Diffuse Large B-cell Lymphoma: Is Cell of Origin Necessary for Treatment Selection?

Andrew D. Zelenetz, MD, PhD
Memorial Sloan Kettering Cancer Center
## WHO 2016: Diffuse Large B Cell Lymphoma is Multiples Diseases

<table>
<thead>
<tr>
<th>Diffuse large B-cell lymphoma (DLBCL), NOS</th>
<th>Germinal Center</th>
<th>Activated B-Cell</th>
<th>Unclassified</th>
<th>Cell of origin (COO) to be determined by best available means</th>
</tr>
</thead>
<tbody>
<tr>
<td>T cell/histiocyte-rich large B-cell lymphoma</td>
<td></td>
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<tr>
<td>Primary DLBCL of the CNS</td>
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<tr>
<td>Primary cutaneous DLBCL, leg type</td>
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<tr>
<td>EBV positive DLBCL, NOS</td>
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<tr>
<td>EBV+ Mucocutaneous ulcer</td>
<td></td>
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<tr>
<td>DLBCL associated with chronic inflammation</td>
<td></td>
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<tr>
<td>Lymphomatoid granulomatosis</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
<td></td>
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<tr>
<td>Intravascular large B-cell lymphoma</td>
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<td></td>
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<tr>
<td>ALK positive large B-cell lymphoma</td>
<td></td>
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<tr>
<td>Plasmablastic lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HHV8 positive DLBCL, NOS</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Cell of Origin (COO) in DLBCL Contributes to Biological and Clinical Heterogeneity

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- **COO determination**
  - Identifies tumors with distinct biology
  - May provide prognostic information
  - May be predictive for treatment selection

COO is not the whole story: Increased complexity revealed by targeted sequencing in DLBCL

Intlekofer et al, Blood 2014 124:704
Determining COO in DLBCL
Wright Classifier enables patient level assignment of COO

- Wright classifier: statistical method based on Bayes' rule that estimates the probability of membership in one of two cancer subgroups
  - Included 27 genes which separated patients into: GCB, ABC or ‘Type 3’ (now referred to as unclassifiable)
  - Basis for subsequent classifiers

Methods for determination of COO

- Gene Expression Profiling (GEP) on fresh tissue
  - ‘The gold standard’
  - Needs the Wright classifier to make patient level assignment to ABC, GCB or unclassifiable
  - Not practically applicable in clinical practice
- Immunohistochemistry
  - Widely available
  - Reproducibility may be difficult
  - Many assays (Hans, Choi, Muris)
  - Lack of correlation with GEP in many studies
- GEP of formalin-fixed paraffin-embedded (FFPE) tissue
  - Multiple platforms
  - Hybrid capture/fluorescent reporter emerging as a widely validated assay
Cell of Origin (COO) by immunohistochemistry using the Hans algorithm

Hans et al. Blood 2004;103:275
Cell of Origin (COO) by immunohistochemistry using the Hans algorithm

Cell of Origin (COO) by immunohistochemistry using the Hans algorithm

Hans et al. Blood 2004;103:275
Outcomes prediction with COO determined by GEP and IHC in patients treated with R-CHOP

Outcomes prediction with COO determined by GEP and IHC in patients treated with R-CHOP

Outcomes prediction with COO determined by GEP and IHC in patients treated with R-CHOP

Lymph2Cx assay for cell of origin

Training Cohort
- 19 ABC, 20 GCB, 12 U
- FFPET blocks

MoCha lab
RNA extraction
Quantitation - Nanodrop

BCCA lab

NanoString GEP
93 genes of interest

Gene selection
15 genes of interest
5 “housekeeper” genes

NanoString GEP
15 genes of interest
5 “housekeeper” genes

NanoString COO Model
“Lymph2Cx”
- QC criteria, gene co-efficient and thresholds

Gene selection based on the Wright classifier

Scott DW et al. Blood 2014; 123:1314; Leroy et al ASCO 2016; unpublished observation
Lymph2Cx assay for cell of origin

- Initial validation set
  n=67
  - 2% misclassification
  - Research platform
  200 ng RNA


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Lymph2Cx assay for cell of origin

Inter-laboratory

Highly correlated with "gold standard"

Scott DW et al. Blood 2014; 123:1214; Leroy et al ASCO 2016; unpublished observation
Lymph2Cx assay for cell of origin

