Waldenström’s Macroglobulinemia: Treatment Approach

Steve Treon MD, PhD
Bing Center for Waldenstrom’s Macroglobulinemia
Dana Farber Cancer Institute
Harvard Medical School
# 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
### WM–centric toxicities with commonly used therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>WM Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rituximab</strong></td>
<td>• IgM flare (40-60%)-&gt; Hyperiscosity crisis, Aggravation of IgM related PN, CAGG, Cryos.</td>
</tr>
<tr>
<td></td>
<td>• Hypogammaglobulinemia-&gt; infections, IVIG</td>
</tr>
<tr>
<td></td>
<td>• Intolerance (10-15%)</td>
</tr>
<tr>
<td><strong>Fludarabine</strong></td>
<td>• Hypogammaglobulinemia-&gt; infections, IVIG</td>
</tr>
<tr>
<td></td>
<td>• <strong>Transformation, AML/MDS (15%)</strong></td>
</tr>
<tr>
<td><strong>Bendamustine</strong></td>
<td>• Prolonged neutropenia, thrombocytopenia (especially after fludarabine)</td>
</tr>
<tr>
<td></td>
<td>• <strong>AML/MDS (5-8%)</strong></td>
</tr>
<tr>
<td><strong>Bortezomib</strong></td>
<td>• Grade 2+3 Peripheral neuropathy (60-70%); High discontinuation (20-60%)</td>
</tr>
</tbody>
</table>
Pro-Survival Signaling Driven by Mutated MYD88 in Waldenström's Macroglobulinemia

MYD88 mutations 95-97% WM

Ibrutinib
Acalabrutinib
BGB-3111
SNS-062

IL-6R

TLRs/IL-1R

IBTK

del6q21-25

MYD88

BTK

IRAK4

IRAK1

TRAF6

TAK1

NEMO

IKKα

IKKβ

IBTK

MAPKs

MEK

ERK

HCK

PI3K

PKC

PLCy

PIK3R2

AKT

mTOR

gp-130

NFKB

Ibrutinib

TNFAIP3

HIVEP2

Del6q21-25

MYD88 mutations

Yang et al, Blood 2013
Yang et al, Blood 2016
Hunter et al, Blood 2014
Hunter et al, JCO 2017
Guerrera et al, Haematologica 2018

Degradation

growth survival
Mutations in CXCR4 permit ongoing pro-survival signaling by CXCL12, the ligand for CXCR4 receptor.

CXCR4 receptor remains up with mutation

CXCL12

Bone Marrow Stroma

WM Cell

Drug resistance

CXCR4 mutations in 30-40% WM
Multicenter study of Ibrutinib in Relapsed/Refractory WM (≥1 prior therapy)

NCT01614821

Screening

Registration

420 mg po qD Ibrutinib

Progressive Disease (PD) or Unacceptable Toxicity

Stop Ibrutinib

Event Monitoring

Stable Disease or Response
Continue

Event Monitoring

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

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>MYD88\textsuperscript{Mut} CXCR4\textsuperscript{WT}</th>
<th>MYD88\textsuperscript{Mut} CXCR4\textsuperscript{Mut}</th>
<th>MYD88\textsuperscript{WT} CXCR4\textsuperscript{WT}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>63</td>
<td>36</td>
<td>21</td>
<td>5*</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>91%</td>
<td>100%</td>
<td>85.7%</td>
<td>60%</td>
<td>0.005</td>
</tr>
<tr>
<td>Major (&gt;PR)</td>
<td>78%</td>
<td>97%</td>
<td>67%</td>
<td>0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>VGPR</td>
<td>29%</td>
<td>44%</td>
<td>10%</td>
<td>0%</td>
<td>0.007</td>
</tr>
<tr>
<td>Time to Minor Response (mos.)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.10</td>
</tr>
<tr>
<td>Time to Major response (mos.)</td>
<td>2.0</td>
<td>2.0</td>
<td>6.0</td>
<td>N/A</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*2 patients at initial reporting with major responses were discovered subsequently to have MYD88 mutated disease (S243N, L265P). One patient at initial reporting was subsequently found to CXCR4 mutated disease upon genotyping of CD19-selected WM cells.

