New Agents for Malignant Lymphoma

Won Seog Kim MD, PhD

Medicine

Hematology/Oncology

Samsung Medical Center
Novel Agents for B-cell lymphoma

- Monoclonal antibody
  - Anti-CD20 monoclonal antibody
  - Monoclonal antibody non-CD20 antigen
  - Antibody drug conjugates
  - T-cell engaging antibody
- Immunomodulating agents
- Proteasome inhibitor
- Agents targeting apoptotic pathway
- Cyclin-dependent kinase inhibitor
- mTOR inhibitor
- Histone deacetylase inhibitor
- Miscellaneous agents
B-cell antigen targets

Anti-CD20 antibodies: Type I antibody

Lower apoptosis:
- Few direct effects

Increased ADCC

Increased CDC activity

Rapid translocation of CD20 into lipid rafts

Example: Rituximab
Ofatumumab (HuMax-CD20)

- Human IgG kappa backbone
- Unique binding site
  - Membrane-proximal epitope encompassing small and large loop of CD20
- Phase I/II for NHL/CLL
- Kills rituximab-resistant cell lines
Ofatumumab (HuMax-CD20)

- Type I anti-CD20 monoclonal antibody
  - Strong CDC activity
- Phase II single agent for relapsed DLBCL
  - 8 weekly IV infusion
  - 1st 300mg → 2nd - 8th 1000mg

- **Phase II ofatumumab + ICE or DHAP for relapsed DLBCL**
Veltuzumab (hA20)

- Humanized monoclonal antibody
  - Murine complementarity-determining region with epratuzumab backbone

- Similar mechanism(binding activity) to rituximab
  - Anti-proliferative, apoptotic, and antibody-dependent cytotoxicity
Veltuzumab (hA20)

- **In vitro study with cell lines**
  - Significant slow off-rate
  - Increased complement-dependent cytotoxicity

- **Animal study**
  - Very low dose can deplete B cells

- **Human study**
  - 80-750mg/m² IV were well tolerated
  - Once weekly for four weeks
  - Effective and safe with subcutaneous 80-320mg

- **Phase I/II relapsed B-cell NHL**
  - ORR: 40% (CR/CRu 17 patients)
Veltuzumab (hA20)

- Phase I/II relapsed B-cell NHL
- ORR: 40% (CR/CRu 17 patients)

Anti-CD20 antibodies: Type II antibody

Increased direct cell death
Unique type II epitope & elbow-hinge modification

Increased ADCC
via increased affinity to the 'ADCC receptor' FcγRIIIA

Lower CDC activity
Due to recognition of type II epitope

No translocation of CD20 into lipid rafts
Example: GA101
GA101

- Humanized type II antibody
  - Increased ADCC
  - Increased direct induction of apoptosis
  - Trials for indolent lymphomas

GAUSS: A Study of GA 101 in Indolent NHL
- Relapsed CD20+ indolent B-cell NHL
- Documented history of response of ≥ 6 months duration from last rituximab-containing regimen
Treatment with GA101 (1, 10, 30 mg/kg, q7d x 3, iv) resulted in dose-related superior efficacy in terms of tumour growth inhibition and complete tumour remission compared with rituximab.

All drugs administered q7d x 3, iv.
GA101 Phase I/II study: Study design

- GA101: humanised, glycoengineered, type II anti-CD20 antibody

- Patient population consisted of:
  - Heavily pre-treated NHL patients with relapsed NHL (FL, DLBCL, CLL, WM)
  - Previous MabThera treatment
  - Over 50% had undergone autologous stem cell transplantation

Phase I: Dose finding

- GA101 x 9
  - 50–2000 mg

Phase II: Efficacy + safety
- Expanded cohort
- Dose identified in Ph I

GA101: Analysis of ORR in NHL patients*

<table>
<thead>
<tr>
<th>NHL sub-types</th>
<th>Best response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 FL</td>
<td>5 CR/CRu, 4 PR</td>
</tr>
<tr>
<td>4 MCL</td>
<td>(ORR = 43%)</td>
</tr>
<tr>
<td>1 SLL</td>
<td></td>
</tr>
<tr>
<td>1 lymphoplasmacytoid</td>
<td></td>
</tr>
<tr>
<td>1 WM</td>
<td></td>
</tr>
<tr>
<td>1 DLBCL</td>
<td></td>
</tr>
</tbody>
</table>

