Pharmaceutical care in Lymphoma patients

Trai Tharnpanich B.Pharm, BCP, BCOP
Department of pharmacy, Siriraj hospital
Faculty of medicine, Mahidol university
Outline

• Introduction
  – Hodgkin’s Lymphoma (HL)
  – Non-Hodgkin’s Lymphoma (NHL)
    • T-cell
    • B-cell

• Treatment option

• Pharmacist role
2006 Estimated Thailand Cancer Cases

Men

Women

## Incidence (2015)

**FIGURE X.1: LYMPHOMA INCIDENCE BY AGE GROUP**

<table>
<thead>
<tr>
<th>Type</th>
<th>Male</th>
<th>Female</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant Lymphoma, NOS</td>
<td>0</td>
<td>3</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>HL</td>
<td>8</td>
<td>6</td>
<td>14 (4.2)</td>
</tr>
<tr>
<td>NHL</td>
<td>164</td>
<td>155</td>
<td>319 (95)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>172</strong></td>
<td><strong>64</strong></td>
<td><strong>336</strong></td>
</tr>
</tbody>
</table>

Siriraj cancer registry 2015
Lymph node

(a) Germinal center in follicle
- Capsule
- Subcapsular sinus
- Trabecula
- Efferent lymphatic vessels
- Hilus
- Medullary sinus
- Medullary cord
- Cortex
- Follicle
- Afferent lymphatic vessels
- Internal jugular vein
- Entrance of right lymphatic duct into right subclavian vein
- Entrance of thoracic duct into left subclavian vein
- Thoracic duct
- Aorta
- Cisterna chyli
- Lymphatic collecting vessels

Regional lymph nodes:
- Cervical nodes
- Axillary nodes
- Inguinal nodes

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Lymphoid differentiations
# WHO/REAL Classification of Lymphoid Neoplasms

## B-Cell Neoplasms

- **Precursor B-cell neoplasm**
  - Precursor B-lymphoblastic leukemia/lymphoma
    (precursor B-acute lymphoblastic leukemia)
- **Mature (peripheral) B-neoplasms**
- B-cell chronic lymphocytic leukemia / small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma
- Splenic marginal zone B-cell lymphoma
  (+ villous lymphocytes)*
- Hairy cell leukemia
- Plasma cell myeloma/plasmacytoma
- Extranodal marginal zone B-cell lymphoma of MALT type
- Nodal marginal zone B-cell lymphoma
  (+ monocytoid B cells)*
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
  - Mediastinal large B-cell lymphoma
  - Primary effusion lymphoma*
- Burkitt’s lymphoma/Burkitt cell leukemia§

## Mature (peripheral) T neoplasms

- T-cell chronic lymphocytic leukemia / small lymphocytic lymphoma
- T-cell prolymphocytic leukemia
- T-cell granular lymphocytic leukemia
- Aggressive NK leukemia
- Adult T-cell lymphoma/leukemia (HTLV-1+)
- Extranodal NK/T-cell lymphoma, nasal type*
- Enteropathy-like T-cell lymphoma**
- Hepatosplenic γδ T-cell lymphoma*
- Subcutaneous panniculitis-like T-cell lymphoma*
- Mycosis fungoides/Sézary syndrome
- Anaplastic large cell lymphoma, T/null cell,
  primary cutaneous type
- Peripheral T-cell lymphoma, not otherwise characterized
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, T/null cell,
  primary systemic type

## Hodgkin’s Lymphoma (Hodgkin’s Disease)

- Nodular lymphocyte predominance Hodgkin’s lymphoma
- Classic Hodgkin’s lymphoma
  - Nodular sclerosis Hodgkin’s lymphoma (grades 1 and 2)
  - Lymphocyte-rich classic Hodgkin’s lymphoma
  - Mixed cellularity Hodgkin’s lymphoma
  - Lymphocyte depletion Hodgkin’s lymphoma

- Not described in REAL classification
- Includes the so-called Burkitt-like lymphomas
- Formerly known as intestinal T-cell lymphoma
  - Formerly known as angiocentric lymphoma

### T and NK-Cell Neoplasms

- Precursor T-cell neoplasm
  - Precursor T-lymphoblastic leukemia/lymphoma
    (precursor T-acute lymphoblastic leukemia)

‡ Formerly known as lymphoplasmacytoid lymphoma or immunocytoma

§ Includes the so-called Burkitt-like lymphomas

** Formerly known as intestinal T-cell lymphoma

# Formerly know as angiocentric lymphoma
Lymphoma

Hodgkin (B-cell)  Non-Hodgkin

B-cell

Very aggressive:
BL, LBL, PCL

Aggressive:
DLBCL, MCL, GZL

Indolent:
FL, MZL

T-cell

Aggressive:
PTCL, ALCL (ALK +, -) AITL, PTCL-NOS

Indolent:
CTCL (MF and SS)

FL=Follicular Lymphoma, MZL= Marginal Zone Lymphoma, MCL=Mantle Cell Lymphoma, DLBCL = Diffuse Large B-cell Lymphoma, BL= Burkitt Lymphoma, GZL = Gray Zone Lymphoma, CTCL = Cutaneous T-cell lymphoma, PTCL = Peripheral T-cell lymphoma, ALCL = Anaplastic large cell lymphoma, PTCL-NOS = PTCL – not otherwise specified, AITL = Angioimmunoblastic lymphoma
Signs and symptoms

Lymphadenopathy or “B” symptoms

• Indolent (low-grade)
  – Patients may experience “spontaneous” remission.
  – 15-30% will transform to an aggressive histologic type.

• Aggressive
  – 40-50% of patients present with “B” symptoms (fevers, night sweats, weight loss[>10% in 6 mo.])
  – Rapidly growing tumor
Ann Arbor staging

A: Absence of constitutional symptoms
B: Wt loss > 10% per 6 mo, fever, drenching night sweats
X: Bulky > 10 cm, mediasternal widening to >1/3 of the chest width on CXR
E: Extranodal extension or single, isolated site of extranodal disease
S: Involving spleen
Treatment flow

1\textsuperscript{st} line \quad 2\textsuperscript{nd} line \quad BMT
Hodgkin’s Disease/Lymphoma
In the Beginning

• First described in 1832 by Dr. Thomas Hodgkin

• Reed-Sternberg cell – binucleate Hodgkin cell with owl eye appearance

<table>
<thead>
<tr>
<th>Classification</th>
<th>%Incidence</th>
<th>Characterize</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodular sclerosis</td>
<td>75 (Low grade)</td>
<td>• Classical HL</td>
</tr>
<tr>
<td>Mixed cellularity</td>
<td>13 (HIV+)</td>
<td>• Reed-Sternberg Cells</td>
</tr>
<tr>
<td>Lymphocyte rich classical</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte depleted</td>
<td>1 (High grade)</td>
<td></td>
</tr>
<tr>
<td>Lymphocyte- Predominant</td>
<td>5 (Tx as NHL)</td>
<td>• Pop corn cell</td>
</tr>
</tbody>
</table>
Hodgkin’s Lymphoma/Treatment

Hodgkin's Lymphoma in British Columbia
Outcome by Decade of Diagnosis

Cum Survival

Progression Free Survival (y)

n = 2170
Favorable risk/Prognosis score (IPS)

1. Albumin < 4 g/dL
2. Hemoglobin < 10.5 g/dL
3. Male
4. Age ≥ 45 years
5. Stage IV
6. Leukocytosis
   – WBC at least 15,000/mm$^3$
7. Lymphocytopenia
   – Lymphocyte count < 8% of WBC count and/or lymphocyte count < 600/mm$^3$)

<table>
<thead>
<tr>
<th>Score</th>
<th>% of Patients with Advanced Disease</th>
<th>5-year PFS</th>
<th>5-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-2</td>
<td>58%</td>
<td>74%</td>
<td>86%</td>
</tr>
<tr>
<td>≥ 3</td>
<td>42%</td>
<td>55%</td>
<td>70%</td>
</tr>
</tbody>
</table>

OS = overall survival; PFS = progression-free survival.
St. I / II favorable

Reduced Treatment Intensity in Patients with Early-Stage Hodgkin’s Lymphoma

1370 Patients underwent randomization

- 346 Were assigned to group 1 (4xABVD + 30 Gy IFRT)
- 340 Were assigned to group 2 (4xABVD + 20 Gy IFRT)
- 341 Were assigned to group 3 (2xABVD + 30 Gy IFRT)
- 343 Were assigned to group 4 (2xABVD + 20 Gy IFRT)

Result

A. Chemotherapy Comparison

- 4xABVD (groups 1 and 2)
- 2xABVD (groups 3 and 4)

Difference at 5 yr, −1.9 percentage points (95% CI, −5.2 to 1.4)
Hazard ratio, 1.17 (95% CI, 0.82 to 1.67)

