UPDATE IN TREATMENT OF DIFFUSE LARGE B CELL LYMPHOMA

Auayporn Nademanee, M.D.
Jane & Mace Professor in Hematology and Hematopoietic Cell Transplantation
Director, Matched Unrelated Donor Program
Disclosure

• Speaker’s Bureau for Seattle Genetics
• Advisory Board for Seattle Genetics and Gilead
• OFF Label use lenalidomide, ibrutinib, bortezomib
Objectives

• Review the histology, cell of origin and molecular profile
• Review the prognostic factors
• Update on the treatment of DLBCL
• Update on CNS prophylaxis for DLBCL
Most Common NHLs

- DLBCL, 31%
- FL, 22%
- MALTL, 8%
- MCL, 6%
- SLL/CLL, 7%
- PTCL, 7%
- PMLBCL, 2%
- ALCL, 2%
- BL, 2%
- MZL, nodal, 2%
- T-LL, 2%
- Other, 9%

EPIDEMIOLOGY OF DLBCL

• The most common lymphoma accounts for 25-30% of all NHLs in the developed world
• The incidence of DLBCL is 7 cases per 100,000 persons per year in US and England
• Incidences varies by Ethnicity, caucasian >Black>Asians> American Indian
• DLBCL is the most frequent subtype in central and South America, account for 40% of NHL
• Male predominance, 55% of cases
• Incidence increases with age, median age 64 years
• Familial aggregation of DLBCL and other NHL subtypes has been noted.
## Overview of DLBCL

### Morphology
- Centroblastic, immunoblastic, T-cell/histiocyte rich, or anaplastic

### Immuno-phenotyping
- Pan B-cell antigens (CD19, CD20, CD22, CD79a), CD45
- 50-75% express surface or cytoplasmic Ig(IgM)
- CD30+ in 25% (anaplastic), CD5 + rare

### Genetic features
- t(14;18) BCL2 oncogene (10% - 25% of cases)
  - but 60% overexpress bcl2 protein
- der 3q27 BCL6 oncogene (35% of cases)
- t(8;14) C-MYC oncogene (5-15%)

### Clinical features
- Aggressive behavior
- Heterogeneous clinical response
Key oncogenic pathways in DLBCL. The 2 major molecular subtypes of DLBCL are shown: the GCB and the ABC type.

**GCB**

- **Histone modification**
  - EZH2 mutations
  - MLL2 mutations
  - CREBBP mutations
  - EP300 mutations

- **Blocks to terminal differentiation**
  - BCL6 expression, EZH2 mutations

- **Cell cycle activation +/− blocks to apoptosis**
  - MYC and BCL2 translocations (DHI) and protein over-expression

- **MTOR pathway activation**

- **Signaling cascades**
  - PTEN del/loss (PI3K and AKT activation)

**ABC**

- **BCR/NF-κB signaling**
  - CD79A/B, CARD11, MYD88 mutations, TNFAIP3 (A20) deletions

- **Histone modification**
  - MLL2 mutations
  - CREBBP mutations
  - EP300 mutations

- **Blocks to terminal differentiation**
  - BCL6 translocations, PRDM1 loss/mutations

- **Cell cycle activation +/− blocks to apoptosis**
  - MYC translocations, MYC and BCL2 protein over-expression

- **MTOR pathway activation**

- **Signaling cascades**
  - PI3K and AKT activation

- **Cytokine signaling/JAK-STAT pathway activation**

Laurie H. Sehn, and Randy D. Gascoyne Blood 2015;125:22-32
Identify Disease Subtype

- Molecular risk assessment should be performed in all cases including:
  - Evaluation for c-MYC, BCL-2, BCL-6 by IHC or FISH
  - Evaluation of cell of origin by IHC (Hans Algorithms), or Lymph2Cx platform, or gene expression profile
  - Subclassify cases into:
    - GCB
    - ABC (non-GCB)
    - Double-Hit DLBCL
    - Double Expressor DLBCL
The relationship of cell of origin and high BCL2 and MYC expression in DLBCL. Most cases of double-hit lymphoma are of germinal center B cell (GCB) origin whereas most cases of double-expresser lymphomas, without any hits, are of activated B cell (ABC) origin. (Dunleavy 2015)
Hans and Tally methods for determining cell of origin in diffuse large B cell lymphoma

Hans algorithm

- **CD10**
  - (+) → **GCB**
  - (-) → **BCL6**
- **BCL6**
  - (+) → **MUM1**
  - (-) → **GCB**
- **MUM1**
  - (+) → **Non-GCB**
  - (-) → **GCB**
- **Non-GCB**

Tally method

1) Measure GCB markers: CD10 (+ or -) and GCET1 (+ or -)
2) Measure ABC markers: MUM1 (+ or -) and FOXP1 (+ or -)
   (For each of the above, score 1 point for "+" and 0 points for "-")
3) Compare GCB score versus ABC score:
   - if GCB > ABC, then classify as GCB
   - if GCB < ABC, then classify as ABC
   - if GCB = ABC, then measure LMO2:
     - if LMO2 ≥ 30%, then classify as GCB
     - if LMO2 < 30%, then classify as ABC

The Hans algorithm and Tally method use immunohistochemical stains to predict the cell of origin (GCB versus ABC or non-GCB) for cases of diffuse large B cell lymphoma. Each is approximately 80% concordant with gene expression profile results.