Based on validated Wright classifier

Reproducible

Highly correlated with "gold standard"

Is Cell of Origin Prognostic?
Prognostic value of Lymph2Cx assay

- Population registry-based analysis of patients with de novo DLBCL treated with R-CHOP; n=344, 5 excluded for low tumor content 339 analyzed
- Lymph2Cx assay permitted assigning COO 335/339 (99%) cases
  - ABC: 32% (108 of 335); GCB 56% (189 of 335); Unclassified 11% (38 of 335)

GEP on FFPE tissue does not universally show a prognostic difference

RICOVER60: Retrospective application of Lymph2Cx

REMoDL-B: Prospective COO by Illumina DASL array

Pfreunschuh, personal communication; Davies, ASH 2015
Can chemotherapy influence outcome by COO?
# Dose-Adjusted (DA)-EPOCH-R

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>375 mg/m² day 1 IVPB</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>10 mg/m²/day × 4 by CI</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.4 mg/m²/day × 4 by CI</td>
</tr>
<tr>
<td>Etoposide</td>
<td>50 mg/m²/day × 4 by CI</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>750 mg/m² day 5 IVBP</td>
</tr>
<tr>
<td>Prednisone</td>
<td>60 mg/m² BID days 1-5 oral</td>
</tr>
<tr>
<td>Filgrastim*</td>
<td>Weight-adjusted dose starting day 5 until ANC &gt; 5000/µL</td>
</tr>
</tbody>
</table>

*Recent data from MSKCC showed identical rate of dose-adjustment with filgrastim or pegfilgrastim

- Dosed every 21 days if ANC > 1/µL and PLTS > 100KµL
- Dose-adjusted based on ANC nadir:
  - >500/µL, increase cytotoxic drugs by 20%
  - <500/µL for 1-3 days, no change
  - <500/µL for >3 days or FN, decrease cytotoxic drugs by 20%

Wilson, J Clin Oncol 2008 26: 2717-2724; Lunning et al. SHO, abstract
Testable hypothesis: DA-EPOCH-R is particularly favorable for GCB DLBCL
**CALGB 50303: DA-EPOCH-R vs RCHOP21**

- **OBJECTIVES:**
  - **Primary**
    - EFS untreated de novo DLBCL treated with RCHOP vs DA-R-EPOCH
    - Determine molecular predictors of outcome (using molecular profiling) in patients treated with these regimens.
  - **Secondary**
    - Compare ORR and OS
    - Compare the toxicity of these regimens in these patients.
    - Correlate the clinical parameters (i.e., toxicity, response, survival outcomes, and laboratory results) with molecular profiling in patients treated with these regimens.
    - Determine the use of molecular profiling for pathological diagnosis

n= 478 patients (239 per treatment arm)

**Data to be presented at ASH 2016**
Sequential Non-cross resistant chemotherapy
**MSKCC 01-142/08-146: DLBCL -- Risk Adapted for Therapy**

- Prospective, biopsy controlled determination of “positive PET”
- Treatment is adapted by biopsy, not PET
- No radiation therapy permitted except for testicular disease
- IT methotrexate for aaHR, paranasal sinus, testis, BM
- Two studies with highly similar outcomes, combined analysis

**Treatment Schedules:**

1. **CS IIIX, III or IV disease, age-adjusted IPI 1, 2, or 3 Risk Factors, Transplant Eligible**
   - **R-C_{1000}HO_{uncapped}P-14 \times 4**
     - **PET**
       - **Repeat Bx**
         - **Bx+**
           - **IC \times 2**
             - **RICE \times 1**
             - followed by HDT/ASCT
       - **Bx-**
         - **IC \times 3**
           - followed by Observation

2. **CS IIIX, III or IV disease, age-adjusted IPI 1, 2, or 3 Risk Factors, Transplant Eligible**
   - **R-R-C_{1000}HO_{uncapped}P-14 \times 3**
     - **PET**
       - **Repeat Bx**
         - **Bx+**
           - **IC \times 3**
             - followed by Observation
       - **Bx-**
         - **\geq 80\%**
           - **Ki-67 < 80\%**
             - **Augmented RICE \times 2**
               - followed by Observation
             - **ICE \times 3**
               - followed by Observation

