Diffuse Large B-Cell Lymphoma: Treatment Beyond R-CHOP

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Learning Objective:
- Interpret the findings from clinical trials on the use of novel therapeutic strategies and how these strategies can be incorporated into current treatment paradigms

Summary
- We are rapidly moving beyond R-CHOP for all patients
- Determination of cell of origin is essential for patient selection.
- Targeted agents interact with specific pathways necessitating patient selection based on either cell of origin or mutation status (or both!)
- Several agents (lenalidomide, ibrutinib, and bortezomib) appear to overcome the adverse impact of the non-GCB DLBCL

The History of CHOP in DLBCL
2 large randomized studies, 1530 patients, 7 years (overlapping studies)

- Gordon et al NEJM 1992; 327:1342
  - No difference in TTF and OS between CHOP and m-BACOD
  - Higher "received" dose intensity with CHOP despite higher "perceived" dose intensity
  - More toxicity with m-BACOD
- Fisher et al NEJM 1993; 328:1002
  - No difference in TTF or OS among 4 regimens
  - More toxicity with regimens other than CHOP

Analysis of Prognostic Factors in DLBCL
Gordon et al Cancer 1996; 75(3):865

Figure 7: Kaplan-Meier plot of survival for the 296 patients analyzed by pre-study serum LDH level. Patients are divided into groups based on LDH less than normal, LDH 1-3x normal, greater than normal, and LDH more than 3 times greater than normal. Survival rates are worse as the LDH level increases.
Revised IPI
Sehn et al. BLOOD 2007; 109(5):1857

IPI in the Rituximab era
- Retrospective analysis of DLBCL patients treated with R-CHOP
- Revised IPI defines 3 groups: [very good, good, poor]
- No group with <50% chance of survival

NCCN IPI in DLBCL
Zhou et al. BLOOD 2014;123(6):837

Optimal Cut Points for Survival in Rituximab Era
- CD 5
- Ki-67

Optimal Cut Points for Survival in Pre-Rituximab Era
- Bcl-2
- Bcl-6
- HLA-DR
- MUM-1

MYC in DLBCL
Savage et al. BLOOD 2009;114:3533

• PFS and OS in MYC+ vs. MYC-
• Time to CNS relapse in MYC+ vs. MYC-

Lunenburg Consortium
Salles et al. BLOOD 2011;117(26):7070

• TMA from 1514 patients
• IHC for BCL2, BCL6, CD5, CD10, MUM1, Ki67, HLA-DR
• Prognostic model using IPI, BCL2, Ki67 identified 4 risk groups
• IPI remains the best index

Lunenburg Consortium
Salles et al. BLOOD 2011;117(26):7070

- TMA from 1514 patients
- IHC for BCL2, BCL6, CD5, CD10, MUM1, Ki67, HLA-DR
- Prognostic model using IPI, BCL2, Ki67 identified 4 risk groups
- IPI remains the best index
**Gene Expression Profiling (GEP) in paraffin embedded tissue predicts survival of DLBCL treated with R-CHOP**

Rimsa et al BLOOD 2008;112:3425

- Levels of HLA-DR (low is predictive) and c-MYC (high is predictive)

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**Studies examining prognostic factors in DLBCL**

Molecular Biology predicts outcome

- Biologic score based on non-GC subtype, low SPARC, and high microvascular density (Perry et al BLOOD 2012; 120(11): 2250).

- Ox Phos vs. BCR vs. HR by GEP (Monti et al BLOOD 2005; 105:1851)

- CD 20 Expression in DLBCL predicts survival (Johnson et al BLOOD 2009; 113: 3773)

- BCL-6 and p21 are prognostic in DLBCL (Winter et al BLOOD 2006; 107:4207 and Winter et al CCR 2010;16(8):2435)

- HIF 1α predicts outcome in DLBCL (Evens et al J Clin Oncol 2010; 28: 1017)

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**“Double Hit” Lymphomas**

Petrich et al Cancer 2014 (Jul 24; Epub ahead of print)

