ASCO 2021: Advances in Waldenström macroglobulinemia

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University of Texas M. D. Anderson Cancer Center

Disclosures

- Ascentage:
  - Research Funding, Advisory Board
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  - Advisory Board
- BMS
  - Research Funding
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  - Research Funding
- Pharmacyclics
  - Advisory Board
- X4 Pharma
  - Research Funding
- Xencor
  - Research Funding
### Presentations to Review

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Framework for Context

NCCN Guidelines Version 1.2021
Waldenström Macroglobulinemia/
Lymphoplasmacytic Lymphoma

Indefinite Duration Therapy
- Ibrutinib +/- Rituximab

Fixed Duration Therapy
- Rituximab +/- Dexamethasone
- Bortezomib
- Carfilzomib
- Ixazomib
- Cyclophosphamide
- Bendamustine
- Fludarabine
- Cladribine
- Rituximab
Prognostic impact of depth of response in Waldenström macroglobulinemia patients treated with fixed duration chemoimmunotherapy.

Chemoimmunotherapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Major Response Rate</th>
<th>PFS (mos)</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-Bendamustine</td>
<td>90-96%</td>
<td>65-69</td>
<td>Rapid response</td>
</tr>
<tr>
<td>R-Cy-Dex</td>
<td>74-87%</td>
<td>34-35</td>
<td>Well tolerated. Med time to response 4.1 mos.</td>
</tr>
</tbody>
</table>

Considerations
- Risk of 2ndary MDS/leukemia
- Cytopenias
- Activity appears unaffected by MYD88 mutation status
  - R-Benda and R-Cy-Dex

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<th>Major Response Rate</th>
<th>PFS (mos)</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-Bortezomib-Dex</td>
<td>68%</td>
<td>42</td>
<td>PN &gt; than Car or Ixa, better sc and wkly</td>
</tr>
</tbody>
</table>

Considerations
- No 2nd malignancy risk
- No Stem cell toxicity
- BDR – median time to response 4-8 weeks

Kastritis et al. 2015 Blood 126 (11) 1392-4.
Dimopoulos et al. Blood 2013

Prognostic impact of depth of response in Waldenström macroglobulinemia patients treated with fixed duration chemoimmunotherapy

Data Source
Analyzed 1st line data from patients treated at 4 cancer centers in 2 countries:
- Dexamethasone Rituximab-Cyclophosphamide (41%)
- Bendamustine-Rituximab (32%)
- Bortezomib-Rituximab-Dexamethasone (27%)

Question Posed
Does quality of response at 6 months from start of chemo impact:
- progression-free survival (PFS)
- time to next therapy (TTNT)
- overall survival (OS)

N = 256 patients
% patients with a major response = 74%

Results

<table>
<thead>
<tr>
<th>Major Response Rate</th>
<th>Five year PFS Rates</th>
<th>Five year TTNT Rates</th>
<th>Five year OS Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>71%</td>
<td>84%</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>58%</td>
<td>74%</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Perera et al. J Clin Oncol 39, 2021 (suppl 15; abstr 8049)
Cost-effectiveness of zanubrutinib versus ibrutinib in adult patients with Waldenström macroglobulinemia in the United States

Jorge J. Castillo, Keri Yang, Rongzhe Liu, Yu Wang, Aileen Cohen, Todd M. Zimmerman, Qian Zhao, Gijs van de Wetering, Xin Gao, Boxiong Tang

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Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Indefinite Duration Therapy

Ibrutinib +/- Rituximab

BTK inhibitors

Acalabrutinib
Zanubrutinib
Pirtobrutinib
MK 1026
TG 1701

Fixed Duration Therapy

Rituximab +/- Dexamethasone

Bortezomib
Carfilzomib
Ixazomib
Rituximab

Cyclophosphamide
Bendamustine
Fludarabine
Cladribine
Cost-effectiveness of zanubrutinib versus ibrutinib in adult patients with Waldenström macroglobulinemia in the United States

Indefinite Duration Therapy

Ibrutinib +/- Rituximab

Phase 3 ASPEN Study: Ibrutinib vs. Zanubrutinib (Enrolled previously treated and untreated patients)