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Sequential R-CHOP→ICE: Overall and Progression-Free Survival by COO
Sequential R-CHOP→ICE: Overall and Progression-Free Survival by COO

Testable hypothesis: Sequential R-CHOP→ICE is particularly favorable for ABC DLBCL
Patients: Untreated DLBCL, age 18-59, aaIPI score = 1 (high LDH, stage III/IV, ECOG PS >1)

*No radiotherapy in both arms

LNH03-2B: Influence of Cell of Origin

Randomly assigned (N = 380)*

Assigned to receive R-ACVBP (n = 196)
  - Had DLBCL at central pathology review (n = 156)
  - Had available samples for immunohistochemical study (n = 141)
  - Could be classified using Hans algorithm (n = 107)
    - Germinal center B-cell type (n = 46)
    - Non-germinal center B-cell type (n = 61)

Assigned to receive R-CHOP (n = 184)
  - Had DLBCL at central pathology review (n = 161)
  - Had available samples for immunohistochemical study (n = 146)
  - Could be classified using Hans algorithm (n = 122)
    - Germinal center B-cell type (n = 55)
    - Non-germinal center B-cell type (n = 67)

LNH03-2B: Influence of Cell of Origin

LHN03-2B: Influence of Cell of Origin

- Does the R-ACVBP result confirm the hypothesis for sequential R-CHOP → ICE?
- After all these are different regimens
- Or are they....

### Comparison of R-CHOP/ICE and ACVBP with Consolidation

<table>
<thead>
<tr>
<th>Drug (cytotoxic)</th>
<th>DI mg/m²/week</th>
<th>Total mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R-CHOP/ICE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>187.5</td>
<td>1500</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>25</td>
<td>200</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>500</td>
<td>4000</td>
</tr>
<tr>
<td>Vincristine</td>
<td>0.7</td>
<td>5.6</td>
</tr>
<tr>
<td>Prednisone</td>
<td>*250</td>
<td>*2000</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>2500</td>
<td>15000</td>
</tr>
<tr>
<td>Etoposide</td>
<td>150</td>
<td>900</td>
</tr>
<tr>
<td>Carboplatin</td>
<td><strong>2.5</strong></td>
<td><strong>15</strong></td>
</tr>
</tbody>
</table>

*FLAT dosing **Dose as AUC

<table>
<thead>
<tr>
<th>Drug (cytotoxic)</th>
<th>DI mg/m²/week</th>
<th>Total mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACVBP + Consolidation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab</td>
<td>187.5</td>
<td>3000</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>37.5</td>
<td>300</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600</td>
<td>4800</td>
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<tr>
<td>Vindesine</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>*10</td>
<td>*80</td>
</tr>
<tr>
<td>Prednisone</td>
<td>150</td>
<td>1200</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1500</td>
<td>6000</td>
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<tr>
<td>Ifosfamide</td>
<td>750</td>
<td>6000</td>
</tr>
<tr>
<td>Etoposide</td>
<td>150</td>
<td>1200</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>400</td>
<td>800</td>
</tr>
</tbody>
</table>

New Agents in DLBCL
## Lenalidomide for DLBCL: Impact of Cell of Origin

**Table: Lenalidomide cycles and response in GCB and Non-GCB DLBCL**

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>GCB</th>
<th>Non-GCB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenalidomide cycles</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>2 (1-35)</td>
<td>2 (1-21)</td>
<td>4 (1-35)</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>6 (15.0)</td>
<td>1 (4.3)</td>
<td>5 (29.4)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (12.5)</td>
<td>1 (4.3)</td>
<td>4 (23.5)</td>
</tr>
<tr>
<td>SD</td>
<td>7 (17.5)</td>
<td>7 (30.4)</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>21 (52.5)</td>
<td>14 (60.9)</td>
<td>7 (41.2)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2.5)</td>
<td>0</td>
<td>1 (5.9)</td>
</tr>
<tr>
<td>ORR (CR + PR)</td>
<td>11 (27.5)</td>
<td>2 (8.7)</td>
<td>9 (52.9)</td>
</tr>
<tr>
<td><strong>PFS, mo</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2.6</td>
<td>1.7</td>
<td>6.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.9-4.2</td>
<td>0.3-3.1</td>
<td>2.9-9.6</td>
</tr>
</tbody>
</table>