**Table 3: Reported Outcomes From Retrospective Studies With Various Regimens in Patients With Double-hit lymphomas**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Effective therapy</th>
<th>Outcome</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al (2016) 1</td>
<td>n=132</td>
<td>R-CHOP</td>
<td>n=98</td>
<td>Higher ORR, longer PFS and OS</td>
</tr>
<tr>
<td>Greven et al (2009) 2</td>
<td>n=19</td>
<td>R-CHOP or R-CVP</td>
<td>n=11</td>
<td>Higher ORR, longer PFS and OS</td>
</tr>
<tr>
<td>Greven et al (2008) 3</td>
<td>n=12</td>
<td>RCHOP</td>
<td>n=8</td>
<td>Higher ORR, longer PFS and OS</td>
</tr>
<tr>
<td>Weiner et al (2006) 4</td>
<td>n=30</td>
<td>R-CHOP or R-CVP</td>
<td>n=19</td>
<td>Higher ORR, longer PFS and OS</td>
</tr>
<tr>
<td>Hu et al (2010) 5</td>
<td>n=30</td>
<td>Rituximab, IFN</td>
<td>n=20</td>
<td>Higher ORR, longer PFS and OS</td>
</tr>
<tr>
<td>Greven et al (2007) 6</td>
<td>n=167</td>
<td>R-CHOP or R-CVP</td>
<td>n=111</td>
<td>Higher ORR, longer PFS and OS</td>
</tr>
</tbody>
</table>

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**Targeting Lymphoma: Tumor Cells and The Microenvironment**

Successful targeted therapy needs to identify the biological Achilles heel of the tumor to alter clinical outcomes

- Lymphoma cells are found in a microenvironment exerting positive and negative growth signals

- The tumor can be targeted via cell surface molecules

- The tumor can be targeted by attacking signal or metabolic pathways or critical cellular processes such as apoptosis

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**IMIDs exert their pleotropic effects by binding to cereblon and altering substrate specificity**

- Lenalidomide enhances IkappaB-α binding to cereblon promoting ubiquitination and degradation

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BTK is Involved in BCR and Other Key Signaling Pathways


Multiple Critical Signaling Pathways: Targets for Modern Therapy


Tumor Heterogeneity in DLBCL

- Heterogeneous outcome with R-CHOP
- Cell of origin identifies distinct disease with different outcomes
- Different pathways are activated in distinct subtypes
- Recurrent mutations identify potential targets


Value of the Lymph2Cx assay

- It is a robust 20-gene predictor of GCB vs. ABC built for FFPE tissue samples using NanoString
- Accurately assigns cell-of-origin categories
- Inexpensive (< $40) and can be done in less than 36 hours
- It is highly reproducible between laboratories
- It retains prognostic power compared to Affymetrix GEP of fresh tissue


Patient outcomes according to COO in the independent validation cohort

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Cell of Origin Using NanoString Technology on formalin fixed paraffin embedded tissue
Scott et al of BLOOD 2014;123(8):1214

A 20-gene gene expression based assay accurately and robustly assigns COO subtypes of DLBCL using formalin fixed paraffin embedded tissue

B-cell Receptor Signaling Pathway and potential targets

Card11 coiled-coil mutation
Card11 wild type

Treatment:
- IKKγ inhibitor
- Proteasome inhibitor
- Neddylation inhibitor

Treatment:
- BTK inhibitor
- LYN inhibitor
- SYK inhibitor (+/-)
- PKCγ inhibitor

Lenalidomide for DLBCL: Impact of Cell of Origin

<table>
<thead>
<tr>
<th></th>
<th>ALL</th>
<th>GCB</th>
<th>Non-GCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemic blasts</td>
<td>1.31 ± 0.20</td>
<td>0.99 ± 0.10</td>
<td>1.83 ± 0.20</td>
</tr>
<tr>
<td>CD10</td>
<td>0.31 ± 0.10</td>
<td>0.62 ± 0.10</td>
<td>0.35 ± 0.10</td>
</tr>
<tr>
<td>BCL6</td>
<td>0.53 ± 0.10</td>
<td>0.87 ± 0.10</td>
<td>0.31 ± 0.10</td>
</tr>
<tr>
<td>IRF4</td>
<td>0.43 ± 0.10</td>
<td>0.31 ± 0.10</td>
<td>0.83 ± 0.10</td>
</tr>
</tbody>
</table>