21 patients

6 of 9 responses still ongoing (response duration 7.5+ to 17+ months)

GAUSS (BO21003): Phase I dose escalation
Maintenance Dosing Schema

- Patients achieving PR or CR with induction eligible
- Administered every three months at cohort dose level
- Response assessed every 3 months by CT
Anti-CD20 antibodies with enhanced binding to FcγRIIIA

- PRO131921
  - Humanized
  - B-cell depletion superior to rituximab in murine models
- AME-133
  - Humanized
  - 10-fold higher cell killing than rituximab
Comparison of anti-CD20 antibodies

<table>
<thead>
<tr>
<th>Agent</th>
<th>ADCC</th>
<th>CDC</th>
<th>Apoptosis</th>
<th>Binding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ofatumumab (HuMax-CD20)</td>
<td>⇐</td>
<td>⇑</td>
<td>⇐</td>
<td>⇑</td>
</tr>
<tr>
<td>Veltuzumab (hA20)</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
<td>⇐</td>
</tr>
<tr>
<td>PRO131921 (rhuMAb v114)</td>
<td>⇑</td>
<td>⇑</td>
<td>⇐</td>
<td>⇑</td>
</tr>
<tr>
<td>AME-133</td>
<td>⇑</td>
<td>⇐</td>
<td>⇑</td>
<td>⇑</td>
</tr>
<tr>
<td>GA101</td>
<td>⇑</td>
<td>⇑</td>
<td>⇑</td>
<td>⇐</td>
</tr>
</tbody>
</table>
Monoclonal antibodies for non-CD20 targets

- Galiximab
  - Chimeric anti-CD80

- Epratuzumab
  - Humanized anti-CD22

- Dacetuzumab (SGN-40)
  - Humanized anti-CD40
Galiximab

- CD80: a member of B7 ligand family
- Phase I/II study for relapsed FL (n = 64)
  - 4 weekly infusion of galiximab + 1 dose rituximab (375mg/m²)
  - Recommended phase II dose: 500mg/m²
  - ORR: 66%, CR/CRu rate: 33%
- No study for DLBCL
# Epratuzumab

Pilot study with Epratuzumab/rituximab + CHOP in newly diagnosed DLBCL

## Treatment Schedule

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose (mg/m²)</th>
<th>Route</th>
<th>Day</th>
<th>ReRx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epratuzumab</td>
<td>360</td>
<td>IV</td>
<td>1</td>
<td>Every 21 d</td>
</tr>
<tr>
<td>Rituximab*</td>
<td>375</td>
<td>IV</td>
<td>1 or 2†</td>
<td>Every 21 d</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750</td>
<td>IV</td>
<td>1 or 2†</td>
<td>Every 21 d</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50</td>
<td>IV</td>
<td>1 or 2†</td>
<td>Every 21 d</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 (max, 2 mg)</td>
<td>Oral</td>
<td>5 d† (D 1–5 or D 2–6)</td>
<td>Every 21 d</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## No. of patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>13</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infusion-related</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anemia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Neurologic</td>
<td>5</td>
<td>1*</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR (%)</td>
<td>10/15 (67)</td>
</tr>
<tr>
<td>PR (%)</td>
<td>3/15 (20)</td>
</tr>
</tbody>
</table>

Dacetuzumab (SGN-40)

- Phase I study
  - Dosage: 2mg/kg → 8mg/kg
  - Weekly infusion for 4 weeks
  - ORR: 6/50 (1CR, 12%)
  - Fatigue, headache etc
Antibody drug conjugate

- Inotuzumab ozogamicin
  - Humanized anti-CD22 antibody conjugated to calicheamicin
  - MTD: 1.8mg/m$^2$
Phase 1/2 CMC-544 + Rituximab in Recurrent B-Cell Lymphomas

Recurrent B-cell  NHL CD22+

28 Day Cycle
Day 1: Rituximab 375 mg/m²
Day 2: CMC-544 0.8, 1.3, 1.8 mg/m²
Treatment: 4 cycles
Additional 4 cycles (8 max) if clinical benefit

Re-Stage

Enrollment

Dose level
1= 0.8 mg/m²
2=1.3 mg/m²
3=1.8 mg/m²
Response Rate with inotuzumab ozogamicin at 1.8 mg/m²