DLBCL: diffuse large B cell lymphoma; GCB: germinal center B cell; ABC: activated B cell.

References:

Prognostic Subgroups in DLBCL

DNA microarray analysis can be used to predict survival after chemotherapy

Multi-center study of DA-EPOCH-rituximab in untreated diffuse large B-cell lymphoma outcomes based on biomarkers.

Gene-Expression Predictors of Survival among Patients with Diffuse Large-B-Cell Lymphoma Treated with R-CHOP

Outcomes in patients with DLBCL after treatment with R-CHOP according to cell of origin by Lymph2Cx assay using FFPET.

David W. Scott et al. JCO 2015;33:2848-2856
Time to progression for patients with DLBCL after treatment with R-CHOP according to cell of origin and IHC for MYC and BCL2.

David W. Scott et al. JCO 2015;33:2848-2856
Prognostic Factors for DLBCL

• Clinical factors: International Prognostic Index (IPI), Absolute lymphocyte and monocyte count
• Functional Imaging: FDG PET
• Immunohistochemistry for cell of origin, Germinal center B-cell (GCB) vs. activated B-Cell (ABC)
• Gene expression profile for cell of origin
• Molecular factor, FISH for MYC and BCL2 rearrangement
• Cellular expression; CD 37, PD-L1
• Provisional prognostic factors
  – Free light chain
  – Serum 25-hydroxyl vitamin D levels
  – Serum cytokines/chemokines
# International Prognostic Index (IPI)

## Factor | Adverse
--- | ---
Age | >60 years
PS | ≥2
LDH | >Normal
Extranodal sites | ≥2
Stage | III-IV

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Number of Factors Present</th>
<th>5-year DFS (%)</th>
<th>5-year OS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Low/Intermediate</td>
<td>2</td>
<td>50</td>
<td>51</td>
</tr>
<tr>
<td>High/Intermediate</td>
<td>3</td>
<td>49</td>
<td>43</td>
</tr>
<tr>
<td>High</td>
<td>4-5</td>
<td>40</td>
<td>26</td>
</tr>
</tbody>
</table>

## Age-Adjusted

| Factor | Adverse
--- | ---
PS | ≥2
LDH | >Normal
Stage | III-IV

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Number of Factors Present</th>
<th>5-year OS Age&gt;60 (%)</th>
<th>5-year OS Age≤60 (%)</th>
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<tbody>
<tr>
<td>Low</td>
<td>0</td>
<td>56</td>
<td>83</td>
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<tr>
<td>Low/Intermediate</td>
<td>1</td>
<td>44</td>
<td>69</td>
</tr>
<tr>
<td>High/Intermediate</td>
<td>2</td>
<td>37</td>
<td>46</td>
</tr>
<tr>
<td>High</td>
<td>3</td>
<td>21</td>
<td>32</td>
</tr>
</tbody>
</table>

Outcome according to the revised International Prognostic Index (R-IPI).

Revised International Prognostic Index (R-IPI) for diffuse large B-cell lymphoma

Revised International Prognostic Index (R-IPI) for diffuse large B-cell lymphoma

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk group</th>
<th>4-yr OS, percent</th>
<th>4-yr PFS</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Very good</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>1 or 2</td>
<td>Good</td>
<td>79</td>
<td>80</td>
</tr>
<tr>
<td>3 or more</td>
<td>Poor</td>
<td>55</td>
<td>53</td>
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</table>

The NCCN-IPI

<table>
<thead>
<tr>
<th>NCCN-IPI</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, year</td>
<td></td>
</tr>
<tr>
<td>&gt;40 to ≤60</td>
<td>1</td>
</tr>
<tr>
<td>&gt;60 to ≤75</td>
<td>2</td>
</tr>
<tr>
<td>&gt; 75</td>
<td>3</td>
</tr>
<tr>
<td>LDH x Normal</td>
<td></td>
</tr>
<tr>
<td>&gt; 1 to ≤ 3</td>
<td>1</td>
</tr>
<tr>
<td>&gt; 3</td>
<td>2</td>
</tr>
<tr>
<td>Ann Arbor Stage III-IV</td>
<td>1</td>
</tr>
<tr>
<td>Extranodal disease*</td>
<td>1</td>
</tr>
<tr>
<td>Performance status ≥ 2</td>
<td></td>
</tr>
</tbody>
</table>

* Disease in BM, CNS, liver, GI tract, or lung

NCCN IPI vs IPI in risk stratification in the NCCN DLBCL training cohort.

L 0-1, L-I 2-3, H-I 4-5, H ≥6

NCCN IPI vs IPI in risk stratification in the BCCA DLBCL validation cohort.

