New Insights into the Biology and Therapy of Waldenström’s Macroglobulinemia

Steven P. Treon, MD, MA, MS, PhD
Professor of Medicine
Waldenström's Macroglobulinemia – first described by Jan Gosta Waldenström in 1944.
Manifestations of WM Disease

Bone Marrow

↓Hb>>> ↓PLT> ↓WBC

Hyperviscosity Syndrome:
Epistaxis, Headaches
Impaired vision
>6,000 mg/dL or >4.0 CP

Cold Agglutinemia (5%)
Cryoglobulinemia (10%)
IgM Neuropathy (22%)
Amyloidosis (10-15%)

Hepcidin
↓Fe Anemia

≥20% at diagnosis; 50-60% at relapse.

Hyperviscosity Related Retinal Changes in WM

- Retinal vein dilatation seen IgM >3,000 mg/dL
- Retrograde flow and hemorrhages >6,000 mg/dL

Cryoglobulinemia in a patient with Waldenstrom’s macroglobulinemia
Peripheral Neuropathies in WM

- 20-25% of WM patients
- Usually a sensory demyelinating neuropathy related to anti-Myelin Associated Glycoprotein (MAG) IgM antibody.

**MAG IgM**

- Amyloid neuropathy is rare and associated with axonal degeneration.

Waldenstrom’s Macroglobulinemia: Genetic Predisposition

• Strong familial predisposition (20-25%)
• Ashkenazi Jews (20%)
• Rare in African Americans (<5%)
• IgM MGUS 1.8-2% annual progression rate: 40-90% progress to WM.

Sequenced the germline of over 800 patients with sporadic and familial disease.

- Targeted sequencing used to identify variants in genes flagged by whole genome sequencing. Results expected Spring 2017.
NCCN Guidelines for Initiation of Therapy in WM

- Hb ≤10 g/dL on basis of disease
- PLT <100,000 mm³ on basis of disease
- Symptomatic hyperviscosity
- Moderate/severe peripheral neuropathy
- Symptomatic cryoglobulins, cold agglutinins, autoimmune-related events, amyloid.

## Primary Therapy of WM with Rituximab

<table>
<thead>
<tr>
<th>Regimen</th>
<th>ORR</th>
<th>VGPR/CR</th>
<th>TTP (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab x 4</td>
<td>25-30%</td>
<td>0-5%</td>
<td>13</td>
</tr>
<tr>
<td>Rituximab x 8</td>
<td>40-45%</td>
<td>5-10%</td>
<td>16-22</td>
</tr>
<tr>
<td>Rituximab/thalidomide</td>
<td>70%</td>
<td>10%</td>
<td>30</td>
</tr>
<tr>
<td>Rituximab/cyclophosphamide i.e. CHOP-R, CVP-R, CPR, CDR</td>
<td>70-80%</td>
<td>20-25%</td>
<td>30-36</td>
</tr>
<tr>
<td>Rituximab/nucleoside analogues i.e. FR, FCR, CDA-R</td>
<td>70-90%</td>
<td>20-30%</td>
<td>36-62</td>
</tr>
<tr>
<td>Rituximab/Proteasome Inhibitor i.e. BDR, VR, CaRD</td>
<td>70-90%</td>
<td>20-40%</td>
<td>42-66</td>
</tr>
<tr>
<td>Rituximab/bendamustine</td>
<td>90%</td>
<td>30-40%</td>
<td>69</td>
</tr>
</tbody>
</table>

Reviewed in Dimopoulos et al, Blood 2014; 124(9):1404-11; Treon et al, Blood 2015; How I Treat WM
Bendamustine-R vs. CHOP-R: WM Subset Analysis

Rituximab induced IgM Flare in WM Patients

$P$ denotes patient-required plasmapheresis for hyperviscosity.

Clinical Sequelae of Rituximab IgM Flare

• Symptomatic hyperviscosity possible in patients with high serum IgM (>4,000 mg/dL).