Response
- CR: 6 (15.0) 1 (4.3) 5 (29.4)
- PR: 5 (12.5) 1 (4.3) 4 (23.5)
- SD: 7 (17.5) 7 (30.4) 0
- PD: 21 (52.5) 14 (60.9) 7 (41.2)
- Unknown: 1 (2.5) 0 1 (5.9)

ORR (CR + PR): 11 (27.5) 2 (8.7) 9 (52.9)

PFS, mo
- Median: 2.6 1.7 6.2
- 95% CI: 0.9-4.2 0.3-3.1 2.9-9.6

Hernandez-Ilizaliturri et al, Cancer 2011 117:5058

Lenalidomide: Exploiting synthetic lethality by inhibiting NF-κB and augmenting negative INFβ signaling

Novel agents (e.g., Lenalidomide)
Lenalidomide + R-CHOP (R²-CHOP) in DLBCL or FL: Phase II Study Designs

- Two trials with slightly different dose schedules of lenalidomide
- Compared with historical R-CHOP control (with similar baseline characteristics)

Lenalidomide + R-CHOP21 in Elderly Untreated DLBCL: Efficacy

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>45 (92)</td>
</tr>
<tr>
<td>PR</td>
<td>42 (88)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

- Median follow-up: 22 months
  - 2-year OS = 92%
  - 2-year PFS = 73% overall
  - 86% (R1)
  - 83% (R2)

R²-CHOP Treatment Schedule

Cycle = 21 days; 6 Cycles of Treatment

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Day of Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lenalidomide</td>
<td>25 mg</td>
<td>po</td>
<td>1–10</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>50 mg/m²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>1.4 mg/m²</td>
<td>IV</td>
<td>1</td>
</tr>
<tr>
<td>Prednisone</td>
<td>100 mg/m²</td>
<td>po</td>
<td>1–5</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>6 mg</td>
<td>SC</td>
<td>2</td>
</tr>
<tr>
<td>Asparin</td>
<td>325 mg</td>
<td>po</td>
<td>daily</td>
</tr>
</tbody>
</table>

Lenalidomide + R-CHOP-21 in Elderly Untreated DLBCL: Conclusions

- The addition of 15 mg lenalidomide on days 1–14 to R-CHOP 21 is safe, feasible, and effective in elderly untreated DLBCL patients
- The primary objective of the phase 2 study was met
  - ORR 92% (86% CR)
- At median follow-up of 22 months, 2-year OS = 92% and 2-year PFS = 73%
- Addition of lenalidomide did not impair administration of R-CHOP 21
- Lenalidomide + R-CHOP-21 efficacy in elderly DLBCL patients needs to be investigated in a large phase 3 randomized trial

R²-CHOP - Eligibility

- ≥18 years of age (no upper age limit)
- Newly diagnosed CD20 positive stages II-IV DLBCL or grade 3 FL
- Measurable disease
- ECOG performance status 0–2
- Preserved organ function
- Patients with a history of life threatening or recurrent thrombosis/embolism were excluded unless they were on anticoagulation during the treatment

R²-CHOP – Response Rates (N=47 evaluable patients)

- 47 of 51 patients were evaluable
- 4 non-evaluable patients:
  - 3 refusals (refusal of travel to treatment center)
  - 1 death before evaluation

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**Conclusions**

- Lenalidomide + R-CHOP (R2-CHOP) is well tolerated, including in elderly patients
- Efficacy appears to be promising when compared to R-CHOP
- Addition of lenalidomide may ameliorate the negative effect of non-GCB phenotype on outcome
- Randomized study will be required to evaluate R2-CHOP vs. R-CHOP (ECOG 1412 in development)