Treon et al, EHA 2018
Ibrutinib in Previously Treated WM: Updated PFS

All patients

MYD88 and CXCR4 Status

5 year PFS: 60% (95% CI 46-71%).

Treon et al, EHA 2018
Ibrutinib Related Adverse Events in previously treated WM patients

Toxicities >1 patient; N=63

Number of Subjects with Toxicity

- Neutropenia: 22% (No change)
- Anemia: 14% (No change)
- Thrombocytopenia: 5% to 11% with longer follow-up
- Arrhythmia: 2% to 8% with longer follow-up
- Lung Infection
- Skin Infection
- Diarrhea
- Post-procedure bleed
- Epistaxis
- Dehydration
- Pre/Syncope
- Hypertension
- Mucositis

Update on Adverse Events (Grade >2) in >5% of patients: Neutropenia (22%); Thrombocytopenia (14%), Pneumonia (9%); GERD (8%); Hypertension (8%); anemia (6%); and skin infection (5%). Seven patients (11%) had atrial arrhythmia [Grade 1 (n=1); Grade 2 (n=5); Grade 3 (n=1)], and 6 continued ibrutinib following medical management.

Treon et al, EHA 2018
Ibrutinib Monotherapy in Symptomatic Treatment Naive WM

MYD88, CXCR4 Mutation Status

✔

Treon et al, JCO 2018

NCT02604511
Time to and depth of response to ibrutinib are impacted by CXCR4 mutations.

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{WT}</th>
<th>MYD88\textsuperscript{MUT} CXCR4\textsuperscript{MUT}</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{N=}</td>
<td>30</td>
<td>16</td>
<td>14</td>
<td>N/A</td>
</tr>
<tr>
<td>Overall Response Rate-no. (%)</td>
<td>30 (100%)</td>
<td>16 (100%)</td>
<td>14 (100%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Major Response Rate-no. (%)</td>
<td>25 (83%)</td>
<td>15 (94%)</td>
<td>10 (71%)</td>
<td>0.16</td>
</tr>
<tr>
<td>\textbf{Categorical responses}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor responses-no. (%)</td>
<td>5 (17%)</td>
<td>1 (6%)</td>
<td>4 (29%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Partial responses-no. (%)</td>
<td>19 (63%)</td>
<td>10 (63%)</td>
<td>9 (64%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Very good partial responses-no. (%)</td>
<td>6 (20%)</td>
<td>5 (31%)</td>
<td>1 (7%)</td>
<td>0.18</td>
</tr>
<tr>
<td>\textbf{Median time to response (months)}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor response (≥Minor response)</td>
<td>1.0 0.9 1.7</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major response (≥Partial response)</td>
<td>1.9 1.8 7.3</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data cutoff: Jan. 22, 2018  
Median f/u: 14.6 (range 1.8-21.6 months)  
Treon et al, JCO 2018
### Adverse Events (≥5%)

<table>
<thead>
<tr>
<th>Event or Abnormality</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total Grades 2-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>3 (10%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Bruising</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (7%)</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>2 (7%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

- Minimal hematological toxicity
- Median serum IgA levels decreased from 62 to 39 mg/dL; p=0.04
- Median serum IgG levels declined from 563 to 462; p=0.003
- Afib medically managed in 2 patients who continue on treatment; cardiac ablation for one patient with left atrial enlargement off treatment.

Treon et al, JCO 2018
Ibrutinib Monotherapy in Frontline WM: PFS

18 mo: PFS 92%;
All patients alive.

PD patients were both CXCR4 mutated.