• IgM Neuropathy, Cryoglobulins, Cold Agglutinins: Rituximab can potentiate symptoms. Consider PP.

• Patients with IGM> 4,000 mg/dL or Symptomatic HV: Avoid Rituximab until IgM in “safe range” either by plasmapheresis or chemotherapy without Rituximab.

Nucleoside Analogues in WM

- Risk of Transformation or MDS/AML is 10-15%;
- Risk of secondary malignant events in 1/3 patients with FCR;
- Stem cell collection impacted by nucleoside analogues: avoid in ASCT candidates;
- Consider Impact on future therapy (Bendamustine);
- Role in CNS Disease (Bing Neel Syndrome)

# Proteasome-Inhibitor Related Peripheral Neuropathy

<table>
<thead>
<tr>
<th></th>
<th>GRADE 1,2</th>
<th>GRADE ≥3</th>
<th>PI-DISCONTINUED</th>
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<tbody>
<tr>
<td>2X WEEK BORT</td>
<td>40-70%</td>
<td>20-30%*</td>
<td>20-30%</td>
</tr>
<tr>
<td>1X WEEK BORT</td>
<td>20-40%</td>
<td>5-20%</td>
<td>10-20%</td>
</tr>
<tr>
<td>CaRD</td>
<td>20%</td>
<td>0%</td>
<td>0%</td>
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</table>

New directions in WM
WHOLE GENOME SEQUENCING IN WM

Congratulations! It only took you 70 years!!

Paired Sequencing from same individuals

NORM

WM

3,000,000,000 nucleotides
MYD88 Mutations in B-cell LPD

93-95% MYD88 L265P
2% Non-L265P MYD88

29% MYD88 L265P
10% Non-L265P MYD88

MYD88 mutations transactivate NFkB

Ngo et al, Nature 2011
Treon et al, NEJM 2012

MYD88 L265P mutated WM cells
Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

Yang et al, Blood 2013; Yang et al, Blood 2016
Ibrutinib binds to and blocks HCK kinase activity

Yang et al, BLOOD 2016
HCK gatekeeper mutant (T333M) promotes resistance in MYD88 mutated WM cells treated with Ibrutinib or A419259

Yang et al, BLOOD 2016
WHIM-like CXCR4 C-tail mutations in WM Warts, Hypogammaglobulinemia, Infection, and Myelokathexis

- 30-40% of WM patients
- >30 Nonsense, Frameshift Mutations
- Segue with MYD88L265P
- Transcriptional silencing of TLR pathway regulators
- Promote SDF-1 hyperactivation, WM cell growth and ibrutinib resistance through enhanced AKT/ERK signaling.

CXCR4 Signaling in WM Patients with WHIM mutations

CXCL12

Ulucuplomab

CXCR4

Ser<sup>346/7</sup>

B-arrestins

WM CELL

ERK

AKT

SURVIVAL

DRUG RESISTANCE

PHASE II STUDY OF ULOCUPLOMAB AND IBRUTINIB IN WALDENSTROM’S

Cao et al, Leukemia 2014
Rocarro et al, Blood 2014
Cao et al, BJH 2015
Multicenter study of Ibrutinib in Relapsed/Refractory WM (≥1 prior therapy)

Progressive Disease (PD) or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

420 mg po qD Ibrutinib

Screening

Registration

Stable Disease or Response Continue

Event Monitoring

MYD88, CXCR4 Mutation Status

R. Advani

L. Palomba
## Baseline Characteristics for Study Participants (n=63)

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<th>Median</th>
<th>Range</th>
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<td>Age (yrs)</td>
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<td>44-86</td>
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<tr>
<td>Prior therapies</td>
<td>2</td>
<td>1-9</td>
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<tr>
<td>Hemoglobin (mg/dL)</td>
<td>10.5</td>
<td>8.2-13.8</td>
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<tr>
<td>Serum IgM (mg/dL)</td>
<td>3,520</td>
<td>724-8,390</td>
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<tr>
<td>B₂M (mg/dL)</td>
<td>3.9</td>
<td>1.3-14.2</td>
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<td>BM Involvement (%)</td>
<td>60</td>
<td>3-95</td>
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<tr>
<td>Adenopathy &gt;1.5 cm</td>
<td>37 (59%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Splenomegaly &gt;15 cm</td>
<td>7 (11%)</td>
<td>N/A</td>
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</table>