L 0-1, L-I 2-3, H-I 4-5, H ≥6

Regulation of PD-1 expression in T cells of the DLBCL microenvironment.

Vassiliki A. Boussiotis Blood 2015;126:2171-2172
PD-L1 expression on tumor cells was associated with poor OS in patients with DLBCL. (A) OS of the entire study cohort.

Junichi Kiyasu et al. Blood 2015;126:2193-2201
Schematic representation of the biologic role of CD37 in B cells.
Expression and prognostic effect of CD37 antigen in patients with DLBCL. (A-B) Representative CD37− and CD37+ (red) IHC results (×60).

Event-free survival according to "early PET" status and IPI

A
Event-Free Survival According to PET Response
Low and Low-Intermediate Risk Group

PET (-), n=26
PET (+), n=11

B
Event-Free Survival According to PET Response
High and High-Intermediate Risk Group

PET (-), n=28
PET (+), n=25

Years After Randomization

Kaplan-Meier survival estimates based on Deauville responses to ST. (A) PFS. (B) OS.

Craig S. Sauter et al. Blood 2015;125:2579-2581
PET-Based therapy for limited-stage DLBCL

Sehn LH, Cancer 2012: 18, 421-426

*1 patient had an indeterminate scan
TTP = time-to-progression
### CHOP with or without Radiotherapy for Early-stage DLBCL

<table>
<thead>
<tr>
<th>Study</th>
<th>Stage I and II Details</th>
<th>Treatment Details</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG trial (Miller TP et al)</td>
<td>Stage I and II, non-bulky</td>
<td>CHOP (3 cycles) plus RT vs CHOP (8 cycles)</td>
<td>At 9 years, DFS and TTP favored CHOP-RT, with less toxicity, but OS was similar</td>
</tr>
<tr>
<td>GELA LNH 93-1 (Reyes F et al)</td>
<td>&lt; 61 yrs, Stage I and II, no adverse prognostic factor</td>
<td>CHOPx3 + IFRT vs ACVBPx3</td>
<td>Chemotherapy alone was superior</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5-year PFS 74% vs 82% for Chemo alone (p=&lt;0.001)</td>
</tr>
<tr>
<td>ECOG trial (Glick J et al; Horning S et al)</td>
<td>Stage I bulky and stage II</td>
<td>CHOP (6-8 cycles) followed by RT vs CHOP in patients with CR to CHOP</td>
<td>At 10 years, DFS and TTP favored CHOP-RT, but disease-specific survival was 81% in both treatment arms</td>
</tr>
<tr>
<td>GELA trial (Fillet G et al)</td>
<td>Elderly, IPI = 0</td>
<td>CHOP (4 cycles) plus RT vs CHOP x 4</td>
<td>No improvement in CR, 5-year EFS, or 5-year OS</td>
</tr>
</tbody>
</table>
Diffuse Large B-Cell Lymphoma

STAGE

Nonbulky (<7.5 cm)

Stage I, II

Bulky (≥7.5 cm)

FIRST-LINE THERAPY

RCHOPn x 3 cycles + RT (category 1) or RCHOP x 6 cycles ± RT

See Pre RT Evaluation (BCEL-4)

RCHOP x 6 cycles ± RT

See Pre RT Evaluation (BCEL-4)

BCEL-3
<table>
<thead>
<tr>
<th>Factors</th>
<th>IPI group</th>
<th>No. of risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 60</td>
<td>Low</td>
<td>0 or 1</td>
</tr>
<tr>
<td>LDH &gt; normal</td>
<td>Low</td>
<td>0 or 1</td>
</tr>
<tr>
<td>PS 2-4</td>
<td>High</td>
<td>2-4</td>
</tr>
<tr>
<td>Stage II or IIE</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment of Advanced Stage DLBCL

• R-CHOP is the standard regimen
• Other regimens: DA-EPOCH-R, R-ACVBP (rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone), R-CHP+ brentuximab vedotin
• Novel regimens for ABC (non-GCB) DLBCL
• Older patients > 80 years old: R-miniCHOP
• Patients who can not receive anthracycline: R-CEOP, R-CEPP, or R-GCVP
• Clinical trials
• Consolidation therapy: auto-HCT during 1CR in selected cases, maintenance therapy such as revlimid
Disease-free survival in patients treated with CHOP and R-CHOP -10 yrs F/U