B. Radiation Therapy Comparison

- 30 Gy IFRT (groups 1 and 3)
- 20 Gy IFRT (groups 2 and 4)

Difference at 5 yr, −0.5 percentage points (95% CI, −3.6 to 2.6)
Hazard ratio, 1.00 (95% CI, 0.68 to 1.47)
Result

Adverse event: ABVD x 4 cycles VS x 2 cycles
- Gr III/IV toxicity $\rightarrow$ 51.7% VS 33.2%
- No difference in 2nd cancer and OS

Conclusion

- **Early-stage HL** and a favorable prognosis, treatment with **ABVD x 2 + 20 Gy** of IFRT is as effective as, and less toxic than, 4 cycles of ABVD followed by 30 Gy of IFRT.
I / II unfavorable

- Patients with newly diagnosed early-stage unfavorable HL
- CMT: COPP x2 + ABVD x2 → radiotherapy of 30 Gy + 10 Gy to bulky disease

<table>
<thead>
<tr>
<th>Regimen</th>
<th>FFTF at 5 years</th>
<th>OS at 5 years</th>
<th>FFTF at 10 years</th>
<th>OS at 10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT +EFRT</td>
<td>85.8%</td>
<td>90.8%</td>
<td>79.8%</td>
<td>86.4%</td>
</tr>
<tr>
<td>CMT +IFRT</td>
<td>84.2%</td>
<td>92.4%</td>
<td>79.7%</td>
<td>87.3%</td>
</tr>
</tbody>
</table>

EFRT = Extended field radiotherapy, IFRT = Involved field radiotherapy, FFTF = Freedom from treatment failure, OS = Overall survival, COPP = Cyclophosphamide, vincristine, procarbazine, and prednisone
Conclusion

• In the EFRT group found more acute side effects including thrombocytopenia, leukopenia and GI toxicity at 5-year follow-up.

• RT volume size reduction from EF to IF after COPP + ABVD chemotherapy for 2 cycles produces similar efficacy and less toxicity in patients with early-stage unfavorable HL.

• ABVD 4 cycle + EFRT 30 Gy

Advanced stage

CHEMOTHERAPY OF ADVANCED HODGKIN’S DISEASE WITH MOPP, ABVD, OR MOPP ALTERNATING WITH ABVD

George P. Canellos, M.D., James R. Anderson, Ph.D., Kathleen J. Propert, Sc.D., Nis Nissen, M.D., M. Robert Cooper, M.D., Edward S. Henderson, M.D., Mark R. Green, M.D., Arlan Gottlieb, M.D.*, and Bruce A. Peterson, M.D.

MOPP (mechlorethamine, vincristine, procarbazine and prednisone, 6-8 cycles) VS

ABVD (6-8 cycles)

VS

MOPP alternating each cycle with ABVD (6 cycles each for a total of 12 cycles).

Table 2. Characteristics of Patients According to Treatment Group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MOPP</th>
<th>ABVD</th>
<th>MOPP–ABVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>123</td>
<td>115</td>
<td>123</td>
</tr>
<tr>
<td>Median age (range) — yr</td>
<td>34 (16-72)</td>
<td>35 (16-71)</td>
<td>32 (16-72)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>66</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Female</td>
<td>57</td>
<td>54</td>
<td>56</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III A2</td>
<td>15</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>III B</td>
<td>19</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>IV A</td>
<td>12</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>IV B</td>
<td>36</td>
<td>33</td>
<td>32</td>
</tr>
<tr>
<td>Previous radiation therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staging laparotomy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance status*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>57</td>
<td>53</td>
<td>54</td>
</tr>
<tr>
<td>1</td>
<td>28</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
ABVD vs MOPP vs MOPP/ABVD

MOPP (n=121): 84 events, 2.54 yr median follow-up
ABVD (n=115): 64 events, 12.36 yr median follow-up
MOPP/ABVD (n=123): 74 events, 6.9 yr median follow-up

MOPP (n=121): 68 events, 13.92 yr median follow-up
ABVD (n=115): 51 events
MOPP/ABVD (n=123): 56 events, 18.54 yr median follow-up

Toxicity

Table 4. Toxicity of Induction Therapy.

<table>
<thead>
<tr>
<th>Type of Toxicity</th>
<th>MOPP</th>
<th>ABVD</th>
<th>MOPP–ABVD</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>47, 21, 1</td>
<td>18, 3, 0</td>
<td>53, 28, 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>36, 15, 1</td>
<td>2, 3, 0</td>
<td>28, 13, 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Anemia</td>
<td>31, 12, 0</td>
<td>5, 0, 0</td>
<td>25, 8, 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>11, 1, 1</td>
<td>2, 0, 0</td>
<td>12, 2, 1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>8, 0, 0</td>
<td>1, 0, 0</td>
<td>2, 0, 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alopecia</td>
<td>5, 0, 0</td>
<td>24, 0, 0</td>
<td>14, 0, 0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>28, 0, 0</td>
<td>33, 0, 0</td>
<td>39, 0, 0</td>
<td>0.09</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>3, 1, 0</td>
<td>4, 0, 3</td>
<td>3, 0, 1</td>
<td>0.34</td>
</tr>
</tbody>
</table>

*MThe first number in each entry denotes the percentage with severe toxicity, the second the percentage with life-threatening toxicity, and the third the percentage with fatal toxicity. Severe toxicity was defined as a granulocyte count ranging from 0.5 to 1.0×10³ per cubic millimeter and a platelet count ranging from 25 to 50×10³ per cubic millimeter. Any counts below these were considered to constitute life-threatening toxicity.

MOPP vs ABVD↑AE
1. Hematologic toxicity
2. Loss of fertility
3. Infections
4. Peripheral neuropathy
(p<0.001)

ABVD versus BEACOPP for Hodgkin’s Lymphoma When High-Dose Salvage Is Planned

• 331 patients were 17 to 60 years of age and had untreated HL in stage IIB, III, or IV with any IPS or in any clinical stage with IPS >3

• Randomly to received ABVD 6-8 cycles vs BEACOPP 8 cycles
BEACOPP vs ABVD

### Table 1. Outcomes and Important Adverse Events Associated with Initial Treatment, According to Regimen.*

<table>
<thead>
<tr>
<th>Outcome or Adverse Event</th>
<th>ABVD (N=168)</th>
<th>BEACOPP (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome of initial treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission at the end of chemotherapy — no. (%)</td>
<td>107 (64)</td>
<td>114 (70)</td>
</tr>
<tr>
<td>Response at the end of chemotherapy and radiotherapy — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete remission</td>
<td>128 (76)</td>
<td>132 (81)</td>
</tr>
<tr>
<td>Partial remission &gt;80%</td>
<td>12 (7)</td>
<td>11 (7)</td>
</tr>
<tr>
<td>Progression</td>
<td>19 (11)</td>
<td>8 (5)</td>
</tr>
<tr>
<td>No response</td>
<td>7 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Response could not be evaluated</td>
<td>2 (1)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Relapse — no. (%)</td>
<td>19 (11)</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Severe adverse events — no. (%)</td>
<td>2 (1)</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Fatal toxic events during therapy‡</td>
<td>1 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Secondary leukemia during follow-up§</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Severe events during therapy leading to permanent discontinuation</strong></td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>22 (13)</td>
<td>15 (9)</td>
</tr>
<tr>
<td><strong>Severe adverse events during administration of initial chemotherapy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least one grade 3 or 4 acute hematologic adverse event — no./total no. (%)**</td>
<td>72/166 (43)</td>
<td>127/156 (81)</td>
</tr>
<tr>
<td>At least one grade 3 or 4 acute nonhematologic adverse event — no./total no. (%)††</td>
<td>12/166 (7)</td>
<td>30/156 (19)</td>
</tr>
<tr>
<td>Death from toxic effects — no./total no. (%)</td>
<td>1/166 (1)</td>
<td>5/156 (3)</td>
</tr>
</tbody>
</table>
Reduced-intensity chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin’s lymphoma (HD15 trial): a randomised, open-label, phase 3 non-inferiority trial

Andreas Engert, Heinz Haverkamp*, Carsten Kobe*, Jana Markova, Christoph Renner, Antony Ho, Josée Zijlstra, Zdenek Král, Michael Fuchs, Michael Hallek, Lothar Kanz, Hartmut Döhner, Bernd Dörken, Nicole Engel, Max Topp, Susanne Klutmann, Holger Arndt, Andreas Bockisch, Regine Kluge, Clemens Kratochwil, Otmar Schober, Richard Greil, Reinhard Andreesen, Michael Kneba, Michael Pfreundschuh, Harold Stein, Hans Theodor Eich, Rolf-Peter Möller, Markus Dietlein, Peter Borchmann, Volker Diehl, on behalf of the German Hodgkin Study Group, the Swiss Group for Clinical Cancer Research, and the Arbeitsgemeinschaft Medikamentöse Tumortherapie†