As treated: received ≥1 dose of test article and had baseline and post-treatment disease assessments

ORR = Overall response rate [complete response (CR) + complete response unconfirmed (CRu) + partial response (PR)]
Ongoing trial

Phase 2 Study of Inotuzumab Ozogamicin + Rituximab in Relapsed/Refractory CD22+ DLBCL, Eligible for ASCT

- Inclusion Criteria
  - CD20/CD22+ DLBCL relapsed after 1 or 2 prior therapies
  - One prior therapy must include anthracyclines and rituximab
  - Relapsed/disease progression within 12 months after start of prior therapy and/or secondary IPI score > 1
  - Eligible for ASCT

Rituximab 375 mg/m²

Inotuzumab 1.8 mg/m²

Every 3 weeks: Max 6 cycles
Antibody drug conjugate

- Veltuzumab-interferon immunocytokine
T-cell engaging antibody

- Blinatumomab (MT103)
  - Bispecific T-cell engager antibody
  - One is for CD3, the other is for CD19
  - Bivalent binding is required to cause T-cell activation
T-cell engaging antibody

- Blinatumomab (MT103)
  - Phase I study
  - Relapsed MCL, FL, MZL, SLL, DLBCL etc
  - Continuous infusion over 4-8 weeks
  - Mean infusion duration: 5.2 weeks
  - Dosage: 0.0005 – 0.090mg/m²/24 hrs
  - Response 41% at dose of > 0.015mg/m²
  - Lymphopenia, pyrexia, leucopenia

Bargou R, et al. 2008 ASH
Lenalidomide: Targeting the Tumor Cell and Its Microenvironment

Tumor Cells

IL-6 ↑
TNF-α ↑
IL-1β ↑

ICAM-1

Blood Vessels

VEGF ↑
bFGF ↑

Dendritic Cells

NK Cells

CD8+ T Cells

CD28

PI3K

NFAT

PDK

IL-2

IFN-γ ↑

bFGF = basic fibroblast growth factor; ICAM = intercellular adhesion molecule; IFN = interferon; IL = interleukin; NFAT = nuclear factor of activated T cells; PKC = protein kinase C; TNF = tumor necrosis factor; VEGF = vascular endothelial growth factor.

# Lenalidomide in Relapsed/Refractory Aggressive NHL

<table>
<thead>
<tr>
<th>Response</th>
<th>ORR</th>
<th>CR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL (n = 73)</td>
<td>29%</td>
<td>4%</td>
<td>25%</td>
</tr>
<tr>
<td>MCL (n = 30)</td>
<td>41%</td>
<td>13%</td>
<td>28%</td>
</tr>
</tbody>
</table>

- Dosing 25 mg/d x 21 d cycled q 28 d
- Median PFS for DLBCL – 1.8 months
- Median PFS for MCL – 7.1 months
- Principal toxicities - cytopenias

Proteasome Inhibitor

- **Rationale**
  - Disrupts pathways involved in pathogenesis of lymphoma
  - Preclinical models show sensitivity of lymphoma cell lines to proteasome inhibitors

Proteasome Inhibitor

- Bortezomib in DLBCL
  - Single agent activity: Not active in DLBCL
  - Gene expression profiles of ABC type: High NF-κB expression

Proteasome Inhibitor

- Bortezomib in DLBCL
  - Stabilization of IkB through proteasome inhibition prevents NF-kB activation
  - Bortezomib may sensitize ABC type DLBCL to chemotherapy
  - Bortezomib may improve outcome of ABC type compared to GCB type.
Bortezomib+DA-EPOCH trial

A

Relapsed/Refractory DLBCL (N=49)

Proceed to Part B if clinically indicated

Part A
Bortezomib (N=23)
Treat until disease progression or maximum allowable cycles

Part B
Bortezomib + DA-EPOCH (N=44)
Treat until disease progression or maximum allowable cycles

Gene expression profiling

Biopsy

Immuno-histochemistry

CD10

BCL6

IRF4/MUM1

ABC DLBCL (N=5)
GCB DLBCL (N=10)

ABC DLBCL (N=12)
GCB DLBCL (N=12)

DLBCL subtype classification by gene expression profiling or IHC

ABC DLBCL (N=12)
GCB DLBCL (N=15)

