What are the Novel Approaches in the Treatment of Waldenstrom's Macroglobulinemia?

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Professor of Medicine, Harvard Medical School
Bing Center for Waldenstrom’s Macroglobulinemia
Disclosures

<table>
<thead>
<tr>
<th>Research Support, Consulting and/or Honoraria received from:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbvie/Pharmacyclics</td>
</tr>
<tr>
<td>Beigene</td>
</tr>
<tr>
<td>BMS</td>
</tr>
<tr>
<td>Eli Lilly</td>
</tr>
<tr>
<td>Janssen Pharmaceuticals</td>
</tr>
<tr>
<td>X4 Pharmaceuticals</td>
</tr>
</tbody>
</table>

IP assigned to DFCI for MYD88, CXCR4, and IRAK and HCK and other inhibitors.
MYD88 directed pro-survival signaling in WM

MYD88 mutations occur in 95-97% WM Patients

Treon et al, NEJM 2012
Yang et al, Blood 2013
Hodge et al, Blood 2014
Yang et al, Blood 2016
Chen et al, Blood 2018
Liu et al, Blood Adv 2020
Munshi et al, BCJ 2020
Munshi et al, Submitted.
The ERK1/2 kinase activity regulator WNK2 is suppressed due to aberrant methylation: MYD88$^{\text{Mut}}$, CXCR4$^{\text{Mut}}$, MYD88$^{\text{Mut6qdel}}$, MYD88$^{\text{WT}}$

Chromosomal region: Chr9:93,197,839-93,197,854
Differentially methylated CpG

Original DNA sequence:

\[
\begin{array}{cccccc}
C & G & A & C & G & T \\
C & G & T & G & T & G \\
C & G & T & G & A & G \\
C & G & T & G & A & G \\
C & G & T & C & G
\end{array}
\]

Bisulfite converted DNA sequence:

\[
\begin{array}{cccccc}
C & G & A & T & C & G \\
C & G & T & G & T & G \\
C & G & T & G & A & G \\
C & G & T & G & A & G \\
C & G & T & C & G
\end{array}
\]

Sample CpG methylation, %

<table>
<thead>
<tr>
<th>WM1</th>
<th>WM2</th>
<th>WM3</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CXCR4$^{\text{WT}}$, 6q intact)</td>
<td>(CXCR4$^{\text{WT}}$, del6q)</td>
<td>(CXCR4$^{\text{Mut}}$, very subclonal del6q)</td>
</tr>
<tr>
<td>8 11 14 8</td>
<td>81 100 75 70</td>
<td>5 5 5 6</td>
</tr>
</tbody>
</table>

Guerrera ML et al, submitted.
Mutated CXCR4 permits ongoing pro-survival signaling by CXCL12

CXCR4 mutations occur in 30-40% of WM patients: Nonsense and Frameshift

AKT and ERK Mediated Drug Resistance

Ibrutinib Activity in Previously Treated WM: Update of the Pivotal Trial (median f/u 59 mos)

<table>
<thead>
<tr>
<th></th>
<th>All Patients</th>
<th>MYD88&lt;sup&gt;MUT&lt;/sup&gt; CXCR4&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;MUT&lt;/sup&gt; CXCR4&lt;sup&gt;MUT&lt;/sup&gt;</th>
<th>MYD88&lt;sup&gt;WT&lt;/sup&gt; CXCR4&lt;sup&gt;WT&lt;/sup&gt;</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=</td>
<td>63</td>
<td>36</td>
<td>22</td>
<td>4</td>
<td>N/A</td>
</tr>
<tr>
<td>Overall Response Rate-no. (%)</td>
<td>90.5%</td>
<td>100%</td>
<td>86.4%</td>
<td>50%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Major Response Rate-no. (%)</td>
<td>79.4%</td>
<td>97.2%</td>
<td>68.2%</td>
<td>0%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Categorical responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor responses-no. (%)</td>
<td>11.1%</td>
<td>2.8%</td>
<td>18.2%</td>
<td>50%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Partial responses-no. (%)</td>
<td>49.2%</td>
<td>50%</td>
<td>59.1%</td>
<td>0%</td>
<td>0.03</td>
</tr>
<tr>
<td>Very good partial responses-no. (%)</td>
<td>30.2%</td>
<td>47.2%</td>
<td>9.1%</td>
<td>0%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Median time to response (months)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor response (≥Minor response)</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.9</td>
<td>0.38</td>
</tr>
<tr>
<td>Major response (≥Partial response)</td>
<td>1.8</td>
<td>1.8</td>
<td>4.7</td>
<td>N/A</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*One patient had MYD88 mutation, but no CXCR4 determination and had SD.