# Phase 3 Trials Evaluating Alternative Regimens to R-CHOP 21

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Regimens</th>
<th>Outcome</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recher et al</td>
<td>380</td>
<td>R-ACVBP vs R-CHOP</td>
<td>3-year PFS 87% vs. 73%</td>
<td>.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-year OS 92% vs. 84%</td>
<td>.007</td>
</tr>
<tr>
<td>Cunningham et al</td>
<td>1080</td>
<td>R-CHOP 14 vs R-CHOP</td>
<td>2-year PFS 75% vs. 75%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2-year OS 83% vs. 81%</td>
<td>NS</td>
</tr>
<tr>
<td>Delarue et al</td>
<td>602</td>
<td>R-CHOP 14 vs R-CHOP</td>
<td>3-year EFS 56% vs. 60%</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3-year OS 83% vs. 72%</td>
<td>NS</td>
</tr>
<tr>
<td>CALGB 50303</td>
<td>524</td>
<td>R-CHOP vs DA-EPOCH-R</td>
<td>Median FU 4.9 years, No difference in EFS or OS</td>
<td>NS</td>
</tr>
<tr>
<td>Wilson et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Phase III Randomized Study of R-CHOP vs. DA-EPOCH-R and Molecular Analysis of Untreated Large B-Cell Lymphoma: CALGB/Alliance 50303


Abstract 469, American Society of Hematology, Dec 4, 2016
No differences between the arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>R-CHOP (%)</th>
<th>DA-EPOCH R (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (range)</td>
<td>58 (18-86)</td>
<td>57 (19-84)</td>
<td>0.677</td>
</tr>
<tr>
<td>ECOG 0-1 vs. 2</td>
<td>88 vs. 12</td>
<td>87 vs. 13</td>
<td>0.518</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 - PMBCL</td>
<td>3</td>
<td>3</td>
<td>0.641</td>
</tr>
<tr>
<td>2</td>
<td>21</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>45</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>26</td>
<td>25</td>
<td>0.405</td>
</tr>
<tr>
<td>2</td>
<td>39</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>4-5</td>
<td>8</td>
<td>13</td>
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## 50303 Treatment Summary

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>DA-EPOCH-R</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed per protocol*</td>
<td>85.9%</td>
<td>79%</td>
<td>0.037</td>
</tr>
<tr>
<td>PD during treatment</td>
<td>2.7%</td>
<td>1.5%</td>
<td>0.361</td>
</tr>
<tr>
<td>Early discontinuation due to AE</td>
<td>1.5%</td>
<td>6.5%</td>
<td>0.004</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Max DA-EPOCH-R Dose level</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>28%</td>
</tr>
<tr>
<td>2</td>
<td>20%↑</td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>44%↑</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>4</td>
<td>73%↑</td>
<td></td>
<td>17%</td>
</tr>
<tr>
<td>5</td>
<td>107%↑</td>
<td></td>
<td>9%</td>
</tr>
<tr>
<td>6</td>
<td>149%↑</td>
<td></td>
<td>2%</td>
</tr>
<tr>
<td>7</td>
<td>200%↑</td>
<td></td>
<td>&lt;1%</td>
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</table>
### 50303 Response

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>DA-EPOCH-R</th>
<th>P-value</th>
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<tbody>
<tr>
<td>ORR</td>
<td>89.3%</td>
<td>88.8%</td>
<td>0.983</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>62.3%</td>
<td>61.1%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>27%</td>
<td>27.2%</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>2.6%</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>1.7%</td>
<td>&lt;1%</td>
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<tr>
<td>Missing</td>
<td>6.4%</td>
<td>6.9%</td>
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</table>
50303 Event Free Survival

Median follow-up 5.0 y
HR=1.14 (0.82-1.61)
p = 0.4386

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>3Y (95%CI)</th>
<th>5Y (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>233</td>
<td>64</td>
<td>0.81 (0.75-0.85)</td>
<td>0.69 (0.62-0.75)</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>232</td>
<td>70</td>
<td>0.79 (0.73-0.84)</td>
<td>0.66 (0.59-0.72)</td>
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</table>
50303 Overall Survival

<table>
<thead>
<tr>
<th>Arm</th>
<th>N</th>
<th>Events</th>
<th>3Y (95% CI)</th>
<th>5Y (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-CHOP</td>
<td>233</td>
<td>44</td>
<td>0.85 (0.80-0.89)</td>
<td>0.80 (0.74-0.85)</td>
</tr>
<tr>
<td>DA-EPOCH-R</td>
<td>232</td>
<td>50</td>
<td>0.85 (0.79-0.89)</td>
<td>0.76 (0.70-0.71)</td>
</tr>
</tbody>
</table>

Median follow-up 5.0 y
HR = 1.18 (0.79-1.77)
p = 0.42
50303 PET sub-study (n=171)  
**EFS by Interim and EOT PET**

*PET neg = Deauville 1-3*

- **Treatment arms combined for analysis**
- **3 yr EFS by Interim PET**  81% (-) vs 69% (+), \( P=0.034 \)
- **3 yr EFS by EOT PET**  80% (-) vs 72% (+), \( P=0.057 \)
Results of an Ongoing Phase 2 Study of Brentuximab Vedotin with RCHP as Frontline Therapy in Patients with High-Intermediate/High-Risk Diffuse Large B Cell Lymphoma (DLBCL)