Bortezomib+DA-EPOCH trial

Phase I/II study of Bortezomb + CHOP every 2 weeks for advanced stage DLBCL

- Newly diagnosed DLBCL < 70 years
- Bulky stage II, stage III/IV

Bortezomb 1.0, 1.3, and 1.6 mg/m²

D1  D4

D1  D5  D14

CHOP

Cyclophosphamide 750 mg/m²
Doxorubicin 50 mg/m²
Vincristine 1.4 mg/m² (max: 2.0 mg/m²)
Prednisolone 100 mg/d PO

G-CSF

D4  D13
Ongoing trial

Bortezomib and Vorinostat for Recurrent MCL or DLBCL

- Relapsed MCL or Relapsed/refractory DLBCL
- No prior allo-SCT
- Phase II study

Bortezomib 1.3 mg/m²

D1 → D4

D1 → D5

D8 → D11

Vorinostat

D8 → D12
Romidepsin (depsipeptide)

• Novel bicyclic peptide
• Potent pan-HDAC inhibitor
  *Greatest activity against:*
  - Class I (HDACs 1, 2, 8)
  - Class II (HDACs 4, 5, 6)
  - Class IV (HDAC 11)
• In vitro efficacy
  - HUT-78 (TCL cell line)
    \[ IC_{50} = 1.4 \times 10^{-9} \text{M} \]
# Romidepsin in CTCL

<table>
<thead>
<tr>
<th>Clinical Stage</th>
<th>N=72</th>
<th>ORR</th>
<th>CR/CCR</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>IB-IIA</td>
<td>24</td>
<td>7 (29%)</td>
<td>1 (4%)</td>
<td>6 (25%)</td>
</tr>
<tr>
<td>IIB</td>
<td>16</td>
<td>9 (56%)</td>
<td>2 (13%)</td>
<td>7 (44%)</td>
</tr>
<tr>
<td>III</td>
<td>18</td>
<td>8 (44%)</td>
<td>1 (6%)</td>
<td>7 (39%)</td>
</tr>
<tr>
<td>IVA</td>
<td>14</td>
<td>6 (43%)</td>
<td>2 (14%)</td>
<td>4 (29%)</td>
</tr>
</tbody>
</table>

Responses in advanced disease (stages IIB-IVA)
- 48% ORR for ≥ IIB
- 8 patients with Sézary syndrome, 4 (50%) had a PR
Phase II Study of Romidepsin in relapsed/refractory MCL or DLBCL

- Romidepsin IV over 4 hours D1, 8, 15
  - Every 28 days for at least 6 courses

- Patients are followed every 3 months until disease progression and then every 6 months until 5 years

- A total of 16-35 patients will be accrued for this study within 8-24 months
Phase I study of belinostat

Belinostat: 600, 900, 1000mg/m\(^2\)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total (n)</th>
<th>Age (yr)</th>
<th>Sex (n)</th>
<th>ECOG performance status (n)</th>
<th>Tumour type (n)</th>
<th>Prior regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16</td>
<td>66.5</td>
<td>10</td>
<td>5</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>53–76</td>
<td></td>
<td>1</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Male</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NHL (diffuse large-cell, including two transformed CLL)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NHL (follicular)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Multiple myeloma</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CLL</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dose (mg/m(^2)/d × 5)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>4</td>
<td>2</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>4</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>4</td>
<td>2</td>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>600</td>
<td>4</td>
<td>2</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>900</td>
<td>5</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>900</td>
<td>8</td>
<td>5</td>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>3</td>
<td>2</td>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>4</td>
<td>2</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>5</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>4</td>
<td>1</td>
<td>NC (possible TLS)</td>
<td></td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>4</td>
<td>1</td>
<td>NC (possible TLS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>3</td>
<td>2</td>
<td>NC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>4</td>
<td>3</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>5</td>
<td>9</td>
<td>SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>7</td>
<td>2</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1000</td>
<td>4</td>
<td>Only 2 d of cycle 1 delivered</td>
<td>PD</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Syk Inhibitors

- **B-cell receptor**
  - Critical for normal B-cell survival
  - Maintained on lymphoma cells
  - Necessary for DLBCL cell survival in vitro

- **Syk**
  - Mediates BCR downstream survival events
  - Syk-dependent downstream signaling enhanced in FL cells
  - Overexpressed in some DLBCL cells