Data cutoff: Jan. 22, 2018
Median f/u: 14.6 (range 1.8-21.6 months)

Treon et al, JCO 2018
Ibrutinib (560 mg/day) induced response in a WM patient with Bing Neel Syndrome

Mason et al, BJH 2016
## Acalabrutinib (ACP-196) in Treatment Naïve and Previously Treated WM

<table>
<thead>
<tr>
<th></th>
<th>TN (n=14)</th>
<th>R/R (n=92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (≥ minor response [MR]), n (%)</td>
<td>13 (93)</td>
<td>86 (94)</td>
</tr>
<tr>
<td>95% CI</td>
<td>66, 100</td>
<td>86, 98</td>
</tr>
<tr>
<td>Major response rate (≥ partial response [PR])</td>
<td>11 (79)</td>
<td>72 (78)</td>
</tr>
<tr>
<td>95% CI</td>
<td>49, 95</td>
<td>68, 86</td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Very good PR</td>
<td>1 (7)</td>
<td>29 (32)</td>
</tr>
<tr>
<td>PR</td>
<td>10 (71)</td>
<td>43 (47)</td>
</tr>
<tr>
<td>MR</td>
<td>2 (14)</td>
<td>14 (15)</td>
</tr>
<tr>
<td>24-mo rate, % (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DOR</td>
<td>90 (47, 99)</td>
<td>84 (73, 90)</td>
</tr>
<tr>
<td>PFS</td>
<td>90 (47, 99)</td>
<td>82 (72, 88)</td>
</tr>
<tr>
<td>OS</td>
<td>92 (54, 99)</td>
<td>89 (80, 94)</td>
</tr>
</tbody>
</table>

Owen et al, ASCO 2018; EHA 2018
Atrial fibrillation occurred in 3 pts (1 Gr 3). Bleeding events occurred in 57% of pts; 4 events were Gr 3/4: There were 5 Gr 5 events: pneumonia, glioblastoma multiforme, esophageal carcinoma, myocardial ischemia, and intracranial hematoma.

Owen et al, ASCO 2018; EHA 2018
### Zanubrutinib in WM

**Phase I/II Data**
- 51 patients out of 67 evaluable for efficacy
- Genotyping unknown for many patients
- 91% PFS at 1 year

---

**Table: Best response by MYD88 Status**

<table>
<thead>
<tr>
<th>Best response, n (%)</th>
<th>OVERALL (n=51)</th>
<th>MYD88&lt;sup&gt;L265P&lt;/sup&gt;/CXCR4&lt;sup&gt;WT&lt;/sup&gt; (n=25)</th>
<th>MYD88&lt;sup&gt;L265P&lt;/sup&gt;/CXCR4&lt;sup&gt;WHIM&lt;/sup&gt; (n=5)</th>
<th>MYD88&lt;sup&gt;WT&lt;/sup&gt; (n=6)</th>
<th>Unknown Status (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>47 (92)</td>
<td>23 (92)</td>
<td>5 (100)</td>
<td>5 (83)</td>
<td>14 (93)</td>
</tr>
<tr>
<td>MRR</td>
<td>41 (80)</td>
<td>21 (84)</td>
<td>4 (80)</td>
<td>3 (50)</td>
<td>13 (87)</td>
</tr>
<tr>
<td><strong>VGPR</strong></td>
<td><strong>22 (43)</strong></td>
<td><strong>14 (56)</strong></td>
<td><strong>2 (40)</strong></td>
<td><strong>1 (17)</strong></td>
<td><strong>5 (33)</strong></td>
</tr>
<tr>
<td>PR</td>
<td>19 (37)</td>
<td>7 (28)</td>
<td>2 (40)</td>
<td>2 (33)</td>
<td>8 (53)</td>
</tr>
<tr>
<td>MR</td>
<td>6 (12)</td>
<td>2 (8)</td>
<td>1 (20)</td>
<td>2 (33)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>SD</td>
<td>4 (8)</td>
<td>2 (8)</td>
<td>0</td>
<td>1 (17)</td>
<td>1 (7)</td>
</tr>
</tbody>
</table>

Trotman et al, EHA 2018
# Zanubrutinib in WM

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>N=67</th>
<th></th>
<th>Adverse Event</th>
<th>N=67</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Gr %</td>
<td>Gr 3-4 %</td>
<td>Gastroesophageal reflex disease</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neutropenia</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td></td>
<td>Rash</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td></td>
<td>Basal cell carcinoma</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>7.5</td>
<td>Hypertension</td>
<td>9.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>1.5</td>
<td>Squamous cell carcinoma</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>7.5</td>
<td>Atrial fibrillation/flutter</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>4.5</td>
<td>3.0</td>
<td>Pyrexia</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>1.5</td>
<td>Pneumonia</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>Actinic keratosis</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td></td>
<td>Major hemorrhage*</td>
<td>3.0</td>
</tr>
<tr>
<td>Urinary track infection</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Trotman et al, EHA 2018
**iINNOVATE Study in WM**