Treon et al, NEJM 2015; Updated JCO 2021
Ibrutinib in Previously Treated WM: Updated PFS

By MYD88 and CXCR4 Mutation Status

All patients

5 year PFS: 54%
5 year OS: 87%

By MYD88 and CXCR4 Mutation Status

Treon et al, NEJM 2015; Updated JCO 2021
iNNOVATE (PCYC-1127; NCT 02165397) Study Design

**Key eligibility criteria**
- Confirmed WM* (N=150)
- Measurable disease (serum IgM >0.5 g/dL)
- RTX sensitive
  - Not refractory to last prior RTX-based therapy
  - Had not received RTX <12 months before first study dose

**1:1 Randomization**
- Stratification
  - IPSSWM (low vs intermediate vs high)
  - Number of prior regimens (0 vs 1-2 vs ≥3)
  - ECOG PS (O-I vs 2)

**Arm A**
- Ibrutinib-RTX
- Oral ibrutinib 420 mg once daily until PD
- RTX 375 mg/m² IV on day 1 of weeks 1-4 and 17-20

**Arm B**
- Placebo-RTX
- Placebo until PD
- RTX 375 mg/m² IV on day 1 of weeks 1-4 and 17-20

**Crossover to single-agent ibrutinib allowed after PD**

ECOG PS, Eastern Cooperative Oncology Group performance status; IPSSWM, International Prognostic Scoring System for Waldenström’s Macroglobulinemia; IRC, independent review committee; IV, intravenous; PD, progressive disease.

*Previously untreated patients were allowed to enroll following a protocol amendment (November 2015); therefore, their enrollment started later than patients who had relapsed.

†Patients in the placebo-RTX arm could receive next-line single-agent ibrutinib in crossover following IRC-confirmed PD.

- **iNNOVATE (PCYC-1127)** was a double-blind, randomized, placebo-controlled, multicenter, international phase 3 study designed to assess the efficacy and safety of ibrutinib-RTX versus placebo-RTX in patients with WM (**Figure 1**).
- The primary endpoint was PFS by IRC. Secondary endpoints included response rate by IRC, time to next treatment, hemoglobin (Hgb) improvement, overall survival (OS), and safety.
- After study closure, patients without PD could continue ibrutinib in an extension program.

Garcia Sanz et al, EHA Abstract EP782
Response Rates by Genotype and Prior Treatment Status

Garcia Sanz et al, EHA Abstract EP782

- Higher response rates with ibrutinib-RTX were independent of genotype or prior treatment status
iINNOVATE: PFS by Genotype

<table>
<thead>
<tr>
<th>54-month PFS</th>
<th>Ibrutinib-RTX</th>
<th>Placebo-RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>MYD88&lt;sup&gt;Mut&lt;/sup&gt;/CXCR4&lt;sup&gt;WT&lt;/sup&gt;</td>
<td>72%</td>
<td>25%</td>
</tr>
<tr>
<td>MYD88&lt;sup&gt;Mut&lt;/sup&gt;/CXCR4&lt;sup&gt;Mut&lt;/sup&gt;</td>
<td>63%</td>
<td>21%</td>
</tr>
<tr>
<td>MYD88&lt;sup&gt;WT&lt;/sup&gt;/CXCR4&lt;sup&gt;WT&lt;/sup&gt;</td>
<td>70%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Garcia Sanz et al, EHA Abstract EP782
Challenges of MYD88 and CXCR4 detection in WM

Sensitivity for mutated CXCR4 detection was 37% by NGS and unselected BM. Low BM involvement and clonality impacted detection.