- 2182 patients with untreated advanced stage HL
  Escalated BEACOPP x 8 cycles
    vs
  Escalated BEACOPP x 6 cycles
    vs
  BEACOPP14 x 8 cycles

- Non-inferiority study design
Result

Result
### Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>8xBEACOPP&lt;sub&gt;escal&lt;/sub&gt; (N=705)</th>
<th>6xBEACOPP&lt;sub&gt;escal&lt;/sub&gt; (N=711)</th>
<th>8xBEACOPP&lt;sub&gt;st&lt;/sub&gt; (N=710)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one event</td>
<td>658/684 (96.2%)</td>
<td>671/696 (96.4%)</td>
<td>619/693 (89.3%)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>613/684 (89.6%)</td>
<td>619/696 (88.9%)</td>
<td>504/693 (72.7%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>425/684 (62.1%)</td>
<td>370/696 (53.2%)</td>
<td>385/693 (55.6%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>429/684 (62.7%)</td>
<td>372/696 (53.4%)</td>
<td>133/693 (19.2%)</td>
</tr>
<tr>
<td>Any haematological</td>
<td>632/684 (92.4%)</td>
<td>638/696 (91.7%)</td>
<td>552/693 (79.7%)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>374/684 (54.7%)</td>
<td>368/696 (52.9%)</td>
<td>369/693 (53.2%)</td>
</tr>
<tr>
<td>Infection</td>
<td>169/684 (24.7%)</td>
<td>155/696 (22.3%)</td>
<td>143/693 (20.6%)</td>
</tr>
<tr>
<td>Nausea or vomiting</td>
<td>88/684 (12.9%)</td>
<td>77/696 (11.1%)</td>
<td>74/693 (10.7%)</td>
</tr>
<tr>
<td>Mucositis</td>
<td>83/684 (12.1%)</td>
<td>73/696 (10.5%)</td>
<td>55/693 (7.9%)</td>
</tr>
<tr>
<td>Pain</td>
<td>90/684 (13.2%)</td>
<td>64/696 (9.2%)</td>
<td>56/693 (8.1%)</td>
</tr>
<tr>
<td>Nervous system</td>
<td>52/684 (7.6%)</td>
<td>35/696 (5.0%)</td>
<td>88/693 (12.7%)</td>
</tr>
<tr>
<td>Respiratory tract</td>
<td>44/684 (6.4%)</td>
<td>26/696 (3.7%)</td>
<td>64/693 (9.2%)</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>47/684 (6.9%)</td>
<td>44/696 (6.3%)</td>
<td>41/693 (5.9%)</td>
</tr>
<tr>
<td>Drug fever</td>
<td>30/684 (4.4%)</td>
<td>28/696 (4.0%)</td>
<td>31/693 (4.5%)</td>
</tr>
</tbody>
</table>

### Secondary Neoplasia

<table>
<thead>
<tr>
<th>Category</th>
<th>8xBEACOPP&lt;sub&gt;escal&lt;/sub&gt; (N=705)</th>
<th>6xBEACOPP&lt;sub&gt;escal&lt;/sub&gt; (N=711)</th>
<th>8xBEACOPP&lt;sub&gt;st&lt;/sub&gt; (N=710)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>33 (4.7%)</td>
<td>17 (2.4%)</td>
<td>22 (3.1%)</td>
</tr>
<tr>
<td>sAML/MDS</td>
<td>19 (2.7%)</td>
<td>2 (0.3%)</td>
<td>8 (1.1%)</td>
</tr>
<tr>
<td>NHL</td>
<td>8 (1.1%)</td>
<td>6 (0.8%)</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Solid tumour</td>
<td>6 (0.9%)</td>
<td>9 (1.3%)</td>
<td>9 (1.3%)</td>
</tr>
</tbody>
</table>

### Causes of Death

<table>
<thead>
<tr>
<th>Category</th>
<th>8xBEACOPP&lt;sub&gt;escal&lt;/sub&gt; (N=705)</th>
<th>6xBEACOPP&lt;sub&gt;escal&lt;/sub&gt; (N=711)</th>
<th>8xBEACOPP&lt;sub&gt;st&lt;/sub&gt; (N=710)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>53 (7.5%)</td>
<td>33 (4.6%)</td>
<td>37 (5.2%)</td>
</tr>
<tr>
<td>Hodgkin's lymphoma</td>
<td>13 (1.8%)</td>
<td>11 (1.5%)</td>
<td>15 (2.1%)</td>
</tr>
<tr>
<td>Treatment-related toxic effects</td>
<td>15 (2.1%)</td>
<td>6 (0.8%)</td>
<td>6 (0.8%)</td>
</tr>
<tr>
<td>Secondary neoplasia</td>
<td>13 (1.8%)</td>
<td>5 (0.7%)</td>
<td>8 (1.1%)</td>
</tr>
<tr>
<td>Toxic effects of salvage treatment</td>
<td>2 (0.3%)</td>
<td>2 (0.3%)</td>
<td>1 (0.1%)</td>
</tr>
<tr>
<td>Other†</td>
<td>6 (0.9%)</td>
<td>6 (0.8%)</td>
<td>4 (0.6%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>4 (0.6%)</td>
<td>3 (0.4%)</td>
<td>3 (0.4%)</td>
</tr>
</tbody>
</table>

Data are number (%) or n/N (%). sAML=secondary acute myeloid leukaemia. MDS=myelodysplastic syndrome. NHL=non-Hodgkin’s lymphoma. *Toxicities with an incidence of at least 3% only. †Suicide (n=3), cardiovascular (n=3), respiratory (n=2), accident (n=2), single reasons (n=6).
Conclusion

• Efficacy:
  – Escalated BEACOPP x 6 = Escalated BEACOPP x 8 > BEACOPP x 8

• Safety:
  – Escalated BEACOPP x 6 < BEACOPP x 8 < Escalated BEACOPP x 8

• However, this is still controversial and not recognized as standard of care at this point because escalated BEACOPP was not compared to ABVD.

Treatment

Adapted for NCCN Clinical Practice Guidelines in Oncology. HL Ver.4.2018.
Hodgkin’s Lymphoma
Salvage Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients</th>
<th>CR/PR to ASCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHAP</td>
<td>102</td>
<td>87-60%</td>
</tr>
<tr>
<td>(dexamethasone, ara-C, cisplatin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-BEAM</td>
<td>89</td>
<td>77-82%</td>
</tr>
<tr>
<td>(BCNU, etoposide, ara-C, melphalan; 2 series)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexa-BEAM</td>
<td>225</td>
<td>75-75%</td>
</tr>
<tr>
<td>(above plus dexamethasone; 3 series)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDP</td>
<td>34</td>
<td>62-88%</td>
</tr>
<tr>
<td>(gemcitabine, dexamethasone, oxaliplatin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICE</td>
<td>65</td>
<td>84- 86%</td>
</tr>
<tr>
<td>(ifosfamide, carboplatin, etoposide)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GND</td>
<td>38</td>
<td>64%</td>
</tr>
<tr>
<td>(gemcitabine, vinorelbine, liposomal doxorubicin)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Brentuximab vedotin (BV)
Indication

• Relapsed refractory Hodgkin’s lymphoma (RRHL)
  – Before or after AutoSCT

• As Consolidation Therapy after AutoSCT

• 1st line therapy in HL

Clinical study (RRHL)

All pts received a 30-min IV of BV 1.8 mg/kg q 3 weeks for up to 4 [27] or 16 [24, 26] cycles, or until disease progression, unacceptable toxicity [25]

<table>
<thead>
<tr>
<th>Study</th>
<th>Observation period [reference]</th>
<th>No. of pts</th>
<th>Overall OR(^a) rate (%)</th>
<th>Median duration (months) OR</th>
<th>Median PFS(^b) (months)</th>
<th>Median OS(^b) (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00848926</td>
<td>Median 18.5 months [24]</td>
<td>102</td>
<td>75(^d)</td>
<td>6.7</td>
<td>5.6</td>
<td>22.4</td>
</tr>
<tr>
<td>(pivotal trial)</td>
<td>Median 33.3 months [28]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01393717</td>
<td>After 4 cycles [27]</td>
<td>37</td>
<td>73</td>
<td>11.2</td>
<td>NYR</td>
<td>9.3</td>
</tr>
<tr>
<td>NCT00947856</td>
<td>Final cut-off date January 2013 [25]</td>
<td>20</td>
<td>60</td>
<td>9.2</td>
<td>9.9</td>
<td>NYR</td>
</tr>
<tr>
<td>JapicCTI-111650</td>
<td>At cut-off date May 2013 [26]</td>
<td>9(^f)</td>
<td>67</td>
<td>NYR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NSS, D5W or LRS to final concentration 0.4 to 1.8 mg/mL (Min 100 mL)
Results of a Pivotal Phase II Study of Brentuximab Vedotin for Patients With Relapsed or Refractory Hodgkin’s Lymphoma


