, 1–9)
• 45 (98%) patients receiving prior rituximab
• 23 (50%) receiving prior bortezomib.
• The median number of cycles on therapy is 21 (range, 2–41).
Response rate

### Response of the phase I

<table>
<thead>
<tr>
<th>Response</th>
<th>N=23 patients</th>
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<tbody>
<tr>
<td>CR</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>MR</td>
<td>10 (43%)</td>
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<tr>
<td>ORR</td>
<td>18 (78%)</td>
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</table>

### Response rate of the phase II

<table>
<thead>
<tr>
<th>Response</th>
<th>N=23 patients</th>
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</thead>
<tbody>
<tr>
<td>CR</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>PR</td>
<td>14 (61%)</td>
</tr>
<tr>
<td>MR</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>ORR</td>
<td>19 (83%)</td>
</tr>
</tbody>
</table>
The Proteasome

- Highly conserved
- Ubiquitously expressed
- Critical component for regulating cellular homeostasis

26S Proteasome

19S Regulatory Particle

20S Core Particle

19S

Constitutive Proteasome (25%) Immunoproteasome (75%)

Unique N-terminal Threonine active sites

Chymotrypsin-like (CT-L)
Required for cell survival
Oprozomib in WM

Development Of Orally Bioavailable Peptide Epoxyketones: Making “Oral Carfilzomib”

- Tripeptides selected for medicinal chemistry effort
- In vitro potency (target and cytotoxicity)
- In vitro ADME
- Potent compounds ($IC_{50}<100$ nM) assessed in mouse PD models
  - >500 compounds tested

CLINICAL PROFILE OF SINGLE-AGENT MODIFIED-RELEASE OPROZOMIB TABLETS IN PATIENTS WITH HEMATOLOGIC MALIGNANCIES: UPDATED RESULTS FROM A MULTICENTER, OPEN-LABEL, DOSE-ESCALATION, PHASE 1B/2 STUDY

Irene M. Ghobrial, Jonathan L. Kaufman, David Siegel, Ravi Vij, Ashraf Badros, Linda Neuman, Hansen Wong, Janet Anderl, Michael Savona

Abstract 3184. 55th Annual Meeting of the American Society of Hematology; December 7–10, 2013; New Orleans, LA
Enrollment and Patient Demographics

- As of November 13, 2013, 57 patients (37 with MM; 18 with WM; 1 with mantle cell lymphoma; 1 with plasma cell leukemia) were enrolled

- 12 dosing cohorts and have received ≥1 modified-release OPZ tablet in the phase 1 portion of the study

- The majority of patients (35 of 57; 61%) had prior exposure to bortezomib;
  - more than half of patients (19 of 35; 54%) with prior bortezomib exposure were refractory or relapsed and refractory to bortezomib

- Median OPZ treatment exposure was 15.3 weeks (range, 1.3–27.4 weeks) in the 2/7 schedule and 10.0 weeks (range, 0.3–46.9 weeks) in the 5/14 schedule
## Dosing Schedule

**OPZ, oprozomib.**

*Enrollment in the 2/7 tablet cohort is ongoing (enrollment initiated November 5, 2012). *OPZ given orally once daily on days 1, 2, 8, and 9 (2/7) or days 1–5 (5/14) of a 14-day cycle. Treatment was administered in 14-day cycles until disease progression, unacceptable toxicity, or study treatment discontinuation for any reason.*

### Patient cohorts

<table>
<thead>
<tr>
<th>Schedule</th>
<th>1 (n=3)</th>
<th>2 (n=4)</th>
<th>3 (n=3)</th>
<th>4 (n=7)</th>
<th>5 (n=3)</th>
<th>6 (n=7)</th>
<th>7 (n=3)</th>
<th>8 (n=8)</th>
<th>9 (n=3)</th>
<th>10 (n=6)</th>
<th>11 (n=7)</th>
<th>12 (n=3)</th>
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<tbody>
<tr>
<td>2/7</td>
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<td>5/14</td>
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</tbody>
</table>

### Daily dose

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>1 (n=3)</th>
<th>2 (n=4)</th>
<th>3 (n=3)</th>
<th>4 (n=7)</th>
<th>5 (n=3)</th>
<th>6 (n=7)</th>
<th>7 (n=3)</th>
<th>8 (n=8)</th>
<th>9 (n=3)</th>
<th>10 (n=6)</th>
<th>11 (n=7)</th>
<th>12 (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg</td>
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<td>210 mg</td>
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<td>240 mg</td>
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</table>

### Planned cumulative treatment exposure per 14-day cycle

<table>
<thead>
<tr>
<th>14-day cycle</th>
<th>1 (n=3)</th>
<th>2 (n=4)</th>
<th>3 (n=3)</th>
<th>4 (n=7)</th>
<th>5 (n=3)</th>
<th>6 (n=7)</th>
<th>7 (n=3)</th>
<th>8 (n=8)</th>
<th>9 (n=3)</th>
<th>10 (n=6)</th>
<th>11 (n=7)</th>
<th>12 (n=3)</th>
</tr>
</thead>
<tbody>
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<td>750 mg</td>
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</table>
Treatment-Emergent Adverse Events
A: Hematologic Adverse Events. B: Nonhematologic Adverse Events.
Summary of Serious Adverse Events

- Six patients (24%) experienced serious adverse events (SAEs) in the 2/7 treatment schedule
- Seven patients (21.9%) experienced SAEs in the 5/14 treatment schedule

GI toxicity leading to fatal outcome in 2 patients with Multiple myeloma.
Subject 14-139-0203

- 60 yo Male with WM, Best Response CR

Prior TX

Rituxan- 8/12 to 9/12 (SD)

OPZ (180mg 5/14 schedule) – 1/13 to Present

Initial DX- Jun 2012

Complete Response- Apr 2013
Changes in IgM from Baseline

![Bar chart showing changes in IgM from baseline for different patient IDs and treatment doses.](chart.png)
Changes in Hematocrit from Baseline

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>% Change from Baseline in Hematocrit</th>
</tr>
</thead>
<tbody>
<tr>
<td>150 mg</td>
<td>-80</td>
</tr>
<tr>
<td>180 mg</td>
<td>-60</td>
</tr>
<tr>
<td>210 mg</td>
<td>-40</td>
</tr>
<tr>
<td>240 mg</td>
<td>-20</td>
</tr>
<tr>
<td>270 mg</td>
<td>0</td>
</tr>
</tbody>
</table>

**Legend:**
- Black: 150 mg
- Blue: 180 mg
- Red: 210 mg
- Green: 240 mg
- Orange: 270 mg

**Patient IDs:**
- 203: CR
- 60: SD
- 57: PR
- 207: PR
- 209: PR
- 154: PR
- 201: PR
- 216: NA
- 211: MR
- 208: PR
- 212: NA
Summary

Ibrutinib

Proteasome inhibitors

CXCR4 inhibitors

IRAK inhibitors?

CXCR4

miRNA155 inhibitors

HDAC inhibitors
IgM MGUS and smoldering WM- new direction of research

• Watch and wait or watch and worry
• Who will progress and who will not?
• Genomic studies of precursor conditions
• Prevention of Progression Clinic
• Clinical trials to prevent progression
• IgM and neuropathy
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Andrea Kolligian

Irene_ghobrial@dfci.harvard.edu