BTK inhibitors

Rituximab

Ibrutinib

Acalabrutinib

Zanubrutinib

Pirtobrutinib

MK 1026

TG 1701

Castillo et al. J Clin Oncol 39, 2021 (suppl 15; abstr e18856)

Phase 3 ASPEN Study: Zanubrutinib vs. Ibrutinib

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. Evaluable</th>
<th>Major Response Rate</th>
<th>≥ VGPR (p = 0.09)</th>
<th>PFS at 18 mos</th>
<th>Median DOR and PFS</th>
<th>AEs leading to dose reduction</th>
<th>AEs leading to treatment discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zanubrutinib bid</td>
<td>102</td>
<td>77%</td>
<td>28%</td>
<td>85%</td>
<td>NR</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>Ibrutinib daily</td>
<td>99</td>
<td>78%</td>
<td>19%</td>
<td>84%</td>
<td>NR</td>
<td>23%</td>
<td>9%</td>
</tr>
</tbody>
</table>

Table 3. ASPEN: Adverse events of interest with 5 months of additional follow-up

<table>
<thead>
<tr>
<th>Class AEs of BTK Inhibitors</th>
<th>Zanubrutinib (n = 101)</th>
<th>Ibrutinib (n = 98)</th>
<th>Zanubrutinib (n = 101)</th>
<th>Ibrutinib (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>3.0%</td>
<td>18.4%</td>
<td>0%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>21.8%</td>
<td>32.7%</td>
<td>3.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>50.5%</td>
<td>60.2%</td>
<td>5.9%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Major hemorrhage</td>
<td>5.9%</td>
<td>10.2%</td>
<td>5.9%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.9%</td>
<td>20.4%</td>
<td>7.9%</td>
<td>15.3%</td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>31.7%</td>
<td>15.3%</td>
<td>22.8%</td>
<td>-</td>
</tr>
<tr>
<td>Infection</td>
<td>69.3%</td>
<td>71.4%</td>
<td>18.8%</td>
<td>23.5%</td>
</tr>
<tr>
<td>Second malignancy</td>
<td>12.9%</td>
<td>12.2%</td>
<td>3.0%</td>
<td>1.0%</td>
</tr>
</tbody>
</table>

*p value <.05, zanubrutinib versus ibrutinib

Tam C et al. J Clin Oncol 38: 2020 (suppl; abstr 8007)
Cost-effectiveness of zanubrutinib versus ibrutinib in adult patients with Waldenström macroglobulinemia in the United States

- Quality of life was assessed at study entry, every 3 cycles (cycles 1-12), then every 6 cycles:
  - Mobility
  - Self-care
  - Usual activities
  - Pain/discomfort
  - Anxiety/depression
- Drug costs were assessed for US payers based on 2020 pricing
- Costs of side effect management, routine care, and end of life care were also considered

Authors conclusions:
- Increased cost of Zanu is primarily due to patients staying on therapy longer due to longer time to treatment failure
- Zanu had lower routine care ($2,935) and terminal care ($2,964) costs compared with Ibrutinib.

Efficacy and safety of zanubrutinib versus rituximab-based chemoimmunotherapy in Waldenström macroglobulinemia (WM):
Matching-adjusted indirect comparisons

Jorge J. Castillo, Keri Yang, Rongzhe Liu, Yu Wang, Aileen Cohen, Todd M. Zimmerman, Qian Zhao, Gijs van de Wetering, Xin Gao, Boxiong Tang
Efficacy and safety of zanubrutinib versus rituximab-based chemoimmunotherapy in Waldenström macroglobulinemia (WM): Matching-adjusted indirect comparisons

**Indefinite Duration Therapy**

- Ibrutinib +/- Rituximab
- BTK inhibitors
  - Acalabrutinib
  - Zanubrutinib
  - Pirtobrutinib
  - MK-1026
  - TG-1701