Lihua Elizabeth Budde¹, Ahmad S. Halwani², Christopher Yasenchak³,²⁴, Charles M. Farber⁴, John M. Burke⁵,²⁴, Luis Fayad⁶, Beata Holkova⁷, Mark Knapp⁸, Kathryn S. Kolibaba⁹,²⁴, Ranjana Advani¹⁰, Stephen M. Ansell¹¹, Dipti Patel-Donnelly¹²,²⁴, Habte A. Yimer¹³,²⁴, Scott Smith¹⁴, Moshe Levy¹⁵, Mahesh Seetharam¹⁶,²⁴, David Belada¹⁷, Donald Brooks¹⁸,²⁴, Edwin C. Kingsley¹⁹,²⁴, Leonard Klein²⁰,²⁴, Nina Wagner-Johnston²¹, Katherine Ruffner²², Nancy L. Bartlett²³

¹City of Hope National Medical Center, Duarte, USA; ²University of Utah, Salt Lake City, USA; ³Willamette Valley Cancer Institute and Research Center, Springfield, USA; ⁴Summit Medical Group-MD Anderson Cancer Center, Carol G. Simon Cancer Center, Morristown, USA; ⁵Rocky Mountain Cancer Centers - Aurora, Aurora, USA; ⁶MD Anderson Cancer Center/University of Texas, Houston, USA; ⁷Virginia Commonwealth University Medical Center, Richmond, USA; ⁸Mid Ohio Oncology/Hematology Inc, Columbus, USA; ⁹Northwest Cancer Specialists, P.C., Vancouver, USA; ¹⁰Stanford Cancer Center, Stanford, USA; ¹¹Mayo Clinic Minnesota, Rochester, USA; ¹²Virginia Cancer Specialists, PC, Fairfax, USA; ¹³Texas Oncology - Tyler, Tyler, USA; ¹⁴Cardinal Bernardin Cancer Center/Loyola University Medical Center, Maywood, USA; ¹⁵Texas Oncology - Baylor Sammons Cancer Center, Dallas, USA; ¹⁶Arizona Oncology Associates, PC - HAL, Glendale, USA; ¹⁷Fakultni nemocnice Hradec Kralove-oddeleni klinicke hematologe, Hradec Kralove; ¹⁸Arizona Oncology Associates, PC - HOPE, Tuscon, USA; ¹⁹Comprehensiv e Cancer Centers of Nevada, Las Vegas, USA; ²⁰Illinois Cancer Specialists/Advocate Lutheran General Hospital, Niles, USA; ²¹Johns Hopkins Medical Center, Baltimore, USA; ²²Seattle Genetics, Inc., Bothell, USA; ²³Washington University School of Medicine, St. Louis, USA; ²⁴US Oncology Research

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Study History

- Originally designed to assess safety and activity between 2 doses of brentuximab vedotin (1.2 or 1.8 mg/kg) combined with RCHOP
- Study amended to include 2 additional parts:
  - 1.8 mg/kg BV + RCHP
  - 1.8 mg/kg BV + RCHP vs. RCHOP alone
- This is an ongoing study
  - Initial results for Part 1 were disclosed at ASH 2014, ASH 2015, and ASCO 2015
  - We will present interim data from Part 2 and follow-up data from patients in Part 1
Eligibility and Study Objectives

Key eligibility criteria
- Standard IPI scores of 3–5 or age-adjusted IPI (aaIPI) scores of 2–3 (high-intermediate/high risk)
- Stage IAX (bulk defined as single lymph node mass >10 cm in diameter), IB-IV disease
- ECOG performance status less than or equal to 2
- Patients in Parts 2 and 3 must have CD30 expression by IHC performed by a local pathology lab
  - CD30 expression confirmed by a central pathology lab
  - Positive CD30 expression defined as ≥1% neoplastic cells CD30 positive

Study objectives
- Assess antitumor activity
  - CR and OR rate at end of treatment (EOT) per Cheson 2007
  - PFS and OS
- Assess safety
  - Type, incidence, severity, seriousness, and relatedness of AEs and lab abnormalities

*a Cheson et al, J Clin Oncol 25: 579-86; 2007*
Study Design

Clinicaltrials.gov NCT01925612

Pretreatment

Screening/Baseline

Randomization 1:1 (Parts 1 & 3 only)

Study Treatment

Part 1:
BV (1.2 mg/kg or 1.8 mg/kg) + RCHOP

Part 2:
BV (1.8 mg/kg) + RCHP

Part 3:
BV (1.8 mg/kg) + RCHP or RCHOP alone

End of Treatment

Follow-up

28 days

21 days
6 x 21-day cycles brentuximab vedotin

Response assessment at 5 wks after last dose.*

Q4 mos from last scan until 24 mos, then Q6 mos until study closure

△ CT/PET  ■ CT  * All other EOT evaluations done 30-37 days after last dose.
## Demographics and Baseline Characteristics