Treon et al, NEJM 2015; 372:1430
Serum IgM and Hb Levels Following Ibrutinib

Serum IgM

Best IgM Response: 3,520 to 880 mg/dL; p<0.001

Hb

Best Hemoglobin Response: 10.5 to 13.8; p<0.001

Best Clinical Responses to Ibrutinib

Median duration of treatment: 19.1 (range 0.5-29.7) months

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<tr>
<th>Response</th>
<th>(N=)</th>
<th>(%)</th>
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<tr>
<td>VGPR</td>
<td>10</td>
<td>16</td>
</tr>
<tr>
<td>PR</td>
<td>36</td>
<td>57</td>
</tr>
<tr>
<td>MR</td>
<td>11</td>
<td>17</td>
</tr>
</tbody>
</table>

ORR: 91%  Major RR (≥ PR): 73%

Median time to ≥ MR: 4 weeks
Median time to ≥ PR or better: 8 weeks

Progression-free and overall survival for 63 previously WM patients treated with ibrutinib.

Median follow-up of 37 months, no change in PFS

Palomba et al, IWWM9, 2016

Ibrutinib Related Adverse Events in previously treated WM patients

Toxicities >1 patient; N=63

- Neutropenia
- Anemia
- Thrombocytopenia
- Arrhythmia
- Lung Infection
- Skin Infection
- Diarrhea
- Post-procedure bleed
- Epistaxis
- Dehydration
- Pre/Syncope
- Hypertension
- Mucositis

Grade 2
Grade 3
Grade 4

# of patients with toxicity

No impact on IGA and IGG immunoglobulins

10% incidence with larger WM Experience; earlier presentation for those patients with prior Afib history.

Treon et al, 2015; Gustine et al, 2016
FDA News Release
FDA expands approved use of Imbruvica for rare form of non-Hodgkin lymphoma
First drug approved to treat Waldenstrom’s
January 29, 2015

EMA Approval for symptomatic previously treated and chemoimmunotherapy unsuitable frontline WM
First ever for Waldenstrom’s
July 8, 2015

April 5, 2016

September, 2015
Responses to ibrutinib are impacted by MYD88 (L265P and non-L265P) and CXCR4 mutations.

<table>
<thead>
<tr>
<th></th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{WT}</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{WHIM}</th>
<th>MYD88\textsuperscript{WT} CXCR4\textsuperscript{WT}</th>
<th>p-value</th>
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<tbody>
<tr>
<td>N</td>
<td>36</td>
<td>21</td>
<td>5</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Overall RR</td>
<td>100%</td>
<td>85.7%</td>
<td>60%</td>
<td>&lt;0.01</td>
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<tr>
<td>Major RR</td>
<td>91.7%</td>
<td>61.9%</td>
<td>0%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

2 patients subsequently found to have other MYD88 mutations not picked up by AS-PCR

Kinetics of major responses following ibrutinib therapy in genotyped WM patients.

Treon et al, NEJM 372: 1430, 2015

MYD88<sup>L265P</sup> CXCR4<sup>WT</sup>
MYD88<sup>L265P</sup> CXCR4<sup>WHIM</sup>
MYD88<sup>WT</sup> CXCR4<sup>WT</sup>
Ibrutinib in Rituximab-Refractory WM Patients: Multicenter, Open-Label Phase 3 Substudy (iNNOVATE™)

Median Prior Therapies: 4 (range 1-7)
Median follow-up: 18.1 (range 6.3-21.1 months)

**ORR: 90%  Major RR (≥ PR): 71%**

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<thead>
<tr>
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<th>(N=)</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VGPR</td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td>PR</td>
<td>18</td>
<td>58</td>
</tr>
<tr>
<td>MR</td>
<td>6</td>
<td>19</td>
</tr>
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</table>