ASSEN Study Design: Zanubrutinib vs Ibrutinib in MYD88MUT WM

Eligible Patients

- Histologic diagnosis of WM
- Meeting ≥1 criterion for treatment initiation
- If treatment naive (TN*), must be considered unsuitable for standard chemoimmunotherapy
- No prior BTK inhibitors

Cohort 1
MYD88MUT WM patients
N=201 (164 R/R)

Cohort 2
MYD88WT WM patients
N=28 (23 R/R)

Data Cut-off: August 31, 2019
Median Follow-up: 19.4 months

Arm A: Zanubrutinib
n= 102
160 mg BID until PD

Arm B: Ibrutinib
n= 99
420 mg QD until PD

Arm C: Zanubrutinib
N=28
160 mg BID until PD

Stratification factors
- CXCR4 status (CXCR4WHM vs CXCR4WT/missing)
- Number of prior lines of therapy (0 vs 1-3 vs >3)

Abstract: e20056

EUDRACT 2016-002980-33; NCT03053440

BID, twice daily; BTK, Bruton tyrosine kinase; CXCR4, C-X-C Motif Chemokine Receptor 4; MYD88, myeloid differentiation primary response gene 88 mutant; PD, progressive disease; QD, daily; R, randomization; R/R, relapsed/refractory; TN, treatment naive; WM, Waldenstrom Macroglobulinemia; WT, wild-type.

CXCR4 mutated patients had lower VGPR responses in both arms in post-hoc analysis using NGS:

<table>
<thead>
<tr>
<th>Mut</th>
<th>Zanu (18% v. 34%)</th>
<th>Ibru (10% v. 24%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRR</td>
<td>77.8%</td>
<td>77.5%</td>
</tr>
<tr>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VGPR</td>
<td>19.2%</td>
<td>28.4%</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR + VGPR Rate difference = 10.2$^\dagger$ (-1.5, 22.0)  
$p$-value = 0.0921

CR, complete response; IRC, independent review committee; ITT, intention-to-treat; MRR, major response rate; MR, minor response; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SD, stable disease; VGPR, very good PR.

*CXCR4 mutated patients had lower VGPR responses in both arms in post-hoc analysis using NGS:

Zanu (18% v. 34%)
Ibru (10% v. 24%)

Tam et al, Blood 2020
### ASPEN: AE Categories of Interest (BTKi Class AEs)

<table>
<thead>
<tr>
<th>AE Categories, n (%) (pooled terms)</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ibrutinib (n = 98)</td>
<td>Zanubrutinib (n = 101)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Atrial fibrillation/ flutter$^\dagger$</td>
<td>15 (15.3%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>Diarrhea (PT)</td>
<td>31 (31.6%)</td>
<td>21 (20.8%)</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>58 (59.2%)</td>
<td>49 (48.5%)</td>
</tr>
<tr>
<td>Major hemorrhage$^a$</td>
<td>9 (9.2%)</td>
<td>6 (5.9%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17 (17.3%)</td>
<td>11 (10.9%)</td>
</tr>
<tr>
<td>Neutropenia$^b$†</td>
<td>13 (13.3%)</td>
<td>30 (29.7%)</td>
</tr>
<tr>
<td>Infection</td>
<td>66 (67.3%)</td>
<td>67 (66.3%)</td>
</tr>
<tr>
<td>Second Malignancy</td>
<td>11 (11.2%)</td>
<td>12 (11.9%)</td>
</tr>
</tbody>
</table>

Higher AE rate in bold blue with ≥ 10% difference in any grade or ≥ 5% difference in grade 3 or above.
No tumor lysis syndrome was reported. Opportunistic infection Ibrutinib (n=2), zanubrutinib (n=1).
AE, adverse event; BTKi, Bruton tyrosine kinase inhibitor; PT, preferred term.
$^a$Defined as any grade ≥ 3 hemorrhage or any grade central nervous system hemorrhage.
$^b$Including PT terms of neutropenia, neutrophil count decreased, febrile neutropenia, agranulocytosis, neutropenic infection and neutropenic sepsis.
$^\dagger$Descriptive two-sided $P$-value < 0.05.