# Safety

**Table 3.** Drug-Related Adverse Events Reported by ≥ 10% of Patients and Grade 3 or 4 Incidence of These Events Regardless of Relationship to Brentuximab Vedotin

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Events Related to Brentuximab Vedotin (any grade)</th>
<th>Any Grade 3 Events</th>
<th>Any Grade 4 Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>43</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>35</td>
<td>34</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>12</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>11</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>11</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Alopecia</td>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>
Summary

- **Indication**
  - Relapsed refractory Hodgkin’s lymphoma (RRHL)
    - Before AutoSCT: **4 cycles**
    - After AutoSCT: **16 cycles** or unacceptable toxicity
  - As Consolidation Therapy after AutoSCT (AETHERA)
    - Start 30–45 days after transplantation 1.8 mg/kg for **16 cycles**
  - **1st line therapy in HL (ECHELON-1)**
    - BV **1.2 mg/kg** + Doxo 25 mg/m², VBL 6 mg/m², and dacarbazine 375 mg/m² (A+AVD) D 1 and 15 q 3 wk. until progression or unacceptable toxicity

Summary

• S/E
  – Hematologic
    • Anemia
    • Neutropenia
    • Thrombocytopenia
  – Non Hematologic
    • Peripheral neuropathy
    • Fatigue
    • Nausea
    • URTI
Treatment

Adapted for NCCN Clinical Practice Guidelines in Oncology. HL Ver.4.2018.
Non-Hodgkin’s Lymphoma

Deep Breath...

Stand up...

Stretch...
Non Hodgkin Lymphoma

**Indolent**
- **B cell**
  - Follicular (FL)
  - SLL/CLL
  - Marginal zone LP (WM)
- **T/NK cell**
  - Mycosis fungoides
  - Sezary syndrome
  - Primary cut ALCL

**Aggressive**
- **B cell**
  - DLBCL
  - Mantle cell
  - **T/NK cell**
    - ALCL
    - Extranodal NK/T nasal
    - PTCL nos

**Highly Aggressive**
- **B cell**
  - Pre-B lymphoblastic
  - Burkitt
- **T/NK cell**
  - Peripheral T-cell Lymphoma (PTCL)
  - Pre-T lymphoblastic

**Multiple Myeloma**
Non-Hodgkin’s Lymphoma

<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (%)</th>
<th>5-Year Overall Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>22.1%</td>
<td>72%</td>
</tr>
<tr>
<td>Marginal zone B-cell, MALT</td>
<td>7.6%</td>
<td>74%</td>
</tr>
<tr>
<td>Marginal zone B-cell, nodal</td>
<td>1.8%</td>
<td>57%</td>
</tr>
<tr>
<td>DLBCL</td>
<td>30.6%</td>
<td>46%</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>6%</td>
<td>27%</td>
</tr>
<tr>
<td>Primary mediastinal large B-cell</td>
<td>2.4%</td>
<td>50%</td>
</tr>
<tr>
<td>Anaplastic large T/null cell</td>
<td>2.4%</td>
<td>77%</td>
</tr>
<tr>
<td>High grade B-cell, Burkitt-like</td>
<td>2.1%</td>
<td>47%</td>
</tr>
<tr>
<td>Peripheral T-cell</td>
<td>7%</td>
<td>25%</td>
</tr>
</tbody>
</table>

Non-Hodgkin’s Lymphoma Specific Types

• DLBCL
• Follicular lymphoma
• Mantle cell lymphoma
• Burkitt lymphoma
• T-cell lymphoma
  – Cutaneous T-cell lymphoma
  – Peripheral T-cell lymphoma
DLCL: IPI vs OS

International Prognostic Index (IPI)

Patients of all ages

- Age
- PS
- LDH level
- Extranodal involvement
- Stage (Ann Arbor)

Risk Factors

- >60 years
- 2-4
- Elevated
- >1 site
- III-IV

Patients ≤60 years (age-adjusted)

- PS
- LDH
- Stage

- 2-4
- Elevated
- III-IV

National High-Priority Lymphoma Study
For aggressive lymphoma

Groupe d’Etude des Lymphomes de l’Adulte (GELA/LNH-98.5)

CHOP compared with CHOP plus Rituximab

- Patients 60-80 years old with untreated DLCL
- Primary endpoint: event-free survival
  - events: progression, relapse, new alternative treatment, death from any cause
- Intent-to-treat analysis
- 399 patients with a median follow-up of 2 years

Cyclophosphamide 750 mg/m²
Doxorubicine 50 mg/m²
Vincristine 1.4 mg/m²
Prednisone 40 mg/m²/d x 5 d

CHOP
Rituximab 375 mg/m²

Event-Free Survival (aaIPI)

Overall Survival (aaIPI)

Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles

- RCT Phase III multicentre
- Aged ≥18 years, Untreated bulky stage IA to stage IV DLBCL
- R-CHOP-14x6+R x2 + G-CSF vs R-CHOP-21 x8
### Safety

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP-21 (n=534)</th>
<th>R-CHOP-14 (n=534)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>All toxicity</td>
<td>380 (71%)</td>
<td>290 (54%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>318 (60%)</td>
<td>167 (31%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>58 (11%)</td>
<td>28 (5%)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>28 (5%)</td>
<td>50 (9%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Infection</td>
<td>125 (23%)</td>
<td>96 (18%)</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>10 (2%)</td>
<td>14 (3%)</td>
<td></td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>2 (&lt;1%)</td>
<td>11 (2%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (4%)</td>
<td>22 (4%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (3%)</td>
<td>19 (4%)</td>
<td></td>
</tr>
<tr>
<td>Neurological toxicity</td>
<td>38 (7%)</td>
<td>53 (10%)</td>
<td></td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated. R-CHOP-21=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 21 days. R-CHOP-14=cycles of rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone every 14 days. *Only p values judged to be significant in multiple testing are provided.

**Table 4: Grade 3 or 4 adverse events**
Conclusion

- R-CHOP-14 + GCSF is not superior to R-CHOP-21 for previously untreated DLBCL in all ages

- R-CHOP-21 is STANDARD of Treatment
1\textsuperscript{st} line Tx Conclusion

DLBCL

Stage I,II
- Non-bulky (<7.5 cm)
  - RCHOP x 3 + RT or RCHOP x 6 ± RT

Stage III,IV
- Bulky (≥7.5 cm)
  - RCHOP x 6 ± RT
- Bulky (≥7.5 cm)
  - RCHOP x 6 (Interim PET after 2-4 cycles)

DA-REPOCH

Special population

Poor left ventricular function

- R-CEPP
- R-CDOP
- DA-R-EPOCH
- R-CEOP
- R-GCVP

> 80 years of age with comorbidities or failed

- R-mini CHOP (↓50% CHOP )

R-CDOP = rituximab, cyclophosphamide, liposomal doxorubicin, vincristine and prednisone; R-CEOP = rituximab, cyclophosphamide, etoposide, vincristine and prednisone; R-CEPP = rituximab, cyclophosphamide, etoposide, procarbazine and prednisone; R-GCVP (rituximab, gemcitabine, cyclophosphamide, vincristine and prednisolone

Double-hit lymphomas

- MYC + BCL2 or BCL6 rearrangement
  - Triple-hit lymphoma $\rightarrow$ MYC + BCL2 + BCL6

- Treatment $\rightarrow$ BMT
  - DA-R-EPOCH
  - R-HyperCVAD
  - R-CODOX-M/R-IVAC
CNS involvement

• Prophylaxis
  – IT MTX ± Ara-C 4-8 doses
  – IV HDMTX (≥3 gm/m2) on D_{15} of a 21 day R-CHOP cycle

• Treatment (parenchymal disease)
  – IV HDMTX (≥3 gm/m2) on D_{15} of a 21 day R-CHOP cycle
### 2nd line

<table>
<thead>
<tr>
<th>BMT candidate</th>
<th>Non-BMT candidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHAP ± R</td>
<td>Bendamustine ± R</td>
</tr>
<tr>
<td>ESHAP ± R</td>
<td>CEPP ± R</td>
</tr>
<tr>
<td>GDP ± R</td>
<td>CEOP ± R</td>
</tr>
<tr>
<td>ICE ± R</td>
<td>DA-EPOCH ± R</td>
</tr>
<tr>
<td>MINE ± R</td>
<td>GDP ± R</td>
</tr>
</tbody>
</table>