Treatment Naïve + Previously Treated

45 centers in 9 countries

1:1 Randomization

**N = 150**

**ARM A:** ibrutinib 420mg + Rituximab 375mg/m² x 8 infusions (weeks 1,2,3,4,17,18,19, and 20)

**ARM B:** Placebo + Rituximab 375mg/m² x 8 infusions (weeks 1,2,3,4,17,18,19, and 20)

**ARM C:** ibrutinib 420mg

Subjects considered refractory to prior rituximab

**N=31**

**ABC patients genotyped for MYD88 and CXCR4**
Responses in Innovate AB Study: Update

**Overall**

- **ORR 95%**
  - Ibrutinib: 25
  - Placebo: 16
  - Major: 79%
  - MR: 53

- **ORR 48%**
  - Ibrutinib: 38
  - Placebo: 3
  - Major: 94%
  - MR: 29

**MYD88L265P/CXCR4WT**

- **ORR 100%**
  - Ibrutinib: 38
  - Placebo: 1
  - Major: 94%

**MYD88L265P/CXCR4WHIM**

- **ORR 96%**
  - Ibrutinib: 58
  - Placebo: 9
  - Major: 73%
  - MR: 44

**MYD88WT/CXCR4WT**

- **ORR 91%**
  - Ibrutinib: 27
  - Placebo: 22
  - Major: 64%
  - MR: 33

**Median time to ≥PR, months (range)**

- 1b (1–28)
- 6 (2–26)
- 2 (1–28)
- 5 (2–17)
- 3 (1–19)
- 11 (4–18)
- 6 (1–17)
- 6 (5–26)

**Median time to ≥MR, months (range)**

- 1 (1–18)
- 3 (1–24)
- 1 (1–18)
- 3 (1–24)
- 1 (1–11)
- 3 (1–8)
- 2 (1–17)
- 3 (2–17)

Busket et al, ASH 2018
Progression-Free Survival Benefit With Ibrutinib-RTX Independent of MYD88/CXCR4 Genotype

- Improved PFS across all genotypes with ibrutinib-RTX
- 36-month PFS rates
  - MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{WT}: 84\% vs 29\%
  - MYD88\textsuperscript{L265P}/CXCR4\textsuperscript{HIM}: 64\% vs 26\%
  - MYD88\textsuperscript{WT}/CXCR4\textsuperscript{WT}: 82\% vs 44\%

Innovate AB Data: Busket et al, ASH 2018.
Phase I/II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

Ibrutinib

Weekly Ulo
4 weeks

Biweekly Ulo
20 weeks

STOP

Dose Level | Ibrutinib | Ulocuplumab Cycle 1 | Ulocuplumab Cycles 2-6
---|---|---|---
Level 1 –Starting dose | 420mg PO DQ | 400 mg weekly | 800 mg every other week
Level 2 | 420mg PO DQ | 800 mg weekly | 1200 mg every other week
Level 3 | 420mg PO DQ | 800 mg weekly | 1600 mg every other week

ClinicalTrials.gov Identifier: NCT03
Venetoclax (ABT-199) impacted by CXCR4 mutation

Cao et al, BJH 2015
Phase II Study of Venetoclax in Previously Treated WM

Selected inclusion criteria:
- Clinicopathological diagnosis of WM
- Serum IgM >2 x ULN
- Previously treated
- Age ≥18 years
- Good performance
- Normal organ and marrow function

Selected exclusion criteria:
- Serious medical condition
- Concurrent anti-cancer agent
- Known CNS lymphoma
- Active HIV, HBV, HCV infection
- Lactating or pregnant women