- **Fostamatinib disodium**
  - Prodrug of the spleen tyrosine kinase (Syk) inhibitor R-406
  - ATP-competitive Syk inhibitor

Friedberg. ASH. 2008
Phase I/II Trial: Fostamatinib in Relapsed/Refractory B-Cell NHL

- Phase I (N=13)
  - DLBCL (N=3), FL (5), MCL (3), CLL/SLL (2)
  - Fostamatinib 200 mg (N=6) or 250 mg (N=7) BID
  - Dose-limiting toxicities: neutropenia, thrombocytopenia, diarrhea
- Phase II (N=68)
  - DLBCL (N=23), FL (21), CLL/SLL (11), MCL (9), LPL (1), MZL (3)
  - 200 mg BID

<table>
<thead>
<tr>
<th>Response</th>
<th>Group</th>
<th>N</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>23</td>
<td>22%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>FL</td>
<td>21</td>
<td>10%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CLL/SLL</td>
<td>11</td>
<td>55%</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MCL</td>
<td>9</td>
<td>11%</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AE</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>41%</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>41%</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31%</td>
<td>17%</td>
</tr>
<tr>
<td>Anemia</td>
<td>27%</td>
<td>7%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24%</td>
<td>3%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Friedberg. *ASH*. 2008
**Bendamustine**

- Bendamustine cross-links DNA single and double strands, *inhibiting DNA replication, repair, and transcription* \(^1\)
- Significantly more double-strand breaks when compared with conventional alkylating agents \(^2\)
- Double-strand breaks more durable when compared with conventional alkylating agents \(^2\)
- Extent and durability of effect contributes to “mitotic catastrophe” \(^3,4\)

---


Figure adapted from Hurley. *Nat Rev Cancer.* 2002;2:188.
Bendamustine trial for Indolent B-cell lymphomas

Patients with Frontline iNHL or MCL (N = 549) → Randomized

- CHOP-R q 21 days for 6 cycles (n = 253)*
- B-R q 28 days for 6 cycles (n = 260)*

n = 513 evaluable

Bendamustine 90 mg/m^2
- D1
- D2

Rituximab 375 mg/m^2

*evaluable patients

## Results

Median observation time: 32 months

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CHOP-R</th>
<th>B-R</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>92.7</td>
<td>91.3</td>
<td></td>
</tr>
<tr>
<td>CR, %</td>
<td>30.8</td>
<td>40.1</td>
<td>.0323</td>
</tr>
<tr>
<td>PFS, mos</td>
<td>34.8</td>
<td>54.9</td>
<td>.00012</td>
</tr>
<tr>
<td>EFS, mos</td>
<td>31</td>
<td>54</td>
<td>.0002</td>
</tr>
</tbody>
</table>

- Significant PFS benefit for MCL, WM, FL subtypes
- PFS for FL: CHOP-R 46.7 months vs BR not reached (\( P = .0281 \))
- Significant TTNT benefit overall (\( P = .0002 \))

## Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>CHOP-R, %</th>
<th>BR, %</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious AE</td>
<td>74</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Neutropenia gr 3/4</td>
<td>46.5</td>
<td>12.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Leukocytopenia gr 3/4</td>
<td>38.2</td>
<td>4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>G-CSF</td>
<td>20</td>
<td>4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Alopecia</td>
<td>62</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Infectious complication</td>
<td>121</td>
<td>95</td>
<td>.043</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>73</td>
<td>18</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>47</td>
<td>16</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Skin reaction</td>
<td>23</td>
<td>42</td>
<td>.0122</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>73</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>
Ongoing trial

Bendamustine + Rituximab for DLBCL

- Relapsed or Refractory DLBCL
- Total cycle: 6 cycles
- Primary end point: Overall response rate
- Target response rate: 70%

Bendamustine 120 mg/m²

D1  D2

D1

Rituximab 375 mg/m²
Ongoing trial

Bendamustine + Rituximab + Lenalidomide for DLBCL

- Phase I/II
- Relapsed or Refractory DLBCL or FL (G3) not eligible for ASCT
- Up to 6 cycles
- Primary end point: MTD/Efficacy

Bendamustine:
- D1
- D2

Rituximab:
- D1

Lenalidomide:
- D1
- D21

Every 28 days
A lot of new agents?

All glitters is not gold.