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<thead>
<tr>
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<th>Part 1</th>
<th>Part 2</th>
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<tbody>
<tr>
<td></td>
<td>1.2 or 1.8 mg/kg BV+RCHOP</td>
<td>1.8 mg/kg BV+RCHP</td>
</tr>
<tr>
<td></td>
<td>N=51</td>
<td>N=11</td>
</tr>
<tr>
<td>Age (yrs); median (range)</td>
<td>67 (21,81)</td>
<td>59 (22,78)</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>32/19</td>
<td>7/4</td>
</tr>
<tr>
<td>Stage III-IV, n (%)</td>
<td>49 (96)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>ECOG = 2, n (%)</td>
<td>14 (27)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>IPI 4-5, aalPI 3, n (%)</td>
<td>19 (37)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>IPI 3, aalPI 2, n (%)</td>
<td>32 (63)</td>
<td>9 (82)</td>
</tr>
</tbody>
</table>
# Summary of Response

<table>
<thead>
<tr>
<th></th>
<th>Part 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Part 2</th>
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<tbody>
<tr>
<td></td>
<td>1.2 or 1.8 mg/kg BV+RCHOP</td>
<td>1.8 mg/kg BV+RCHP</td>
<td></td>
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<tr>
<td>CD30 Negative N=24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ORR, n (%) [95% CI]</strong></td>
<td>20 (83) [62.6, 95.3]</td>
<td>21 (84) [63.9, 95.5]</td>
<td>10 (91) [58.7, 99.8]</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>15 (63)</td>
<td>19 (76)</td>
<td>9 (82)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>5 (21)</td>
<td>2 (8)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>PD, n (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2 (8)</td>
<td>2 (8)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>CD30 Positive N=25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Patients N=11</td>
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</table>

<sup>a</sup> Data were presented at ASH 2015; CD30 status not available for 2 patients

<sup>b</sup> The patient with PD in Part 2 was CD30-negative as confirmed by IHC via the central laboratory
Progression-free Survival
Part 1 (1.2 or 1.8 mg/kg BV+RCHOP) Follow-up

Estimated PFS at 24 months (95% CI):
CD30 Positive = 79% (57, 91)
CD30 Negative = 52% (30, 70)
All = 63% (48, 75)

CD30-expression confirmed by IHC via the central laboratory
Conclusions

• Part 1 (1.2 or 1.8 mg/kg BV+RCHOP)
  ◦ The PFS and OS for patients with CD30-expressing DLBCL who received BV+RCHOP appear encouraging

• Part 2 (1.8 mg/kg BV+RCHP)
  ◦ 1.8 mg/kg BV+RCHP is active as frontline treatment in CD30-expressing, high-intermediate/high-risk DLBCL
  ◦ When combined with RCHP, 1.8 mg/kg BV appears to be more tolerable than combination with RCHOP
    - No grade 3 neuropathy or motor neuropathy
    - Lower incidence of febrile neutropenia
  ◦ The majority of patients with CD30-expressing, high-intermediate or high-risk DLBCL treated with BV+RCHP experienced disease response without unacceptable side effects

• These results support further evaluation of the combination of brentuximab vedotin with frontline therapy for lymphoma
Prevention of relapse post-Induction Chemotherapy for DLBCL

- Autologous HCT during 1\textsuperscript{st} remission in selected high-risk patients
  - Several randomized trials did not confirm the benefit
  - Heterogeneous patients, treatment regimens
  - SWOG trials showed improved survival in High-IPI

- Post-remission maintenance Therapy
  - Maintenance lenalidomide-Positive study
  - Enzasturin-PRELUDE Study- No difference in survival
Original Article

Autologous Transplantation as Consolidation for Aggressive Non-Hodgkin's Lymphoma


N Engl J Med
Volume 369(18):1681-1690
October 31, 2013
Survival Rates among All Eligible Patients Who Underwent Randomization.

CHOP ± R x 6 cycles

CR/PR

CHOP ± R x 2

HDT+ ASCT

Survival Rates among Eligible Patients Who Underwent Randomization, According to IPI Risk Category.

To assess the benefit of lenalidomide maintenance after response to R-CHOP in patients aged 60 to 80 years with untreated DLBCL, FL3b, or transformed lymphoma

Available from: https://clinicaltrials.gov/NCT01122472
Induction

R-CHOP
6 or 8 cycles

Maintenance: 24 months

Lenalidomide
25 mg/day* for 21/28 days

Placebo

Registration 1

Registration 2

CR PR
C6 C12 C21

*10 mg lenalidomide for patients with CrCl <30 cc/min.

Response evaluation

Available from: https://clinicaltrials.gov/NCT01122472
REMARC: Progression-Free Survival (Central Review)

At a median follow-up of 40 months, median PFS was not reached (NR) for Lenalidomide and 58.8 months for Placebo.