+ R = relapse after a reasonable remission (> 6 months)

DHAP = dexamethasone, cisplatin and cytarabine; DA-R-EPOCH = rituximab, etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin; DHAP = dexamethasone, cytarabine and prednisone; ESHAP = etoposide, methylprednisolone, cytarabine and cisplatin; GDP = gemcitabine, dexamethasone and cisplatin; GemOx = gemcitabine and oxaliplatin; ICE = ifosfamide, carboplatin and etoposide; MINE = mesna, ifosfamide, mitoxantrone and etoposide.
Follicular lymphoma (FL)

- Low-grade lymphoma
- Indication for treatment

<table>
<thead>
<tr>
<th></th>
<th>5-year</th>
<th>10-year</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>82%</td>
<td>73%</td>
<td>11 years*</td>
</tr>
</tbody>
</table>
## Prognosis

*FLIPI - 1 CRITERIA*<sup>a,c,d</sup>

<table>
<thead>
<tr>
<th>Age</th>
<th>Ann Arbor stage</th>
<th>Hemoglobin level</th>
<th>Serum LDH level</th>
<th>Number of nodal sites&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥60 y</td>
<td>III–IV</td>
<td>&lt;12 g/dL</td>
<td>&gt;ULN (upper limit of normal)</td>
<td>≥5</td>
</tr>
</tbody>
</table>

**Risk group according to FLIPI chart**

<table>
<thead>
<tr>
<th>Number of factors</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>2</td>
<td>≥3</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Overall score</th>
<th>%5 yr OS</th>
<th>%10 yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>90.6</td>
<td>70.7</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>77.6</td>
<td>50.9</td>
</tr>
<tr>
<td>High</td>
<td>≥3</td>
<td>52.5</td>
<td>35.5</td>
</tr>
</tbody>
</table>

Treatment

Follicular lymphoma

Grading

Gr I/II

GrIII
Tx as DLBCL

St I/II (non bulky)
ISRT ± R-CMT

St II (bulky), III and IV

Indications for treatment:
- Candidate for clinical trial
- Symptoms
- Threatened end-organ function
- Cytopenia secondary to lymphoma
- Bulky disease
- Steady progression

St II (bulky), III and IV

• **Aim**: Palliative treatment

• **First-line Therapy**
  – Bendamustine + rituximab (B-R) (category 1)
  – RCHOP (category 1)
  – RCVP (category 1)
  – Rituximab (375 mg/m weekly for 4 doses) (Weekly R)
  – Lenalidomide + rituximab (category 3)

• **Maintenance Therapy**
  – Rituximab

Bendamustine + rituximab

Bendamustine + rituximab

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-CHOP</td>
<td>B-R</td>
<td>R-CHOP</td>
<td>B-R</td>
</tr>
<tr>
<td>Leucocytopenia</td>
<td>13 (5%)</td>
<td>52 (19%)</td>
<td>39 (15%)</td>
<td>80 (30%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (2%)</td>
<td>30 (11%)</td>
<td>19 (8%)</td>
<td>61 (23%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>52 (2%)</td>
<td>14 (5%)</td>
<td>72 (29%)</td>
<td>38 (14%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>115 (46%)</td>
<td>102 (38%)</td>
<td>84 (33%)</td>
<td>44 (16%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>89 (35%)</td>
<td>104 (39%)</td>
<td>20 (8%)</td>
<td>19 (7%)</td>
</tr>
</tbody>
</table>

B-R = bendamustine plus rituximab. R-CHOP = CHOP plus rituximab. *p<0.0001 between groups.

Table 3: Haematological toxic events in patients receiving at least one dose of study treatment.

<table>
<thead>
<tr>
<th>B-R (n=261)</th>
<th>R-CHOP (n=253)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>245 (100%)*</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>18 (7%)</td>
<td>73 (29%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16 (6%)</td>
<td>47 (19%)</td>
</tr>
<tr>
<td>Skin (erythema)</td>
<td>42 (16%)</td>
<td>23 (9%)</td>
</tr>
<tr>
<td>Skin (allergic reaction)</td>
<td>40 (15%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Infectious episodes</td>
<td>96 (37%)</td>
<td>127 (50%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (&lt;1%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

B-R = bendamustine plus rituximab. R-CHOP = CHOP plus rituximab. *Includes only patients who received three or more cycles.

Table 4: All grades of non-haematological toxic events in patients receiving at least one dose of study treatment.

Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: the BRIGHT study

- RCT, Phase III open-label
- B-R vs R-CHOP or R-CVP for treatment naïve indolent NHL or MCL x 6 cycles
Result

<table>
<thead>
<tr>
<th>Response category, n (%)</th>
<th>BR (n = 213)</th>
<th>R-CHOP/R-CVP (n = 206)</th>
<th>CR-rate ratio*</th>
<th>P (Nl)†</th>
<th>P (Sup)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>67 (31)</td>
<td>52 (25)</td>
<td>1.26</td>
<td>.0225</td>
<td>.1269</td>
</tr>
<tr>
<td>95% CI</td>
<td>(25.3, 38.2)</td>
<td>(19.5, 31.7)</td>
<td>(0.93, 1.73)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td></td>
<td></td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Stable disease</td>
<td>139 (65)</td>
<td>135 (66)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>6 (3)</td>
<td>18 (9)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Overall response (CR + partial response)</td>
<td>206 (97)</td>
<td>187 (91)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>95% CI</td>
<td>(93.3, 98.7)</td>
<td>(86.0, 94.4)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 3. IRC assessment of response by histologic subtypes (evaluable analysis)

<table>
<thead>
<tr>
<th>Histologic subtype, n/N (%)</th>
<th>CR</th>
<th>CR + partial response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BR</td>
<td>R-CHOP/R-CVP</td>
</tr>
<tr>
<td>Indolent NHL</td>
<td>49/178 (28)</td>
<td>43/174 (25)</td>
</tr>
<tr>
<td>Follicular</td>
<td>45/148 (30)</td>
<td>37/149 (25)</td>
</tr>
<tr>
<td>Marginal zone</td>
<td>5/25 (20)</td>
<td>4/17 (24)</td>
</tr>
<tr>
<td>Lymphoplasmacytic</td>
<td>0/5</td>
<td>1/6 (17)</td>
</tr>
<tr>
<td>MCL</td>
<td>17/34 (50)</td>
<td>9/33 (27)*</td>
</tr>
</tbody>
</table>
Safety

- BR > R-CHOP/R-CVP (P < .05)
  - N/V + HSR

- R-CHOP/R-CVP > B-R (P < .05).
  - Peripheral neuropathy/paresthesia and alopecia
Asymptomatic patients (aged ≥18 years) with low grade FL (grades 1, 2, and 3a)

Rituximab 375 mg/m² weekly for 4 weeks (R-induction)

vs

R-induction → 2-monthly intervals for 2 years (R-maintenance)

vs

Wait and see (WAS)
Result

QOL

- R-maintenance group $\uparrow$ QOL ($D_0$ to $D_{210}$)
  - Mental Adjustment to Cancer scale score ($p=0.0004$)
  - Illness Coping Style score ($p=0.0012$)

- Rituximab induction vs WAS $\leftrightarrow$ QoL
Conclusion

• B-R vs RCHOP/R-CVP
  – B-R can increased PFS and fewer toxic effects if compare to R-CHOP/R-CVP\textsuperscript{1,2}

• Weekly R vs watch-and-wait
  – Weekly R ↓ time to start of new Tx in 3 yr.\textsuperscript{3}

Relapsed follicular lymphoma

- FCM-R (Category 1)
- Radioimmunotherapy (Category 1)
  - Ibritumomab-yttrium-90
- Fludarabine + rituximab
- Lenalidomide + rituximab

Mantle cell lymphomas (MCL)

• Median survival was only 36 months

• 10-year OS rate of only 8%

• Based on poor results with doxorubicin-based therapies (e.g., CHOP)
Treatment

MCL

- St. I or II
  - RT
- Stage II bulky, III and IV
  - Aggressive induction
  - Less Aggressive induction

1\text{st} \text{ line for aggressive regimen}

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Overall Response Rate</th>
<th>CR + CRu</th>
<th>3-Year Failure Free Survival (FFS)—Including &gt; 65y/o</th>
<th>3-Year Failure Free Survival (FFS)—Excluding &gt; 65 y/o</th>
<th>Overall Survival (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab + HyperCVAD</td>
<td>94/97 (97%)</td>
<td>75 + 9/97 (87%)</td>
<td>64%</td>
<td>73%</td>
<td>82%</td>
</tr>
</tbody>
</table>

• GCSF + prophylactic antibiotics
• ↓ FFS and ↑ toxicities in patients > 65 yr.
• R-HyperCVAD is not recommended in ≥ 65 yr.
Less aggressive
BR vs R-CHOP (StiL study)