*Hernandez-Illaliturri et al, Cancer 2011 117:5058*
Frontline R-CHOP + Lenalidomide (RL-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)

Italian Series: Lenalidomide + R-CHOP21 in Elderly Untreated DLBCL: Efficacy

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
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</thead>
<tbody>
<tr>
<td>ORR</td>
<td>45 (92)</td>
</tr>
<tr>
<td>CR</td>
<td>42 (86)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (6)</td>
</tr>
<tr>
<td>SD</td>
<td>0</td>
</tr>
<tr>
<td>PD</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Chiappella et al. ASH 2012, Abstract 903.
# RL-CHOP vs R-CHOP Control Patients Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>R2CHOP (N=64)</th>
<th>RCHOP (N=87)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Median (range)</td>
<td>65 (22-87)</td>
<td>61 (41-86)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>Male</td>
<td>40 (62.5%)</td>
<td>50 (57.5%)</td>
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</tr>
<tr>
<td>IPI</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Low</td>
<td>7 (10.9%)</td>
<td>18 (20.7%)</td>
<td></td>
</tr>
<tr>
<td>Low-Intermed.</td>
<td>24 (37.5%)</td>
<td>16 (18.4%)</td>
<td></td>
</tr>
<tr>
<td>High-Intermed.</td>
<td>24 (37.5%)</td>
<td>38 (43.7%)</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>9 (14.1%)</td>
<td>15 (17.2%)</td>
<td></td>
</tr>
<tr>
<td>Ann Arbor Stage</td>
<td></td>
<td></td>
<td>0.04</td>
</tr>
<tr>
<td>2</td>
<td>7 (10.9%)</td>
<td>20 (23.0%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>19 (29.7%)</td>
<td>14 (16.1%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>38 (59.4%)</td>
<td>53 (60.9%)</td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td>0.36</td>
</tr>
<tr>
<td>0</td>
<td>30 (46.9%)</td>
<td>32 (36.8%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>28 (43.8%)</td>
<td>41 (47.1%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (9.4%)</td>
<td>11 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0 (0.0%)</td>
<td>3 (3.4%)</td>
<td></td>
</tr>
</tbody>
</table>

- 87 DLBCL consecutive contemporary patients treated with RCHOP
- Identified in MCR lymphoma database
- Same eligibility: stage 2-4 disease
- No major differences in clinical characteristics

Nowakowski et al. ASH 2012, ASCO 2014
Mayo Series: Outcomes for RL-CHOP v R-CHOP Case Match Control by Cell of Origin

Nowakowski et al. ASH 2012, ASCO 2014
E1412: RL-CHOP vs. R-CHOP

**Stratification**
- Age
- IPI

N=100 evaluable pts

**RL-CHOP**

**R-CHOP**

N=100 evaluable pts

10% path ineligibility rate total ~220 pts#

# up to 300 patients can be enrolled to meet a goal of 50 ABC DLBCL patients per arm as defined by GEP
ROBUST (NCT02285062): Lenalidomide Plus R-CHOP Chemotherapy (R2-CHOP) Versus Placebo Plus R-CHOP Chemotherapy in Subjects With Untreated ABC-DLBCL, Phase 3, double-blind, placebo-controlled

Inclusion
- DLBCL, ABC-type, untreated
- COO by Lymph2Cx
- Measurable disease by CT/MRI
- ECOG 0-2
- Age 18-80
- IPI ≥2

Exclusion
- Lymphoma other than DLBCL
- HIV, HBV, HCV active infections
- LVEF <45%
- Peripheral neuropathy, grade ≥2
- Other malignancies < 5 years disease free

Sample Size/Statistical Plan
- Sample size: 560
- 90% to detect increase in PFS of 60%

Clinical Endpoints
- Primary: Progression-free survival
- Secondary: OS, CRR, Duration of CR, TTNT, ORR, QOL

Evaluation
- Interim evaluation after cycle 4
- EOT (6 cycles) FDG-PET

Double-blind, placebo controlled
Randomization 1:1

Placebo + R-CHOP × 4

Placebo + R-CHOP × 2

Lenalidomide + R-CHOP × 4

Lenalidomide + R-CHOP × 2

Interim Evaluation NR off study

EOT Evaluation IWG 2007 with Deauville PET

Study Start Date: January 2015
- Estimated Study Completion Date: September 2022
- Estimated Primary Completion Date: June 2018