**Fixed Duration Therapy**

- Rituximab +/- Dexamethasone
- Cyclophosphamide vs.
- Bendamustine

**Chemoimmunotherapy**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Major Response Rate</th>
<th>PFS (mos)</th>
<th>When to use?</th>
</tr>
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<tr>
<td>R-Bendamustine</td>
<td>90-96%</td>
<td>65-69</td>
<td>Rapid response needed; Pts with LAD/organomegaly</td>
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<td>R-Cy-Dex</td>
<td>74-87%</td>
<td>34-35</td>
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**Considerations**

- Risk of 2ndary MDS/leukemia
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- Activity appears unaffected by MYD88 mutation status
  - R-Benda and R-Cy-Dex

Efficacy and safety of zanubrutinib versus rituximab-based chemoimmunotherapy in Waldenström macroglobulinemia (WM): Matching-adjusted indirect comparisons

**Objective**

Compare efficacy between zanubrutinib and BR or DRC

**Data Sources**

Used data from 3 clinical trials (retrospective):

- Zanubrutinib (102 patients)
- Bendamustine-Rituximab (71 patients)
  - Age
  - Prior lines of therapy
  - IgM concentration
  - International Prognostic Scoring System for WM score
  - Extramedullary disease (EMD)
- Dexamethasone-Rituximab-Cyclophosphamide (72 patients)
  - Age
  - Platelet count
  - Hemoglobin
  - EMD

**PFS, OS and adverse events of zanubrutinib vs. BR/DRC pre- and post-matching adjustments**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Zanubrutinib pre-matching (N = 102)</th>
<th>Zanubrutinib vs DRC (n\textsubscript{eff} = 53)</th>
<th>DRC (N = 72)</th>
<th>Zanubrutinib vs BR (n\textsubscript{eff} = 50)</th>
<th>BR (N = 71)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS, 12-month rate, %</td>
<td>94</td>
<td>92</td>
<td>85</td>
<td>94</td>
<td>79</td>
</tr>
<tr>
<td>PFS, 24-month rate, %</td>
<td>85</td>
<td>90</td>
<td>88</td>
<td>81</td>
<td>59</td>
</tr>
<tr>
<td>OS, 12-month rate, %</td>
<td>97</td>
<td>95</td>
<td>92</td>
<td>98</td>
<td>87</td>
</tr>
<tr>
<td>OS, 24-month rate, %</td>
<td>90</td>
<td>94</td>
<td>85</td>
<td>88</td>
<td>77</td>
</tr>
<tr>
<td>Anaemia, %</td>
<td>5.0</td>
<td>4.2</td>
<td>NR</td>
<td>3.6</td>
<td>NR</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>5.9</td>
<td>3.1</td>
<td>NR</td>
<td>9.5</td>
<td>NR</td>
</tr>
<tr>
<td>Neutropenia, %</td>
<td>15.8</td>
<td>14.3</td>
<td>9.7</td>
<td>17.5</td>
<td>35.2</td>
</tr>
<tr>
<td>Pneumonia, %</td>
<td>1.0</td>
<td>0.6</td>
<td>NR</td>
<td>1.5</td>
<td>5.6</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td>5.9</td>
<td>4.4</td>
<td>0.0</td>
<td>5.2</td>
<td>NR</td>
</tr>
</tbody>
</table>

Comparisons of survival and adverse event incidence between treatments were conducted using Cox proportional hazards models and modified Poisson models.

Abbreviations: BR = bendamustine-rituximab; DRC = dexamethasone-rituximab-cyclophosphamide; 
\(n_{\text{eff}}\) = effective sample size; NR = not reported; OS = overall survival; 
PFS = progression-free survival; HR = hazard ratio; RR = risk ratio; 95% CI = 95% confidence interval.

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Preliminary results of the Phase 2 study of zanubrutinib in patients with previously treated B-cell malignancies intolerant to ibrutinib and/or acalabrutinib

Preliminary results of the phase 2 study of zanubrutinib in patients with previously treated B-cell malignancies intolerant to ibrutinib and/or acalabrutinib

Indefinite Duration Therapy

- **Ibrutinib** +/- **Rituximab**

Other BTK inhibitors

- **Acalabrutinib**
- **Zanubrutinib**
- **Pirtobrutinib**
- **MK1026**
- **TG1701**

Gave zanubrutinib: 160 mg twice daily or 320 mg once daily

Question Posed

- Recurrence of side effects seen with ibrutinib or acalabrutinib?
- Any new side effects?