Histology

<table>
<thead>
<tr>
<th></th>
<th>BR</th>
<th>R-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follicular</td>
<td>139 (53%)</td>
<td>140 (55%)</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>46 (18%)</td>
<td>48 (19%)</td>
</tr>
<tr>
<td>Marginal zone</td>
<td>37 (14%)</td>
<td>30 (12%)</td>
</tr>
<tr>
<td>Lymphoplasmacytic*</td>
<td>22 (8%)</td>
<td>19 (8%)</td>
</tr>
<tr>
<td>Small lymphocytic</td>
<td>10 (4%)</td>
<td>11 (4%)</td>
</tr>
<tr>
<td>Low grade, unclassifiable</td>
<td>7 (3%)</td>
<td>5 (2%)</td>
</tr>
</tbody>
</table>

Median (IQR; months)
- B-R: 69.5 (26.1 to not yet reached)
- R-CHOP: 31.2 (15.2 to 65.7)

HR 0.58 (95% CI 0.44–0.74)
p < 0.0001

Result

**FL**
Median (IQR; months)
- B-R: Not reached (22.1 to not yet reached)
- R-CHOP: 40.9 (15.2 to not yet reached)
HR 0.61 (95% CI 0.42–0.87)
p = 0.0072

**MCL**
Median (IQR; months)
- B-R: 35.4 (28.8–54.9)
- R-CHOP: 22.1 (15.1–33.8)
HR 0.49 (95% CI 0.28–0.79)
p = 0.0044

**MZL**
Median (IQR; months)
- B-R: 57.2 (20–90 to not yet reached)
- R-CHOP: 47.2 (20–65.7)
HR 0.70 (95% CI 0.34–1.43)
p = 0.3249

**WSM**
Median (IQR; months)
- B-R: 69.5 (36.6–73.0)
- R-CHOP: 28.1 (17.8–51.0)
HR 0.33 (95% CI 0.11–0.64)
p = 0.0033

Safety

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-CHOP</td>
<td>B-R</td>
<td>R-CHOP</td>
<td>B-R</td>
</tr>
<tr>
<td>Leucocytopenia</td>
<td>13 (5%)</td>
<td>52 (19%)</td>
<td>39 (15%)</td>
<td>80 (30%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 (2%)</td>
<td>30 (11%)</td>
<td>19 (8%)</td>
<td>61 (23%)</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>12 (5%)</td>
<td>14 (5%)</td>
<td>72 (29%)</td>
<td>38 (14%)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>115 (46%)</td>
<td>102 (38%)</td>
<td>84 (33%)</td>
<td>44 (16%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>89 (35%)</td>
<td>104 (39%)</td>
<td>20 (8%)</td>
<td>19 (7%)</td>
</tr>
</tbody>
</table>

R-B=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *p<0.0001 between groups.

Table 3: Haematological toxic events in patients receiving at least one dose of study treatment

<table>
<thead>
<tr>
<th>B-R (n=261)</th>
<th>R-CHOP (n=253)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>0</td>
<td>245 (100%)*</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>18 (7%)</td>
<td>73 (29%)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16 (6%)</td>
<td>47 (19%)</td>
</tr>
<tr>
<td>Skin (erythema)</td>
<td>42 (16%)</td>
<td>23 (9%)</td>
</tr>
<tr>
<td>Skin (allergic reaction)</td>
<td>40 (15%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Infectious episodes</td>
<td>96 (37%)</td>
<td>127 (50%)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>1 (&lt;1%)</td>
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</tbody>
</table>

B-R=bendamustine plus rituximab. R-CHOP=CHOP plus rituximab. *Includes only patients who received three or more cycles.

Table 4: All grades of non-haematological toxic events in patients receiving at least one dose of study treatment

Less aggressive
VR-CAP vs R-CHOP (the LYM 3002 study)

BMT-ineligible patients with newly diagnosed MCL

Treatment

Aggressive induction (BMT candidate)

- CALGB regimen
- R-HyperCVAD
- NORDIC regimen
- R-CHOP / R-DHAP
- Sequential R-CHOP / R-ICE

Less Aggressive induction (Elderly or Fail)

- BR
- VR-CAP
- R-CHOP
- Modified R-HyperCVAD plus rituximab maintenance in patients > 65 y/o

BR = bendamustine and rituximab; CALGB = Cancer and Leukemia Group B; D = day; NORDIC regimen = rituximab + cyclophosphamide, vincristine, doxorubicin and prednisone (maxi-CHOP) alternating with rituximab + high-dose cytarabine; R = rituximab; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-DHAP = rituximab, dexamethasone, cytarabine and cisplatin; R-HyperCVAD = rituximab, cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with rituximab, methotrexate and cytarabine; R-ICE = rituximab, ifosfamide, carboplatin and etoposide; RT = radiation therapy; VR-CAP = bortezomib, rituximab, cyclophosphamide, doxorubicin and rituximab.
Relapsed MCL

- Bendamustine ± R
- Bortezomib ± R
- Cladribine + R
- FC ± R
- FCMR
- FMR
- Ibrutinib
- Lenalidomide ± rituximab
- PCR
- PEPC

FC (fludarabine and cyclophosphamide), FCMR (fludarabine, cyclophosphamide, mitoxantrone and rituximab), FMR (fludarabine, mitoxantrone and rituximab), PCR (pentostatin, cyclophosphamide and rituximab), PEPC (prednisone, etoposide, procarbazine and cyclophosphamide ± rituximab)
Burkitt lymphoma (BL)

- Endemic
- Sporadic
- Immunodeficiency-associated
# Treatment

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Standard of Care</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Low risk disease: normal LDH, completely resected abdominal lesion or single extra-abdominal mass < 10cm | Induction Therapy  
1. R-HyperCVAD alternating with R-Methotrexate/Ara-C (6 to 8 cycles)  
2. *CODOX-M + rituximab (3 cycles) \(^{63}\)  
3. DA-REPOCH (minimum 3 cycles with 1 additional cycles beyond CR) | The difference between low-risk disease and high-risk disease is the number of chemotherapy cycles that can be given. |
| High risk disease                 | Induction Therapy  
1. R-HyperCVAD alternating with R-Methotrexate/Ara-C x 6-8 cycles  
2. R-CODOX-M alternating with \(^R\)-IVAC x 4 cycles total \(^{63}\)  
3. DA-REPOCH x 6 cycles           | With high risk disease, R-CODOX-M alternates with R-IVAC, for a total of 4 cycles. In low-risk disease, the patient would not receive R-IVAC. |
Relapsed BL

• No definitive 2\textsuperscript{nd} regimens
  – R-ICE
  – R-IVAC
  – High-dose cytarabine
  – DA-REPOCH
R-HyperCVAD/R-Methotrexate/Ara-C

• Arm A: R-HyperCVAD q21 days x 3 to 4 cycles
  – R = rituximab 375mg/m2 D1
  – C = cyclophosphamide 300mg/m2 q12h x 6 doses D1 – 3
  – V = vincristine 1.4mg/m2 D4 & 11, Max 2 mg/dose
  – A = doxorubicin 50mg/m2 D4 CIVI
  – D = dexamethasone 40mg PO D 1 – 4, 11-14

• Arm B: R-Methotrexate/Ara-C q21 days x 3 to 4cycles
  – R = rituximab 375mg/m2 D1
  – M = high dose methotrexate 1gm/m2 CIVI over 24 hours D1 with leucovorin rescue
  – Ara-C = cytarabine 3gm/m2 q12h x 4 doses on D2 & 3
T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL)

Peripheral T-cell lymphoma (PTCL)
Cutaneous T-cell lymphoma

- Two subtypes
  - Mycosis fungoides
  - Sezary syndrome

- Classified in 2 groups
  - Stage I – IIA
  - Stage IIB – IV or in early stage patients who have failed multiple topical therapies
Stage I – IIA

• Localized skin involvement
  – Topical corticosteroids
  – Topical chemotherapy (mechlorethamine or carmustine)
  – Local radiation
  – Topical retinoids (bexarotene)