Screening

Informed Consent and Registration

Venetoclax
200 mg PO QD
800 mg PO QD

Progressive Disease or Unacceptable Toxicity
- Stop ABT-199

SD or Response → Continue for 2 years
- Event Monitoring

www.clinicaltrials.gov: NCT02677324

Castillo et al. EHA 2018
## Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>66 (39-80)</td>
</tr>
<tr>
<td>Male sex</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Previous treatments</td>
<td>2 (1-10)</td>
</tr>
<tr>
<td>Prior BTK inhibitors</td>
<td>15 (50%)</td>
</tr>
<tr>
<td>MYD88 L265P</td>
<td>30 (100%)</td>
</tr>
<tr>
<td>CXCR4 mutations</td>
<td>16 (53%)</td>
</tr>
<tr>
<td>Serum IgM level (mg/dl)</td>
<td>3,543 (642-7,970)</td>
</tr>
<tr>
<td>Hemoglobin level (g/dl)</td>
<td>10.6 (6.4-13.5)</td>
</tr>
<tr>
<td>Platelet count (K/ul)</td>
<td>222 (7-445)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>9 (30%)</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>6 (20%)</td>
</tr>
</tbody>
</table>
## Phase II Study of Venetoclax in Previously Treated WM

<table>
<thead>
<tr>
<th>Response</th>
<th>No prior ibrutinib (n=15)</th>
<th>Prior ibrutinib (n=15)</th>
<th>CXCR4 WT (n=14)</th>
<th>CXCR4 MUT (n=16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>14 (93%)</td>
<td>12 (80%)</td>
<td>12 (86%)</td>
<td>14 (87%)</td>
</tr>
<tr>
<td>Major</td>
<td>13 (87%)</td>
<td>9 (60%)</td>
<td>9 (86%)</td>
<td>13 (63%)</td>
</tr>
<tr>
<td>Very good</td>
<td>4 (27%)</td>
<td>1 (7%)</td>
<td>4 (29%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Partial</td>
<td>9 (60%)</td>
<td>8 (53%)</td>
<td>8 (57%)</td>
<td>9 (56%)</td>
</tr>
<tr>
<td>Minor</td>
<td>1 (7%)</td>
<td>3 (20%)</td>
<td>0 (0%)</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Stable</td>
<td>1 (7%)</td>
<td>3 (20%)</td>
<td>2 (14%)</td>
<td>2 (13%)</td>
</tr>
</tbody>
</table>

Median follow-up: 11 months

1 patient had progressive disease at 9 months (MYD88, CXCR4, TP53)

Castillo et al. EHA 2018
Phase II Study of Venetoclax in Previously Treated WM

<table>
<thead>
<tr>
<th>Adverse Event, N (%)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>All Grades</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2 (7)</td>
<td>4 (14)</td>
<td>6 (21)</td>
<td>3 (10)</td>
<td>15 (52)</td>
</tr>
<tr>
<td>Anemia</td>
<td>1 (3)</td>
<td>5 (17)</td>
<td>2 (7)</td>
<td>0</td>
<td>8 (28)</td>
</tr>
<tr>
<td>URI</td>
<td>2 (7)</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (31)</td>
<td>4 (14)</td>
<td>0</td>
<td>0</td>
<td>13 (48)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (7)</td>
<td>3 (10)</td>
<td>0</td>
<td>0</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (14)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Chills</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Mucositis oral</td>
<td>2 (7)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>0</td>
<td>0</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

Laboratory TLS (n=1). No IgM flare. No deaths.

Castillo et al. EHA 2018
Ibrutinib and Venetoclax in Treatment Naïve WM

Ibrutinib 420 mg/day x 4 weeks

Add Venetoclax
- 100 mg/day week 5
- 200 mg/day week 6
- 400 mg/day weeks 7,8

Ibrutinib 420 mg/day
And
Venetoclax 400 mg/day

Observation

4 weeks

24 months

Follow to PD or off study

Jorge Castillo, PI (DFCI)
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** ➞ +Ibrutinib and Rituximab
- Same caveats as above
- If immediate response needed, either BDR or Benda-R

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

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

Hunter et al, JCO 2017; LeBlond IWWM10
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

Hunter et al, JCO 2017