Shadman et al. J Clin Oncol 39, 2021 (suppl 15; abstr e19506)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th># of Patients (Total = 44)</th>
</tr>
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<tbody>
<tr>
<td>CLL</td>
<td>34</td>
</tr>
<tr>
<td>WM</td>
<td>6</td>
</tr>
<tr>
<td>MCL</td>
<td>2</td>
</tr>
<tr>
<td>MZL</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prior BTKi</th>
<th># of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibrutinib</td>
<td>39</td>
</tr>
<tr>
<td>Ibrutinib + Acalabrutinib</td>
<td>4</td>
</tr>
<tr>
<td>Acalabrutinib</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>Incidence rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle Aches</td>
<td>21%</td>
</tr>
<tr>
<td>Bruising</td>
<td>18%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>16%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16%</td>
</tr>
<tr>
<td>Cough</td>
<td>11%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE leading to ibr and aca intolerance, N</th>
<th>Recurrence on zanu, n (%)</th>
<th>Severity change of recurrence on zanu, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibr</td>
<td>72 (82.8)</td>
<td>15 (17.2)</td>
</tr>
<tr>
<td>Acala</td>
<td>9 (77.8)</td>
<td>2 (22.2)</td>
</tr>
</tbody>
</table>

- Dose interruptions: 6 patients
- Dose reductions: 2 patients
- No side effects caused Zanu to be stopped
- No patients have died

Of 26 evaluable patients:

- 10 (38.5%) have maintained response
- 16 (61.5%) had deepening of response

Median follow up = 4.2 months
Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy, and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies


Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies

**Indefinite Duration Therapy**

- **BTK inhibitors**
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
  - Pirtobrutinib
  - MK 1026
  - TG 1701

- **Rituximab**

Castillo et al. J Clin Oncol 39, 2021 (suppl 15; abstr e18856)
Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies

- 20 WM patients
- 1st line therapy: 8 patients
- No prior BTK inhibitor: 20/20 patients

**Side Effects (123 patients)**

<table>
<thead>
<tr>
<th>Side Effects (123 patients)</th>
<th>All Grades</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial Fibrillation</td>
<td>4%</td>
<td>1 patient</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>Bleeding events</td>
<td>19% (all grades 1-2)</td>
<td></td>
</tr>
</tbody>
</table>

- Side effects leading to dose reduction: 6.5%
- Side effects leading to stopping drug: 1.6% (Afib, COVID)

Cheah et al. J Clin Oncol 39, 2021 (suppl 15; abstr 7525)
Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies.

First-in-human study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor (BCL-2i), in patients (pts) with relapsed/refractory (R/R) CLL and other hematologic malignancies (HMs).

Sikander Ailawadhi, Asher Alban Akmal Chanan-Khan, Zi Chen, Bo Huang, Marina Konopleva, Danielle M. Brander, David Rizzieri, Masa Lasica, Constantine Si Lun Tam, Costas K. Yannakou, H. Miles Prince, Matthew Steven Davids, Zhicong He, Ming Lu, Mohammad Ahmad, Mingyu Li, Zhiyan Liang, Boyd Mudenda, Dajun Yang, Yifan Zhai
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**Indefinite Duration Therapy**

- Ibrutinib +/- Rituximab

**BTK inhibitors**

- Acalabrutinib
- Zanubrutinib
- Pirtobrutinib
- MK 1026
- TG 1701

**BCL-2 inhibitors**

- Venetoclax
- Lisaftoclax

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**BCL 2 inhibitor:**

Phase II study of venetoclax in previously treated WM

- BCL2 is highly expressed in WM cells, particularly in pts with MYD88 mutations
- Venetoclax triggered apoptosis of WM cells
  - including primary WM cells from ibrutinib-naïve and ibrutinib-treated patients.