• Generalized skin involvement
  – Phototherapy (ex. PUVA)
  – Total skin electron beam therapy (TSEBT)
## Stage IIB – IV or Failed topical therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Dose Description</th>
<th>Response</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denileukin diftitox</td>
<td>CD25 fusion protein</td>
<td>18mcg/kg IV daily days 1 to 5 every 21 days (18mcg/kg superior to 9mcg/kg dose)</td>
<td>RR: 49.1% CR: 9.1%</td>
<td>Capillary leak syndrome, fever, fatigue, lymphopenia</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Anti-CD52 monoclonal antibody</td>
<td>Escalate to 30mg IV or Subq, 3 times per week for up to 12 weeks (usually start with 3mg for dose 1, 10mg for dose 2, 30mg for dose 3. All patient receive Bactrim and valganciclovir prophylaxis</td>
<td>ORR: 55% CR: 32%</td>
<td>Cytopenias, infusion reactions, infections (CMV), nausea, emesis, fatigue</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Retinoid analogue (RAR X receptor subtype)</td>
<td>300-400mg/m² PO daily</td>
<td>RR: 50%</td>
<td>Rash, edema, hyperlipidemia, leukopenia</td>
</tr>
<tr>
<td>Vorinostat</td>
<td>Histone deacetylase inhibitor</td>
<td>400mg PO daily</td>
<td>RR: 30%</td>
<td>Hyperglycemia, fatigue, diarrhea, proteinuria, thrombocytopenia</td>
</tr>
<tr>
<td>Romidepsin</td>
<td>Histone deacetylase inhibitor</td>
<td>14mg/m² IV on days 1, 8, 15 of 28 day cycle</td>
<td>RR: 34% CR: 6%</td>
<td>ST-T wave changes, QTc prolongation, hypotension, rash, N/V, myelosuppression, fatigue, electrolyte abnormalities</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Antimetabolite</td>
<td>1200mg/m² IV days 1, 8, 15 of 28 day cycle</td>
<td>RR: 70% CR: 12%</td>
<td>Myelosuppression, pulmonary, fever, rash, edema, proteinuria</td>
</tr>
</tbody>
</table>
## Peripheral T-cell lymphoma

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Standard of Care</th>
<th>Chemotherapy Regimen</th>
<th>Comments</th>
<th>Alternative Chemotherapy Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>*ALCL,^ ALK (+) Stage I &amp; II</td>
<td>CHOP x 6 cycles ± radiotherapy (RT) or CHOP x 3 – 4 cycles + RT</td>
<td>CHOP q21days C=cyclophosphamide 750mg/m² IV, D1 H=doxorubicin 50mg/m² IV, D1 O=vincristine 1.4mg/m² IV, D1 cap 2mg P=Prednisone 100mg PO D1-5</td>
<td>No rituximab because t-cell lymphomas are typically not CD-20 (+)</td>
<td>1. CHOEP-21</td>
</tr>
<tr>
<td>ALCL, ALK (+) Stage III &amp; IV</td>
<td>CHOP x 6 cycles ± RT</td>
<td>Same as above</td>
<td></td>
<td>1. CHOEP-21 2. Dose-dense CHOP-14</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Poor LVEF or frail</td>
<td>1. CEOP 2. CEPP 3. CDOP</td>
</tr>
<tr>
<td>NOS, PTCL AITL ALCL, ALK(-)</td>
<td>CHOP x 4 - 6 cycles + locoregional RT or clinical trial</td>
<td>Same as above</td>
<td></td>
<td>1. CHOEP-21 2. Dose-dense CHOP-14</td>
</tr>
<tr>
<td>Stage I &amp; II, low/low-intermediate</td>
<td></td>
<td></td>
<td></td>
<td>3. DA-EPOCH 4. HyperCVAD/alternating with methotrexate/Ara-C</td>
</tr>
<tr>
<td>NOS, PTCL AITL ALCL, ALK(-)</td>
<td>CHOP x 6 - 8 cycles ± RT or clinical trial</td>
<td>Same as above</td>
<td></td>
<td>1. CHOEP-21 2. Dose-dense CHOP-14</td>
</tr>
<tr>
<td>Stage I &amp; II, high/high-intermediate, Stage III &amp; IV</td>
<td></td>
<td></td>
<td></td>
<td>3. DA-EPOCH 4. HyperCVAD/alternating with methotrexate/Ara-C</td>
</tr>
</tbody>
</table>

*ALCL = Anaplastic large cell lymphoma ^ALK = Anaplastic lymphoma kinase
Relapsed PTCL

- ICE
- ESHAP
- Brentuximab for systemic ALCL only
- Pralatrexate
- Romidepsin
Newly coming in B-Lymphoma

• New Anti-CD20
  – Subcutaneous Rituximab
  – Obinutuzumab (GA101)

• CAR-T cell therapy
Rituximab SQ
# Efficacy confirmation

<table>
<thead>
<tr>
<th>Study</th>
<th>End point</th>
<th>IV</th>
<th>SC</th>
<th>Diff: SC-IV (95% CI)</th>
<th>RR ratio: SC/IV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SABRINA(^1) (FL) R(IV) vs R(SQ) +CHOP or CVP</td>
<td>ORR, Induction, OS, PFS</td>
<td>84.9%</td>
<td>84.4%</td>
<td>-0.5% (-7.8 – 6.8)</td>
<td>0.99 (0.92, 1.08)</td>
</tr>
<tr>
<td>MabEase(^2) (DLBCL) R(IV) vs R(SQ) +CHOP</td>
<td></td>
<td>42.1%</td>
<td>47%</td>
<td>4.9% (-3.6 – 13.5)</td>
<td>1.12 (0.92, 1.36)</td>
</tr>
</tbody>
</table>

Treatment Emergent Adverse Events (TEAE)

• Common TEAE (≥25%)
  – FL: neutropenia, nausea
  – DLBCL: neutropenia
  – CLL: neutropenia, nausea, pyrexia, injection site erythema

TEAE with a >5% increase on the rituximab SC arm compared to rituximab IV arm (SC – IV)

<table>
<thead>
<tr>
<th></th>
<th>SABRINA (FL) N=407</th>
<th>MabEase (DLBCL) N=572</th>
<th>SAWYER (CLL) N=174</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (9.6%)</td>
<td></td>
<td></td>
<td>Neutropenia (6.3%)</td>
</tr>
<tr>
<td>Injection site erythema (13.2%)</td>
<td></td>
<td>None overall</td>
<td>Injection site erythema (25.9%)</td>
</tr>
<tr>
<td>Injection site pain (8.1%)</td>
<td></td>
<td></td>
<td>Injection site pain (16.5%)</td>
</tr>
<tr>
<td>Cough (9.5%)</td>
<td></td>
<td></td>
<td>Erythema (8.6%)</td>
</tr>
</tbody>
</table>

• Injection site erythema (2.7%)
• Injection site pain (1.9%)
Patient Assessments

PrefMab Study

CTSQ: Cancer Therapy Satisfaction Questionnaire
RASQ: Rituximab Administration Satisfaction Questionnaire
PrefMab result

• **Patient Preference Questionnaire:**
  - After cycle 6: 80% (CI: 77%, 83%) prefer SC
  - After cycle 8: 81% (CI: 77%, 84%) prefer SC
  - Retained preference between cycle 6 and 8: 83%

• **Reasons after cycle 8 for preferring SC:**
  - Requires less time in the clinic (69%)
  - Feels more comfortable during administration (37%)
  - Feels less emotionally distressing (29%)
  - Lower level of injection site pain (16%)

(Note: percentages add up to >100% as subjects were asked to pick two reasons)
Rituximab SQ summary

• Dose
  – Fixed 1400 SC doses lead to $\geq C_{trough}$ than IV

• ↔ Safety

• ↔ Efficacy

• ↑ Patient Preference
Obinutuzumab
Why modulate glycosylation?

ADCC: Cell lysis mediated by enzymes (granzyme, perforin...)

Phagocytosis

<table>
<thead>
<tr>
<th></th>
<th>FcγRI</th>
<th>FcγRIIa</th>
<th>FcγRIIb</th>
<th>FcγRIIC</th>
<th>FcγRIIIa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monocyte/macrophage</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>NK cell</strong></td>
<td></td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Neutrophil</strong></td>
<td>±</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>Lc B</strong></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td><strong>Dendritic cell</strong></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
<td>+</td>
</tr>
<tr>
<td><strong>Mastocyte</strong></td>
<td>±</td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Platelet</strong></td>
<td></td>
<td></td>
<td></td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>
Paratope modulation

Rituximab
Ofatumumab

Obinutuzumab
Ublituximab
GA101 : New anti-CD20

Low-fucose  \(\uparrow\) ADCC

Modified paratope  
\(\text{CDC} = \emptyset\)

Substitution hinge region  
\(\uparrow\) Apoptosis

Clone B-Ly1

<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>ADCC</th>
<th>CDC</th>
<th>Apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>chIgG1</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>GA 101</td>
<td>huIgG1</td>
<td>+++</td>
<td>0</td>
<td>+++</td>
</tr>
</tbody>
</table>

GADOLIN trial (FL)

Study design

- Rituximab-refractory CD20+ iNHL (incl. FL, MZL, and SLL) (N = 413)

Stratification factors:
- NHL subtype (FL vs. other)
- Prior therapies (≤2 vs. >2)
- Refractory type (R-monorefractory vs. R-chemorefractory)
- Geographic region