Median time to ≥ MR: 4 weeks
Median time to best response: 8 weeks
18 mo PFS: 86%
18 mo OS: 97%

Impact of CXCR4 Mutation Status on IgM and Hgb Response

Dimopoulos et al, IWWM9; Lancet Oncology, 2016 (Accepted)
Phase II Study of Ibrutinib plus Ulucuplomab in Relapsed/Refractory CXCR4<sup>WHIM</sup> WM Patients

Screening

Informed Consent and Registration

Ibrutinib 420 mg po daily + Ulucuplomab

Progressive Disease or Unacceptable Toxicity

Stop Ibrutinib/Ulucuplomab

Event Monitoring

SD or Response Continue

Event Monitoring
Primary Therapy of WM with Ibrutinib

N=30
420 mg a day x 4 years
All patients are undergoing whole genome sequencing at 6, 12, 24, 36, 48 months
Clonal sequencing to determine how individual cells respond to ibrutinib.

Study fully enrolled
Signaling Pathways Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

MYD88

IRAK4

IRAK1

TRAF6

TAK1

TAB2

TAB1

TLRs/IL-1R

Ibrutinib

ACP196

CC-292

BGB-3111

BTK

IL-6

Microenvironment

gp-130

HCK

PI3K

PLCγ

AKT

PKC

mTOR

ERK1/2

IkBα

p50

p65

NEMO

IKKα

IKKβ

Degradation

growth survival

growth

survival
IRAK1/4 kinase survival signaling remains intact in WM cells from ibrutinib treated patients.

On ibrutinib ≥6 cycles

Yang et al, ASH 2015
Combining of Novel IRAK1 inhibitor JH-X-119 with Ibrutinib Shows Synergism in MYD88 Mutated Cells

**BCWM.1**

<table>
<thead>
<tr>
<th>Combination Index</th>
<th>Ibrutinib</th>
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<tbody>
<tr>
<td><strong>μM</strong></td>
<td>4.000</td>
</tr>
<tr>
<td>20.000</td>
<td>0.761</td>
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<tr>
<td>6.325</td>
<td>0.488</td>
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<tr>
<td>2.000</td>
<td>0.605</td>
</tr>
<tr>
<td>0.632</td>
<td>0.573</td>
</tr>
<tr>
<td>0.200</td>
<td>0.561</td>
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**TMD-8**

<table>
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<tr>
<th>Combination Index</th>
<th>Ibrutinib</th>
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<tbody>
<tr>
<td><strong>μM</strong></td>
<td>0.040</td>
</tr>
<tr>
<td>20.000</td>
<td>0.193</td>
</tr>
<tr>
<td>6.325</td>
<td>0.126</td>
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<td>2.000</td>
<td>0.375</td>
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<tr>
<td>0.632</td>
<td>0.914</td>
</tr>
<tr>
<td>0.200</td>
<td>1.112</td>
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</table>
Acquired Resistance in WM Patients on Ibrutinib.

<table>
<thead>
<tr>
<th>Patient*</th>
<th>L265P positive cells with BTK C481R&lt;sup&gt;T&gt;C&lt;/sup&gt;</th>
<th>L265P positive cells with BTK C481S&lt;sup&gt;T&gt;A&lt;/sup&gt;</th>
<th>L265P positive cells with BTK C481S&lt;sup&gt;G&gt;C&lt;/sup&gt;</th>
<th>L265P positive cells with BTK C481Y&lt;sup&gt;G&gt;A&lt;/sup&gt;</th>
<th>L265P positive cells with PLCG2 Y495H&lt;sup&gt;T&gt;C&lt;/sup&gt;</th>
<th>L265P positive cells with CARD11 L878F&lt;sup&gt;C&gt;T&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>P2</td>
<td>32.4%</td>
<td>6.6%</td>
<td>5.8%</td>
<td>1.0%</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>P3</td>
<td>0.3%</td>
<td>34.4%</td>
<td>6.5%</td>
<td>0.3%</td>
<td>None</td>
<td>0.2%</td>
</tr>
<tr>
<td>P4</td>
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<td>None</td>
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<td>None</td>
<td>None</td>
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<td>P5</td>
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<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>P6</td>
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<td>None</td>
<td>10.3%</td>
<td>None</td>
<td>11.9%</td>
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</table>

Targeted next-generation sequencing for MYD88, CXCR4, BTK, PLCG2, CARD11, LYN. All patients are MYD88 Mutated.