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>No. Enrolled</th>
<th>Gene mutations</th>
<th>Median Number of Prior Rx (range)</th>
<th>Major Response Rate</th>
<th>2 year Progression Free Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castillo et al. 2019</td>
<td>Venetoclax x 2 years 200 mg daily days 1-7 400 mg daily days 8-14 Thereafter, 800mg/day</td>
<td>31</td>
<td>100% MYD88mut 55% CXCR4mut</td>
<td>2 (1-10) 52% had prior BTKi</td>
<td>81%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Median time to response 1.9 months (slower TTR in pts with prior BTKi (p<0.001)

Laboratory TLS in 1 pt

**Dose reductions:**

- neutropenia (n=2)
- fatigue (n=1)
- diarrhea (n=1)
- self-reduction (n=1)

**Grade 4 side effects:**

- Neutropenia (n=5 pts)

**Grade 3 side effects:**

- Neutropenia (n=15 pts)
- Anemia (n=4 pts)
- Diarrhea (n=4 pts)
First-in-human study of lisaftoclox (APG-2575), a novel BCL-2 inhibitor (BCL-2i), in patients (pts) with relapsed/refractory (R/R) CLL and other hematologic malignancies (HMs).

- Preliminary data suggests that lisaftoclox may have a better side effect profile than venetoclax
  - tumor lysis syndrome, thrombocytopenia, neutropenia

### Treatment related side effects

<table>
<thead>
<tr>
<th></th>
<th>All grades</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>29%</td>
<td>3%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23%</td>
<td>14%</td>
</tr>
<tr>
<td>Anemia</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>17%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Low platelets</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

**Cohort A:**
- Standard 3+3 (assigned dose at C1D1 without ramp-up)
- Pts with non-CLL HMs and low risk TLS
- 3-6 pts per dose level

**Cohort B:**
- Standard 3+3 with daily ramp-up prior to treatment at C1D1
- Pts with CLL or intermediate/high risk TLS
- 3-6 pts per dose level

- Oral drug
- Administered once daily

Ailawadhi et al. J Clin Oncol 39, 2021 (suppl 15; abstr 7502)
Phase I/II Trial of Lisaftoclax in WM

Previously Untreated

lisaftoclax + ibrutinib

R/R WM Prior BTKi

lisaftoclax

R/R WM No prior BTKi

lisaftoclax + rituximab x 8 doses

Continue treatment until PD or unacceptable toxicity

Multi-center trial
N= 96 pts

Treatment Free Remission (TFR) and Overall Response Rate (ORR) Results in Patients with Relapsed/Refractory Waldenstrom’s Macroglobulinemia (WM) Treated with CLR 131

S Ailawadhi, A Chanan-Khan, J Peterson, J Longcor, K Oliver, M Brown, J Friend, DJ Green
Treatment Free Remission (TFR) and Overall Response Rate (ORR) Results in Patients with Relapsed/Refractory Waldenstrom’s Macroglobulinemia (WM) Treated with CLR 131

**Indefinite Duration Therapy**
- BTK inhibitors
  - Ibrutinib
  - Acalabrutinib
  - Zanubrutinib
  - Pirtobrutinib
  - MK 1026
  - TG 1701

- BCL-2 inhibitors
  - Venetoclax
  - Lisaftoclax

**Fixed Duration Therapy**
- Rituximab +/- Dexamethasone
  - Rituximab
  - Fludarabine
  - Cladribine
  - Bortezomib
  - Carfilzomib
  - Ixazomib
  - Cyclophosphamide
  - Bendamustine

**Radioimmuno-conjugate**
- CLR-131

---

**CLR 131 Phospholipid Drug Conjugate (PDC) Valued Delivery Platform**

- Tumor cells utilize lipids at significantly greater quantities than normal tissue
  - Energy source (b-oxidation)
  - Cell membrane production
  - Signaling molecules

- CLR-131 exploits cancer cells’ needs for lipids to provide targeted delivery
  - Bind to specialized regions on tumor cell surface and internalized
  - Delivers 20-40% of infused drug to tumor