Log-rank $P = 0.0135$
HR 0.708 (0.537-0.933)

1.4x longer PFS = 24 month projected improvement
<table>
<thead>
<tr>
<th>Characteristic, n (%)</th>
<th>Lenalidomide (n = 323)</th>
<th>Placebo (n = 327)</th>
</tr>
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<tbody>
<tr>
<td><strong>Median age</strong></td>
<td>69 years</td>
<td>68 years</td>
</tr>
<tr>
<td>≥70 years</td>
<td>154 (48)</td>
<td>145 (44)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>183 (57)</td>
<td>180 (55)</td>
</tr>
<tr>
<td>Female</td>
<td>140 (43)</td>
<td>147 (45)</td>
</tr>
<tr>
<td><strong>Response after R-CHOP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>251 (78)</td>
<td>244 (75)</td>
</tr>
<tr>
<td>PR</td>
<td>69 (21)</td>
<td>83 (25)</td>
</tr>
<tr>
<td>ORR</td>
<td>320 (99)</td>
<td>327 (100)</td>
</tr>
</tbody>
</table>
Suurvivaal Probabiility

Log-rank $P = 0.5282$

Survival Probability

Log-rank $P = 0.0742$

Unclassified

Log-rank $P = 0.2864$

*318/432 (74%) DLBCL NOS patients had COO results available for assessment.
REMARC: Overall Survival

- At a median follow-up of 52 months, there was no statistical difference between arms
- Multivariate analysis showed that treatment arm was not a statistically significant factor
• REMARC achieved its primary endpoint of a statistically significant and clinically meaningful improvement in PFS for patients receiving lenalidomide

• This is the first report showing that use of an immunomodulatory agent as maintenance therapy prolongs PFS for patients with DLBCL after R-CHOP

• At a median follow-up of 52 months, the analysis of overall survival, a key secondary endpoint, showed no difference between the lenalidomide and placebo arms
Randomized Phase III Trial of Enzastaurin vs. placebo for High-risk DLBCL

CONSORT diagram for the PRELUDE study.

Michael Crump et al. JCO 2016;34:2484-2492
(A) Disease-free survival by treatment arm for the intent-to-treat (ITT) population (N = 758).

- 758 patients
- Stage II bulky, III/IV
- ≥3 IPI risk factors
- CR after 6-8 cycles R-CHOP
- 2:1 enzastaurin 500 mg daily or placebo for 3 years
- Results
- median F/U 48 months
- 4-year DFS 70% vs. 71%

Michael Crump et al. JCO 2016;34:2484-2492
Treatment of Activated B cell (ABC) or non-GCB DLBCL

• R-ACVBP < 60 years old, 1 IPI risk
  – Phase III randomized trial: better OS compared to R-CHOP 3-year OS, 92% vs 84%, p=.007
  – Not highly used due to acute and delayed toxicity and its value in older patients
• R-CHOP plus bortezomib: Randomized Phase II Pyramid Trial
  – R-CHOP 21 x 6 cycles vs bortezomib 1.3 mg/m2 IV on days 1 and 4 of each cycle (VR-CHOP)
  – ORR, VR-CHOP (n=90): 56% CR, 96% CR/PR vs R-CHOP (n=86): 49% CR, 98% CR/PR
  – 2-year PFS: 78% R-CHOP vs 82% VR-CHOP
  – Higher rate of toxicity from peripheral neuropathy
• VR-CAP (rituximab, CY, doxorubicin, prednisone and bortezomib)
R-CHOP vs. R-Bortezomib 1.3 mg IV day 1,4,8,11 + CAP (VR-CAP)

IHC (Hans Method)

Fritz Offner et al. Blood 2015;126:1893-1901
Kaplan-Meier analysis of survival outcomes. R-CHOP vs. VR-CAP for Non-GCB DLBCL

Fritz Offner et al. Blood 2015;126:1893-1901
Treatment of Activated B cell (ABC) or non-GCB DLBCL

- R-CHOP plus lenalidomide (R2-CHOP)
- R-CHOP plus ibrutinib
- Clinical Trials
Lenalidomide plus R-CHOP overcome negative Prognostic impact of Non-GCB Phenotype in DLBCL (Nowakowski et al. 2014)

- Phase II study
- Newly diagnosed DLBCL stage II-IV
- Treatment
  - Lenalidomide 25 mg daily days 1-10
  - R-CHOP every 21 days x 6 cycle
  - Neulasta day 2 of each cycle
  - Aspirin prophylaxis
  - Molecular subtype using IHC
  - Compared with 87 control DLBCL treated with R-CHOP
Historical control R-CHOP compared to R2CHOP based on germinal center B-cell (GCB) versus non-GCB.