P2, P3, P6 are CXCR4 WHIM Mutated.  

Xu et al, IWWM9, Plenary Abstract 001
Serial samples from WM Patient P3 with multiple BTK Cys$_{481}$ mutations

**Patient P3: Fraction of MYD88-L265P positive cells with BTK Cys481 mutations**

<table>
<thead>
<tr>
<th>Sampling date</th>
<th>Cys481ArgT&gt;C</th>
<th>Cys481SerT&gt;A</th>
<th>Cys481SerG&gt;C</th>
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</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Month 11</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Month 22</td>
<td>0.00</td>
<td>0.71%</td>
<td>0.19%</td>
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<tr>
<td>Month 35</td>
<td>2.54%</td>
<td>26.08%</td>
<td>3.62%</td>
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</table>

Xu et al, IWWM9, Plenary Abstract 001
BTK C481S expressing cells displayed persistent activation of BTK and ERK1/2 following Ibrutinib treatment.

<table>
<thead>
<tr>
<th></th>
<th>BCWM.1</th>
<th>Ibrutinib 0.5uM</th>
<th>Ibrutinib 0.1uM</th>
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<tbody>
<tr>
<td></td>
<td>DMSO</td>
<td>Vector</td>
<td>BTK WT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BTK C481S</td>
<td>BTK WT</td>
</tr>
<tr>
<td>p-BTK</td>
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<td>BTK WT</td>
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<td>Vector</td>
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<td></td>
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</tr>
<tr>
<td>p-BTK</td>
<td></td>
<td>BTK C481S</td>
<td>BTK WT</td>
</tr>
<tr>
<td>BTK</td>
<td></td>
<td>Vector</td>
<td>BTK WT</td>
</tr>
<tr>
<td>p-PLCy2</td>
<td></td>
<td>BTK C481S</td>
<td>BTK WT</td>
</tr>
<tr>
<td>PLCy2</td>
<td></td>
<td>Vector</td>
<td>BTK WT</td>
</tr>
<tr>
<td>p-ERK</td>
<td></td>
<td>BTK C481S</td>
<td>BTK WT</td>
</tr>
<tr>
<td>ERK</td>
<td></td>
<td>Vector</td>
<td>BTK WT</td>
</tr>
<tr>
<td>GAPDH</td>
<td></td>
<td>BTK C481S</td>
<td>BTK WT</td>
</tr>
</tbody>
</table>
HCK Inhibitors Overcome BTK-C481S mutation caused Ibrutinib Resistance in WM and ABC-DLBCL cell lines

Yang et al, IWWM9 2016
Ibrutinib (560 mg/day) induced response in a WM patient with Bing Neel Syndrome

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Time post-dose (h)</th>
<th>Ibrutinib (nM)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CSF</td>
<td>Plasma</td>
</tr>
<tr>
<td>Day 1</td>
<td>0</td>
<td>BLQ</td>
<td>BLQ</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>34</td>
<td>1133</td>
</tr>
<tr>
<td>1 Month</td>
<td>3</td>
<td>16</td>
<td>463</td>
</tr>
<tr>
<td>4 Months</td>
<td>2.5</td>
<td>7</td>
<td>318</td>
</tr>
</tbody>
</table>

Mason et al, BJH 2016
BCL-2 is overexpressed in primary WM patient cells by next generation sequencing (RNAseq) in MYD88 and CXCR4 mutated and unmutated patients.

p<0.001 for healthy donor samples versus any MYD88$^{L265P}$CXCR4$^{WT}$ or WHIM

Venetoclax (ABT-199) enhances Ibrutinib killing in CXCR4\textsuperscript{WT} and CXCR4\textsuperscript{WHIM} expressing WM Cells.