- CLR 131: targeted delivery of I-131 (validated therapeutic isotope)
  - Kills tumor cells by creating double stranded breaks in the DNA
CLR 131 WM Global Pivotal Study
Open Label, Single Arm Registration Clinical Study

- Sample size = 50 WM pts
- Includes MYD88^{WT} pts and Bing-Neel patients
- Only 4 (~20min) infusions

Enroll WM patients who received at least 2 prior lines of therapy, including having failed or had a suboptimal response to BTKi

CLR 131 15 mCi/m² per dose
4 doses over 2 cycles
Days 1, 15, & 57, 71

N=50

Primary Endpoint Assessment
(Major Response Rate)

Secondary Endpoint Assessments
(DOR, TFR, ORR)

N=10

Futility, Safety Assessments

Safety Follow-up 3 years

CLR 131 Phase 2 WM Patient Baseline Characteristics
Majority Were High Risk and Multi-drug Refractory

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients with WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>6</td>
</tr>
<tr>
<td>Median Age (range)</td>
<td>69 (54 – 81)</td>
</tr>
<tr>
<td>Sex (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (33.3)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (66.6)</td>
</tr>
<tr>
<td>IPSSWM Score (%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>Medium</td>
<td>1 (16.7)</td>
</tr>
<tr>
<td>High</td>
<td>4 (66.6)</td>
</tr>
<tr>
<td>Median Serum IgM, mg/dL (range)</td>
<td>3978 (1110 – 6267)</td>
</tr>
<tr>
<td>Median Bone Marrow Involvement (range)</td>
<td>65 (14 – 72)</td>
</tr>
<tr>
<td>Extramedullary Disease (cm)</td>
<td>10,479</td>
</tr>
<tr>
<td>Median Prior Lines of Therapy (range)</td>
<td>2 (1 – 5)</td>
</tr>
</tbody>
</table>

- Highly refractory patient population
  - 83.3% of patients were refractory to rituximab combinations
  - 100% of patients were either refractory or had a suboptimal response to ibrutinib

- Only 1 patient had responded to the immediately prior therapy (salvage third line)

- All patients met inclusion/exclusion criteria including requirement for treatment according to the consensus guidelines
CLR 131 Phase 2 WM Best Response by Patient
Demonstrates Activity in All Patients Subtypes

• CLR 131 Responses
  – 100% Overall Response Rate (ORR)
  – 83.3% Major Response Rate (MRR)
  – 100% MRR in MYD88WT patients
  – 16.7% Complete Response Rate (CR)

CLR 131 Phase 2 WM Duration of Response
Over 13 Months of Ongoing Treatment Free Remission Exhibited

• Median time to initial response 22 days of first cycle
• Median time to major response 44 days
• Mean Treatment free remission 1.1 years; ongoing
• Median duration of response (DOR) not reached
• 100% of MYD88WT patients exceed 8.5 months of DOR
CLR 131 Safety: Treatment Emergent Adverse Events
Well Tolerated Safety Profile in WM, MM and Other NHLs

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ALL DOSES Total n = 88 Phase 1 &amp; 2 Pts</th>
<th>≥ Grade 3 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>73 (83)</td>
<td>64 (73)</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>40 (45)</td>
<td>35 (40)</td>
</tr>
<tr>
<td>Decreased White Blood Cell Count</td>
<td>52 (59)</td>
<td>41 (47)</td>
</tr>
<tr>
<td>Anemia</td>
<td>60 (68)</td>
<td>55 (17)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>49 (56)</td>
<td>45 (51)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>51 (60)</td>
<td>12 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>29 (33)</td>
<td>0</td>
</tr>
</tbody>
</table>

Most frequent TEAEs are cytopenias; highly predictable & manageable
- Nadir occurs ~34 days post initial dose; recovery occurs within ~21 days post nadir
- No treatment related deaths, cardiotoxicities, liver, renal or neurologic toxicities, keratopathy, etc.