Tam et al, Blood 2020
Targeting BCL2 in Waldenstrom’s Macroglobulinemia with Venetoclax

Higher BCL2 levels in MYD88 mutated WM

Phase II Study of Venetoclax in Previously Treated WM

ORR: 84%; Major RR: 81%
Median PFS: 30 months

Clinical trials.gov: NCT02677324
Castillo et al, 17th IMW 2019; Manuscript submitted.
Ibrutinib/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
- 22 months
- Follow to PD or off study

Jorge Castillo, PI (DFCI)

CLINICALTRIALS.GOV: NCT04273139
Phase I/II Trial of Ulocuplumab and Ibrutinib in CXCR4 mutated patients with symptomatic WM

Schema

Ibrutinib

Until PD or Intolerance

Weekly Ulo

Biweekly Ulo

STOP

4 weeks

20 weeks

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Ibrutinib</th>
<th>Ulocuplumab Cycle 1</th>
<th>Ulocuplumab Cycles 2-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1 –Starting dose</td>
<td>420mg PO DQ</td>
<td>400 mg weekly</td>
<td>800 mg every other week</td>
</tr>
<tr>
<td>Level 2</td>
<td>420mg PO DQ</td>
<td>800 mg weekly</td>
<td>1200 mg every other week</td>
</tr>
<tr>
<td>Level 3</td>
<td>420mg PO DQ</td>
<td>800 mg weekly</td>
<td>1600 mg every other week</td>
</tr>
</tbody>
</table>


ClinicalTrials.gov Identifier: NCT03225716
Response and PFS Data/Ibrutinib plus Ulo

Median Time to Minor Response

0.9 (95% CI 0.9-1.8) months

1.2 (95% CI 0.9-2.8) months

2-year 90% estimated

Treon et al, Blood 2021
Mavorixafor in combination with ibrutinib in CXCR4 mutated WM

- Non-competitive, allosteric, small molecule antagonist of CXCR4
- Orally Bioavailable; mean t$_{1/2}$ of ~23 hours
- High volume of distribution

ClinicalTrials.gov: NCT04274738
BTK \text{Cys481Ser} expressing cells displayed persistent activation of BTK and ERK1/2 following ibrutinib treatment.

Chen et al, *Blood* 2018
**BTK**\[^{\text{Cys481Ser}}\] mutated clones release cytokines that protect **BTK**\[^{\text{WT}}\] clones from ibrutinib triggered cytotoxicity

Chen et al, Blood 2018
Pirtobrutinib—a non-covalent BTK-Inhibitor Suppresses p-BTK and p-ERK1/2 in Ibrutinib Resistant BTK$^\text{Cys481Ser}$ Expressing Cells

<table>
<thead>
<tr>
<th></th>
<th>BCWM.1</th>
<th></th>
<th>MWCL-1</th>
<th></th>
<th>TMD8</th>
<th></th>
<th>HBL-1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DMSO</td>
<td>IB-0.5µM</td>
<td>PB-0.5µM</td>
<td>DMSO</td>
<td>IB-0.5µM</td>
<td>PB-0.5µM</td>
<td>DMSO</td>
</tr>
<tr>
<td></td>
<td>WT</td>
<td>C481S</td>
<td>WT</td>
<td>C481S</td>
<td>WT</td>
<td>C481S</td>
<td>WT</td>
</tr>
<tr>
<td>V</td>
<td></td>
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<td>V</td>
<td></td>
<td>V</td>
<td></td>
<td>V</td>
</tr>
<tr>
<td>C481S</td>
<td></td>
<td></td>
<td>C481S</td>
<td></td>
<td>C481S</td>
<td></td>
<td>C481S</td>
</tr>
</tbody>
</table>

V-vector only; WT-BTK wild-type; C481S-BTK Cys481Ser mutant; IB, ibrutinib; PB, pirtobrutinib

Munshi et al, Submitted
Pirtobrutinib Overcomes Ibrutinib Resistance Related to $\text{BTK}^{\text{Cys481Ser}}$

Munshi et al, submitted
Pirtobrutinib in Previously Treated Mantle Cell Lymphoma, Waldenström's Macroglobulinemia, and Other NHLs: Phase 1/2 BRUIN Study.