Randomized 1:1

G-B
- Obinutuzumab
  - 1,000 mg IV days 1, 8, and 15, cycle 1; day 1, cycles 2–6 (28-day cycles)
- Bendamustine
  - 90 mg/m²/day IV days 1 and 2, cycles 1–6 (28-day cycles)

G-maintenance
- Obinutuzumab
  - 1,000 mg IV every 2 months for 2 years or until progression
- Bendamustine
  - 120 mg/m²/day IV days 1 and 2, cycles 1–6 (28-day cycles)

B = bendamustine; CR = complete response; FL = follicular lymphoma; G = obinutuzumab; G-B = obinutuzumab, bendamustine; iNHL = indolent non-Hodgkin lymphoma; IV = intravenous; MZL = marginal zone lymphoma; PR = partial response; R = rituximab; SD = stable disease; SLL = small lymphocytic lymphoma

- 1st endpoint: PFS assessed by an independent review committee (IRC)
- 2nd endpoints: PFS as assessed by investigator, best overall response (complete response [CR] and partial response [PR]), duration of response, and overall survival

Bendamustine dosing
- In combination 90 mg/m²/day on D1,2
- Alone at 120 mg/m²/day on D1,2

GADOLIN result

Primary endpoint: IRC-assessed PFS

52% reduction in the risk of disease progression or death

HR=0.48
95% CI, 0.34-0.68; P<0.0001; 21.1-month median follow-up

GAZYVA + bendamustine followed by GAZYVA monotherapy (n=155)
Bendamustine (n=166)

13.8

Probability of PFS

Time (months)

0 6 12 18 24 30 36 42 48 54

0.0 0.2 0.4 0.6 0.8 1.0

n at risk

GAZYVA + bendamustine followed by GAZYVA monotherapy
Bendamustine

IRC, independent review committee; HR, hazard ratio; CI, confidence interval.

### Secondary endpoint: complete and partial response

<table>
<thead>
<tr>
<th></th>
<th>GAZYVA + bendamustine followed by GAZYVA monotherapy (n=155)</th>
<th>15.5%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>Bendamustine (n=166)</td>
<td>18.7%</td>
</tr>
<tr>
<td>Partial response</td>
<td>GAZYVA + bendamustine followed by GAZYVA monotherapy (n=155)</td>
<td>63.2%</td>
</tr>
<tr>
<td></td>
<td>Bendamustine (n=166)</td>
<td>56.0%</td>
</tr>
</tbody>
</table>

*Best response of CR/PR within 12 months of study start.

### Secondary endpoint: investigator-assessed median PFS

<table>
<thead>
<tr>
<th></th>
<th>GAZYVA + bendamustine followed by GAZYVA monotherapy (n=155)</th>
<th>29.2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bendamustine (n=166)</td>
<td>13.7 months</td>
</tr>
</tbody>
</table>

PFS HR=0.48; 95% CI, 0.35-0.67; P<0.0001
Secondary endpoint: overall survival

- GAZYVA + bendamustine followed by GAZYVA monotherapy (n=164)
- Bendamustine (n=171)

HR = 0.62
95% CI, 0.39-0.98

n at risk

GAZYVA + bendamustine followed by GAZYVA monotherapy
164 143 130 113 83 67 44 25 14 3

Bendamustine
171 156 125 107 86 60 39 20 9 2

### The most frequent all-cause ≥ grade 3 AE

- **Neutropenia**
  - 64 [33%] vs 52 [26%]
- **Thrombocytopenia**
  - 21 [11%] vs 32 [16%]
- **Anaemia**
  - 15 [8%] vs 20 [10%]

---

**Safety**

<table>
<thead>
<tr>
<th></th>
<th>Obinutuzumab plus bendamustine (n=194)</th>
<th>Bendamustine monotherapy (n=198)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1+2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>112 (58%)</td>
<td>16 (8%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>102 (53%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>73 (38%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (2%)</td>
<td>27 (14%)</td>
</tr>
<tr>
<td>Cough</td>
<td>54 (28%)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>52 (27%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>51 (26%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>39 (20%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>41 (21%)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>31 (16%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>26 (13%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>8 (4%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td>Headache</td>
<td>25 (13%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>24 (12%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>21 (11%)</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

GALLIUM Trial: GAZYVA vs rituximab in Previously Untreated FL

Patients with previously untreated follicular lymphoma (Grades 1-3a, stage III/IV or stage II bulky disease [≥7 cm]) N=1,202

GAZYVA\textsuperscript{a} + chemotherapy\textsuperscript{*} x 6 or 8 cycles (n=601)

rituximab\textsuperscript{b} + chemotherapy\textsuperscript{*} x 6 or 8 cycles (n=601)

GAZYVA\textsuperscript{a} monotherapy q2 months x 2 years\textsuperscript{c}

rituximab\textsuperscript{b} monotherapy q2 months x 2 years\textsuperscript{c}

**Primary endpoint**: PFS as assessed by Independent Review Committee (IRC)

**Additional endpoints**: Response rates at end of induction (IRC-assessed, assessed by CT ± PET), PFS by chemotherapy regimen (IRC-assessed)

Chemotherapy : Bendamustine 57%, CHOP 33% and CVP 10%

GALLIUM result

Primary Endpoint: PFS (IRC-assessed)

- **GAZYVA based regimen**: 601, 571, 532, 497, 476, 414, 287, 179, 79, 22
- **rituximab-based regimen**: 601, 563, 502, 463, 438, 394, 271, 151, 73, 16

HR = 0.72
95% CI, 0.56-0.93; P = 0.0118; 38-month median observation time

28% reduction in the risk of disease progression or death

### Table 2. Summary of safety

<table>
<thead>
<tr>
<th>Category</th>
<th>Pts with FL (n, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R-chemo (n=597)</td>
</tr>
<tr>
<td>Any AE</td>
<td>587 (98.3)</td>
</tr>
<tr>
<td>Grade ≥3 AEs (≥25% in either arm)</td>
<td>405 (67.8)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>226 (37.9)</td>
</tr>
<tr>
<td>Leucopenia</td>
<td>50 (8.4)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>29 (4.9)</td>
</tr>
<tr>
<td>IRRs*</td>
<td>22 (3.7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>16 (2.7)</td>
</tr>
<tr>
<td>Grade ≥3 AEs of special interest by category</td>
<td></td>
</tr>
<tr>
<td>Infections*</td>
<td>93 (15.6)</td>
</tr>
<tr>
<td>IRRs*</td>
<td>40 (6.7)</td>
</tr>
<tr>
<td>Second neoplasms*</td>
<td>16 (2.7)</td>
</tr>
<tr>
<td>SAEs</td>
<td>238 (39.9)</td>
</tr>
<tr>
<td>AEs leading to treatment discontinuation</td>
<td>85 (14.2)</td>
</tr>
<tr>
<td>Fatal AEs</td>
<td>20 (3.4)</td>
</tr>
<tr>
<td>Median (range) change from baseline in IgG levels at the EOI treatment, g/L††</td>
<td>−1.50 (−22.3–6.5)‡‡</td>
</tr>
</tbody>
</table>

G-chemo gr. had a higher frequency of grade 3-5 AEs (74.6%) and SAEs (46.1%) than R-chemo gr. (67.8% and 39.9%, respectively).
Obinutuzumab summary

- AntiCD20 mAb with **Type1 binding**
  - ↑ADCC → ↑Efficacy → ↑IRR
- Efficacy (↑PFS, RR, OS)
  - GADOLIN (RRFL): GA101 + benda (Dosing)
  - GALLIUM (1st FL): GA101 + CMT
  - CLL-11 (CLL): GA101 + Chlorambucil
- AE: ↑IRR, Neutropenia
- Dosing schedule:
  - C1 → 1000 mg Wk 1,2,3
    - CLL: wk1; 100 mg (25 mg/hr for 4 hr) → 900 mg
  - ≥C2 1000 mg wk1 q 4 wk
  - Maintenance: 1000 mg q 8 wk for 2 year

**Bendamustine dosing**
- In combination 90 mg/m²/day on D1,2
- Alone at 120 mg/m²/day on D1,2

CMT: Bendamustine /CHOP /CVP
Conclusion

• HL ➔ ABVD or A-AVD ➔ Brentuximab
• NHL
  – DLBCL ➔ R-CHOP, DA-REPOCH
  – FL ➔ BR or GB,R or G-CHOP, R or G-CVP, R or G-maintenance
  – MCL ➔ HyperCVAD A,B (Alternate)
  – BL ➔ CODOX-M/IVAC
• CTCL
  – Local Tx ➔ Denileukin diftitox
• PTCL
  – CHOP ➔ Pralatrexate, Brentuximab for systemic ALCL only
Thank you

Email: trai.tha@mahidol.ac.th