**Untreated**

**Ibrutinib >6 mo.**

Cao et al, BJH 2015 (Epub ahead of print)
## Responses to the anti-BCL2 agent Venetoclax (ABT-199) in previously treated NHL Patients

<table>
<thead>
<tr>
<th>Histology</th>
<th>Overall Response (CR + PR)</th>
<th>Complete Response n (%)</th>
<th>Partial Response n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n=33)</td>
<td>53%</td>
<td>3/36 (8)</td>
<td>16/36 (44)</td>
</tr>
<tr>
<td>MCL (n=11)*</td>
<td>82%</td>
<td>1/11 (9)</td>
<td>8/11 (73)</td>
</tr>
<tr>
<td>FL (n=11)</td>
<td>27%</td>
<td>-</td>
<td>3/11 (27)</td>
</tr>
<tr>
<td>DLBCL (n=8)</td>
<td>38%</td>
<td>1/8 (13)</td>
<td>2/8 (25)</td>
</tr>
<tr>
<td>WM (n=3)</td>
<td>100%</td>
<td>1/3 (33)</td>
<td>2/3 (67)</td>
</tr>
<tr>
<td>MZL (n=2)</td>
<td>50%</td>
<td>-</td>
<td>1/2 (50)</td>
</tr>
<tr>
<td>MM (n=1)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Davids et al, ASH 2013
Phase I/II Study of ABT-199 in Previously Treated WM

Screening

Informed Consent and Registration

ABT-199 200→800 mg a Day

Progressive Disease or Unacceptable Toxicity

Stop ABT-199

Event Monitoring

SD or Response
Continue

Event Monitoring
Approach to Frontline Therapy of Symptomatic WM

**Hyperviscosity, Severe Cryos, CAGG, PN** ➞ **Plasmapheresis**

**MYD88 Mutated/No CXCR4 mutation**
No bulky disease, no contraindications ➞ Ibrutinib (if available)
Bulky disease ➞ Benda-R
Amyloidosis ➞ Bortezomib/Dex/Rituximab (BDR)
IgM Peripheral Neuropathy ➞ Rituximab ± Alkylator

**MYD88 Mutated/CXCR4 mutation**
Same caveats as above
If immediate response needed, either BDR or Benda-R

**MYD88 Wild-Type**
✓ non-L265P MYD88 mutations
BDR or Benda-R

- Hold Rituximab until IgM <4000 mg/dL or empiric pheresis is performed.
- Consider Maintenance Rituximab
- Consider Ofatumumab if R intolerant.
Salvage Therapy of Symptomatic WM

Consider repeat primary therapy if response >2 years

**MYD88 Mutated/No CXCR4 mutation**
Same caveats as primary therapy

**MYD88 Mutated/CXCR4 mutation**
Same caveats as primary therapy
If immediate response needed, either BDR or Benda-R

**MYD88 Wild-Type**
Same caveats as primary therapy
✓ non-L265P MYD88 mutations

- Everolimus >2 prior therapies
- Nucleoside analogues (non-ASCT candidates)
- ASCT in multiple relapses, chemosensitive disease
- Consider Maintenance Rituximab
- Consider Ofatumumab if R intolerant.
Can the epigenome give us the next giant leap forward for WM?
Summary

WM can present with broad symptomatology. Asymptomatic patients should be observed.

Treatment options include rituximab alone and in combination. Objectives as well risks of therapy should be considered when making treatment choices.

MYD88 and CXCR4 mutations are common in WM. MYD88 activates BTK and HCK in WM cells.

Ibrutinib represents a novel treatment option for WM. MYD88 and CXCR4 mutation status impacts ibrutinib responses. Multiple mutations common with acquired ibrutinib resistance.
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