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Ibrutinib in Rel/Ref DLBCL: Phase II

Eligibility (N = 70)
- 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

Ibrutinib: 560 mg/d, PO

Only includes pts with post baseline LN measurements

ABC (N = 23)  
GCB (N = 12)  
Unclassifiable (N = 8)  
Unknown (N = 3)

* Best response was PD due to clinical progression

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
    - But were better if mutated
  - MYD88 mutations seemed to cause resistance
    - Unless associated with CD79b mutation
  - CARD11 mutation did not respond
    - Expected result since BTK is upstream of CARD11
- 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

## R-CHOP + Ibrutinib: Phase 1b

### Schema

| PART 1: Newly diagnosed: FL, MCL, DLBCL | R-CHOP+Ibrutinib 3 dosing cohorts: 280 mg 420 mg 560 mg |
| PART 2: DLBCL only | R-CHOP+Ibrutinib 560 mg |

R-CHOP x 6 cycles maximum; Ibrutinib dosed from daily starting day 3

- **Dose reductions;**
  - 4 patients required dose reduction of ibrutinib
    - Febrile neutropenia (FN) G3 (N=2)
    - Diarrhea G3 (N=1)
    - Prolonged bleed time (N=1)
  - 2 patients required dose reduction of doxorubicin due to FN
  - 7 patients required dose reduction of vincristine with the majority in cycle 4/5

- **Efficacy (N=22)**
  - ORR 100%: CR 91%, PR 9%
  - Non-GC DLBCL: CR 4/4
  - GC DLBCL: CR 12/14, PCR 2/14
  - Not assigned: CR 4/4

Younes et al. ASH 2013, Abstract 852
**PHEONIX (NCT01855750): Ibrutinib in Combination With R-CHOP in Subjects With Newly Diagnosed Non-Germinal Center Diffuse Large B-Cell Lymphoma, Phase 3, double-blind, placebo-controlled**

### Inclusion
- DLBCL, non-GC, untreated
- Stage II (not candidates for RT), III, IV
- ≥1 measurable site
- R-IPI ≥ 1
- ECOG 0-2
- LVEF WNL

### Exclusion
- Major surgery within 4 weeks
- CNS disease
- Prior indolent lymphoma
- Warfarin
- Concomitant CYP3A inhibitors

### Sample Size/Statistical Plan
- Sample size: 800
- Study completion: 50% deaths or 7 years

**ACCURAL COMPLETE**
- Interim analysis after 270 EFS events
- Cure 40 to 50%; HR for uncured 0.75

### Double-blind, placebo controlled
Randomization 1:1

- **Arm A:** placebo + R-CHOP × 4
- **Arm A:** placebo + R-CHOP × 2-4
- **Arm B:** ibrutinib + R-CHOP × 4
- **Arm B:** ibrutinib + R-CHOP × 2-4

**Interim Evaluation**
NR off study

**EOT Evaluation**
Lugano Revised Criteria

### Study Start Date:
- September 2013

### Estimated Study Completion Date:
- June 2020

### Estimated Primary Completion Date:
- June 2018

### Evaluation
- Interim evaluation after cycle 4
- EOT (6-8 cycles) FDG-PET

### Clinical Endpoints
- **Primary:** Event-free survival
- **Secondary:** PFS, OS, CRR, QOL, ibrutinib: clearance, volume of distribution, AUC, minimal concentration, AEs

**Stratifications**
- RIPI 1-2 v 3-5
- US v Rest of World
- 6 v 8 cycles
Cell of origin in DLBCL

- Cell of origin identifies tumors with distinct biology
- Determination of cell of origin by IHC is inexact, GEP of FFPE is superior and emerging as a clinical assay
- Prognostic significance of COO still controversial
  - Retrospective studies consistently demonstrate GCB with better outcomes than ABC
  - Prospective studies have not always confirmed this?
    - Accrual biases?
- Treatments appear to be influenced by cell of origin
  - Lenalidomide and ibrutinib have activity in ABC DLBCL explained by underlying biology
- Somatic mutations, chromosomal amplification and loss, epigenetic changes, and expression of particular genes (MYC, BCL2 and BCL6) also influence outcome
- COO is an important consideration but is not the only factor that influences treatment and outcome
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