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**E1412: RL-CHOP vs. R-CHOP**

N=100 evaluable patients

**Ibrutinib (PCI-32765): First-in Class Inhibitor of BTK**

- Forms a specific and irreversible bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC50 = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- Blocks mantle cell migration and adhesion
- Blocks pERK, pJNK, and NF-kB pathways in mantle cell lymphoma lines.
Ibrutinib in Rel/Ref ABC-subtype DLBCL: Phase II Study Design

- Relapsed/refractory de novo DLBCL
- Progressive disease (PD) after ASCT or ineligible for ASCT
- Archival tissue for central review
- No primary mediastinal DLBCL, transformed DLBCL or CNS involvement

- Gene expression profiling of biopsy tissues using Affymetrix arrays to identify DLBCL subtype (ABC, GCB, unclassifiable)
- Mutations in tumor samples analyzed by PCR and DNA sequencing
- ABC DLBCL: tumors analyzed for mutations in CD79B, MYD88 and CARD11 genes

Ibrutinib: 560 mg/d, PO

ASCT = autologous stem cell transplant

Ibrutinib in Rel/Ref ABC-subtype DLBCL: Efficacy

<table>
<thead>
<tr>
<th>Efficacy (N=70)</th>
<th>ABC subtype (n=35)</th>
<th>GCB subtype (n=29)</th>
<th>Total (N = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical to prior treatment</td>
<td>41%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>41%</td>
<td>3%</td>
<td>23%</td>
</tr>
<tr>
<td>PR</td>
<td>27%</td>
<td>0%</td>
<td>56%</td>
</tr>
<tr>
<td>ORR</td>
<td>26%</td>
<td>0%</td>
<td>46%</td>
</tr>
<tr>
<td>Median DL, mo</td>
<td>0.9</td>
<td>3.5</td>
<td>NA</td>
</tr>
</tbody>
</table>

R-CHOP vs R-CHOP+ibrutinib in non-GC DLBCL is ongoing.

Ibrutinib in Rel/Ref ABC-subtype DLBCL: Conclusions

- Ibrutinib showed a clinically meaningful response rate in relapsed/refractory ABC DLBCL, but not in other molecular subtypes
  - ORR: 23% all patients, 41% ABC (17% CR), 5% GCB (all PR)
  - Responses by mutational status
    - Did not require CD79b mutation
    - CARD11 mutation did not respond, suggesting an impact upstream of BCR
    - MYD88 mutations seemed to cause resistance
  - Results were consistent with an essential role of BCR signaling in ABC DLBCL
  - Future clinical trials of ibrutinib in DLBCL should screen for DLBCL subtype

Ibrutinib in Rel/Ref ABC-subtype DLBCL: Waterfall Plot

- Only includes pts with post baseline BM measurements
- * Best responder was PD due to clinical progression

Phase III Validation: R-CHOP ± Ibrutinib for Non-GC DLBCL

Non-GCB DLBCL

Based on Hans model (CD10, BCL6, MuM1/IRF4A)

R-CHOP + Placebo

R-CHOP + Ibrutinib

CHOP-R + bortezomib as initial therapy for diffuse large B-cell lymphoma (DLBCL)

- Treatment: Bortezomib 0.7 to 1.3 mg/m² on Day 1 & 4 of each R-CHOP-21 cycle
- Patient characteristics (n = 40):

<table>
<thead>
<tr>
<th>Age</th>
<th>56 (20-87) years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage III/IV</td>
<td>88%</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>75%</td>
</tr>
<tr>
<td>High int HIGH IPI</td>
<td>50%</td>
</tr>
<tr>
<td>1.3 mg/m²</td>
<td>70%</td>
</tr>
<tr>
<td>Non-germinal center histology</td>
<td>56%</td>
</tr>
</tbody>
</table>

**Abstract**

et al. (ASH) 2013;122: Abstract 4080

**Randomized evaluation of molecular guided therapy in DLBCL with bortezomib**

- All patients undergo biopsy for profiling at diagnosis
- All patients receive cycle 1 R-CHOP
- Randomized from cycle #2-6 to receive bortezomib 1.3 mg/m² d 1 and 8
- All patients initially randomized, designed to close for GCB subjects if evidence of futility
- Up to 940 patients, minimum 260 ABC subtype