Grzegorz S. Nowakowski et al. JCO 2015;33:251-257
Lenalidomide plus R-CHOP21 in elderly patients with untreated DLBCL
Results of the REAL07 open-label, multicentre, phase 2 Trial

45 patients
Age 60-80 yrs
Stage II-IV

Treatment
Lenalidomide 15 mg day 1-14
+ R-CHOP 21x 6 cycles

Toxicity
Grade 3-4 neutropenia 31%
Grade 3-4 thrombocytopenia 13%,
No grade 4 non-hematologic ADR

Response
92% response
86% CR, 6% PR

Conclusion
Lenalidomide + CHOP 21 is safe and effective in elderly DLBCL

Ibrutinib +R-CHOP as Frontline Therapy for DLBCL Phase 1b study (Younes et al. 2014)

- **Treatment plan**
  - Ibrutinib 280, 420, or 560 mg daily +R-CHOP q 3 wks
  - Phase 2 dose Ibrutinib 560 mg daily +R-CHOP x 6
- **Toxicity**
  - neutropenia 73%, thrombocytopenia 21%, febrile neutropenia 18%, anemia 18%
- **Results**
  - Overall response rate 95%
    - 71% CR for GCB subtype (7 patients)
    - 100% CR for non-GCB (4 patient)
- **Conclusion**
  - Ibrutinib 560 mg can be given safely with R-CHOP
  - Phase 3 study R-CHOP vs Ibrutinib +R-CHOP in Non-GCB DLBCL is being conducted
Which patients should receive CNS prophylaxis?

- Should be given in patients with testicular, epidural, or sinus involvement.
  - Should be considered in patients with breast, ovarian, bone marrow involvement, high IPI or numerous extranodal sites of diseases.

- Novel prognostic scores from BC and German High Grade lymphoma study group using IPI risk factors including
  - age > 60, LDH> normal ,PS>1, stage 3-4, >1 extranodal site and Renal or adrenal gland involvement

- Which Prophylaxis? Depending on the chemotherapy
  - IT chemotherapy given with each cycle
  - Systemic high-dose MTX 3.5 gm/m2 with leucovorin rescue at day +15 on cycle 2,4.and 6 of R-CHOP, or at completion of induction chemotherapy
Prognostic Model to Assess the Risk of CNS Disease

- Age > 60 years
- Serum LDH > normal
- Performance status > 1
- Stage III or IV
- Extranodal involvement > 1 site
- Kidney or adrenal gland involvement

<table>
<thead>
<tr>
<th>No. of risk factors</th>
<th>2-year CNS relapse risk</th>
</tr>
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<tbody>
<tr>
<td>0-1</td>
<td>0.8%</td>
</tr>
<tr>
<td>2-3</td>
<td>3.9%</td>
</tr>
<tr>
<td>4-6</td>
<td>12%</td>
</tr>
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Low risk
Intermediate-risk
High-risk

0–1
2–3
4–6
Risk of CNS relapse by involvement of kidneys and/or adrenal glands in the German High-Grade Non-Hodgkin Lymphoma Study Group/MabThera International Trial data set.

Norbert Schmitz et al. JCO 2016;34:3150-3156
Risk of CNS relapse by number of risk factors in the German High-Grade Non-Hodgkin Lymphoma Study Group/MabThera International Trial data set.

Norbert Schmitz et al. JCO 2016;34:3150-3156
Risk of CNS relapse according to the CNS International Prognostic Index.

Norbert Schmitz et al. JCO 2016;34:3150-3156
Treatment of Relapsed DLBCL

- Salvage chemo-immunotherapy
  - RICE, R-DHAP, R-ESHAP, R-GEM/OX, R-GDP
  - Clinical trials:
    - Ofatumumab alone or in combination with chemotherapy
    - R-EPOCH+Ibrutinib+revlimid,
    - RICE ± SGN-CD19A
    - Others for non-transplant candidates
  - Autologous Stem cell transplant for chemosensitive ds.
    - Clinical trials for chemoresistant relapse
  - Allogeneic Stem cell transplant in selected cases: persistent BM involvement or inability to collect stem cell
- CAR-T cell
  - Salvage therapy for chemorefractory disease
Ofatumumab-DHAP vs. R-DHAP for Relapsed/Refractory DLBCL
The ORCHARD study


R = rituximab x 4
O = ofatumumab x 4
Cycle = 21 days
Ofatumumab-DHAP vs. R-DHAP for relapsed DLBCL
The ORCHARD study

Randomised phase III study of R-ICE versus R-DHAP in relapsed patients with DLBCL followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study.

Christian Gisselbrecht et al.
JCO 2010;28:4184-4190
(A) Overall survival according to the first random assignment (intent to treat).
Prevention of Relapse Post auto-HCT for DLBCL

- Maintenance therapy post-transplant to prevent relapse
  - Ibrutinib, ALLIANCE/BMT CTN Randomized Phase III Ibrutinib vs. placebo during and following auto-HCT for ABC DLBCL
  - Anti-PD1
- CAR-T cell
  - During auto-transplant
Summary and Conclusion

• The prognosis of patients with DLBCL has improved with the addition of rituximab to CHOP
• R-CHOP remains the standard of care especially for GCB subtype
• Patients with non-GCB type have poorer prognosis and should be enrolled in clinical trial. The new regimen of R(X)CHOP appears promising but must await phase 3 trials due to additional toxicity
• Patients who fail R-CHOP continue to have poor outcome
• Future studies designing treatment based on cell of origin/molecular profile, target therapy and availability of biomarker will allow the possibility of individualized risk-adapted therapy.