Novel Approaches to Treatment of WM

- **BTK inhibitors**
  - Acalabrutinib
  - Zanubrutinib
  - Pirftbrutinib
  - MK-1026
  - TG-1701
  - Ibrutinib + ixazomib

- **Monoclonal Antibodies**
  - Daratumumab (anti-CD38 monoclonal Ab)
  - Daratumumab + ibrutinib
  - Obinutuzumab (anti-CD20 monoclonal Ab)

- **IRAK4 inhibitor**
  - CA-4948

- **Bi-specific Antibody**
  - Plamotamab (XmAb 13676)

- **CXCR4 antagonists**
  - ulocuplumab
  - mavorixafor

- **Radioimmuno-conjugate**
  - CLR-131
Real-world treatment patterns, adherence, costs, and healthcare resource utilization associated with Waldenström macroglobulinemia in the United States

Keri Yang, Jorge J. Castillo, Anna Ratiu, Rachel Delinger, Todd Zimmerman, Boxiong Tang

Methods

Looked at commercial and Medicare claims between 2014-2019.

Sum of inpatient, outpatient, and pharmacy costs per-patient-per-month (PPPM).

Treatment regimens, costs, and hospitalizations were examined overall and by line of therapy.

Results

<table>
<thead>
<tr>
<th>Line of Therapy</th>
<th>Costs PPPM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line chemo (452 patients)</td>
<td>$18,682</td>
</tr>
<tr>
<td>2nd line chemo (143 patients)</td>
<td>$19,171</td>
</tr>
<tr>
<td>3rd line chemo (24 patients)</td>
<td>$36,878</td>
</tr>
</tbody>
</table>

Yang et al. J Clin Oncol 39, 2021 (suppl 15; abstr e18766)
Financial Assistance Resources

- https://iwmf.com/financial-assistance/
- The Leukemia & Lymphoma Society (LLS) Co-Pay Assistance Program
- The Leukemia & Lymphoma Society (LLS) Patient Travel Assistance Program
- Patient Access Network (PAN) Foundation WM Assistance Program
- HealthWell Foundation [https://www.healthwellfoundation.org/](https://www.healthwellfoundation.org/)
- Cancer Financial Assistance Coalition [https://www.cancerfa.org](https://www.cancerfa.org)
- Gooddays ([https://www.mygooddays.org/](https://www.mygooddays.org/) (link is external)
- Family Reach ([http://familyreach.org](http://familyreach.org))
- Miracle Flights: [www.miracleflights.org](http://www.miracleflights.org)
- Lazarex Care Patient Assistance Program
- Cancer Support Community/Airbnb
- CancerCare – Pet Assistance & Wellness (PAW) Program

- Johnson & Johnson Patient Assistance Foundation at 800-652-6227 or visit its website at [www.jjpaf.org](http://www.jjpaf.org) (ibrutinib)
- ThisIsLivingWithCancer ([https://www.thisislivingwithcancer.com](https://www.thisislivingwithcancer.com))
- Partnership for Prescription Assistance (PPA – [https://www.pparx.org](https://www.pparx.org))
- Teva Pharmaceuticals- CORE program (bendamustine, rituximab-abbs)
WhiMSICAL: the only global WM registry of patient-derived data, capturing clinical and patient-reported outcome data.
A scientific and ethically-approved portal for patients’ voices globally.
• With 520 participants WhiMSICAL is now generating big data, capturing insights into real-world treatment outcomes & QoL, complementing trial data
• Participants please update your data by mid-July for an ASH Abstract.
• If not already participating, join WhiMSICAL Registry at www.cart-wheel.org
• For information: https://wmozzies.com.au/index.php/whimsical/ or email: whimsical@iwmf.com

WhiMSICAL: A global Waldenström’s Macroglobulinemia patient-derived data registry capturing treatment and quality of life outcomes

Ibrahim Tohidi-Esfahani, Andrew Warden, Elena Malans, Peter L. Dehairs, Javier Haurat, Marta Black, Stephen Opi, Damien Kee, Shirley DSa, Marie José Kersten, Ruth L. Spearin, Maria Lia Palomba, Adam I. Olowska, Carl Harrington, Clare L. Scott, Judith Treiman. See fewer authors

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Thank you for your attention

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