**Antibody Drug Conjugate: Mechanism of Action**

- Drug or toxin
- Protease-cleavable linker
- Monoclonal antibody to desired target
- ADC binds to target
- ADC-target complex traffics to lysosome
- Drug/toxin is released
- E.g. MMAE disrupts
- Microtubule network
- Drug/toxin is released
- E.g. MMAE disrupts
- Microtubule network
- G2/M cell cycle arrest
- Apoptosis

**Previous Phase I/II: Single Agents**

- CD 22
- CD 79b

**ROMULUS Study Design**

- R-CHOP 21 x6
- Bortezomib 1.3 mg/m², d 1, 4
- Rituximab 375 mg/m², d 1
- Cyclophosphamide 750 mg/m², d 1
- Doxorubicin 50 mg/m², d 1
- Prednisone 1.4 mg/m², d 1
- Vincristine 1.4 mg/m², d 1
- Rituximab 100 mg/m², d 1-5

**PYRAMID study design**

- DLBCL diagnosis & subtyping
- Randomize 1:1
- Not enrolled
- Follow-up every 3 months for 2 yrs

**Randomized evaluation of molecular guided therapy in DLBCL with bortezomib**

- All patients undergo biopsy for profiling at diagnosis
- All patients receive cycle 1 R-CHOP
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- All patients initially randomized, designed to close for GCB subjects if evidence of futility
- Up to 940 patients, minimum 260 ABC subtype
### Investigator-Assessed Best Responses in Treated Patients

<table>
<thead>
<tr>
<th></th>
<th>DLBCL</th>
<th>FL</th>
</tr>
</thead>
<tbody>
<tr>
<td>R+CD22 ADC</td>
<td>R+CD79b ADC</td>
<td></td>
</tr>
<tr>
<td>(N=42)</td>
<td>(N=21)</td>
<td></td>
</tr>
<tr>
<td>Objective response, n (%)</td>
<td>24 (57%)</td>
<td>22 (58%)</td>
</tr>
<tr>
<td>Complete Response</td>
<td>10 (24%)</td>
<td>13 (62%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>5-15%</td>
<td>11-32%</td>
</tr>
<tr>
<td>Partial Response</td>
<td>14 (33%)</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>20-50%</td>
<td>33-14%</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>3 (7%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>0-10%</td>
<td>5-40%</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>7 (17%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Median Duration of Response, mo. (95% CI)</td>
<td>6.0 (2.0-12.2)</td>
<td>6.3 (2.4-10.1)</td>
</tr>
</tbody>
</table>

*Patients who received 1 dose of study treatment; patients unable to evaluate did not have a post-baseline tumor assessment.

NR = Not reached

### Summary

- We are rapidly moving beyond R-CHOP for all patients
- Determination of cell of origin is essential for patient selection.
- Targeted agents interact with specific pathways necessitating patient selection based on either cell of origin or mutation status (or both!)
- Several agents (lenalidomide, ibrutinib, and bortezomib) appear to overcome the adverse impact of the non-GCB DLBCL

### SGN-CD19A: Dose Escalation

- No dose limiting toxicity (DLT) observed in Cycle 1
- Enrollment to 6 mg/kg discontinued due to later cycle adverse events
- Doses 3, 4, and 5 mg/kg expanded

### Conclusions

- ORR 30% (11 of 37 patients)
- CR 16% (6 of 37 patients)
- SGN-CD19A is generally well tolerated
  - No DLTs have been observed to date in Cycle 1
  - Superficial corneal changes and ocular symptoms managed with steroid eye drops and dose modifications
  - Grade 3/4 anemia, thrombocytopenia, or neutropenia each observed in <10% of patients
- Preclinical data demonstrate synergy with relevant standard of care agents
- Encouraging antitumor activity with manageable toxicities enables novel combination regimens