- 15 evaluable for efficacy
- 60% previously exposed to covalent BTK inhibitors
- ORR 60%
  - 1 VPGR
  - 4 PR
  - 4 MR

Wang et al. ASH 2020
Trial Design

- Single-arm, open-label phase II study
- Multicenter: DFCI/MGH, MSKCC, Mayo, SCCA, Stanford, Colorado Cancer Center.
- Pirtobrutinib at 200 mg orally QD on 28-day cycles
- Dose reduction allowed for toxicity.
- Participants will continue pirtobrutinib until PD or toxicity and will be followed for up to 2 years after completion of 48 cycles of treatment or until death.

Jorge Castillo, PI (DFCI)
Shayna Sarosiek, Co-Inv. (DFCI)
MYD88 directed pro-survival signaling in WM

- MYD88 mutations occur in 95-97% WM Patients

References:
- Treon et al, NEJM 2012
- Yang et al, Blood 2013
- Hodge et al, Blood 2014
- Yang et al, Blood 2016
- Chen et al, Blood 2018
- Liu et al, Blood Adv 2020
- Munshi et al, BCJ 2020
- Munshi et al, Submitted.
Development of a dual HCK/BTK Inhibitor: KIN-8194
Efficacy Studies in BTK wild-type TMD8 xenografted mice

Mean Tumor Volume ± SEM

<table>
<thead>
<tr>
<th>Study Days</th>
<th>Vehicle</th>
<th>Ibrutinib (50 mg/kg)</th>
<th>KIN-8194 (50 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td></td>
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<td></td>
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<tr>
<td>35</td>
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<td></td>
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<tr>
<td>49</td>
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<tr>
<td>63</td>
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<td>77</td>
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<td>91</td>
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<td></td>
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<td>105</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>119</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tumor Volume (mm³)

- 2500
- 2000
- 1500
- 1000
- 500
- 0

Day 33

P = 0.0045

Treatment Stopped

Survival proportions

Percent survival

- Vehicle
- Ibrutinib
- KIN-8194

Days elapsed

<table>
<thead>
<tr>
<th>Days elapsed</th>
<th>0</th>
<th>14</th>
<th>28</th>
<th>42</th>
<th>56</th>
<th>70</th>
<th>84</th>
<th>98</th>
<th>112</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent</td>
<td>100</td>
<td>75</td>
<td>50</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
</tbody>
</table>

Treatment stopped

Median Survival

<table>
<thead>
<tr>
<th>Median Survival</th>
<th>Vehicle</th>
<th>Ibrutinib (50 mg/kg)</th>
<th>KIN-8194 (50 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(days)</td>
<td>31</td>
<td>90</td>
<td>Undefined</td>
</tr>
</tbody>
</table>

Log-rank (Mantel-Cox) test, P<0.0001

Yang et al, Blood 2021
Development of a dual HCK/BTK Inhibitor: KIN-8194
Efficacy Studies in BTK Cys481 mutated TMD8 xenografted mice

<table>
<thead>
<tr>
<th>Median Survival</th>
<th>Vehicle</th>
<th>Ibrutinib 50mg/kg</th>
<th>KIN-8194 50mg/kg</th>
<th>KIN-8194 75mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>(days)</td>
<td>29</td>
<td>25</td>
<td>57.5</td>
<td>70.5</td>
</tr>
</tbody>
</table>

Log-rank (Mantel-Cox) test, P=0.0007

Yang et al, Blood 2021