New developments in NHL: ASCO 2009

John P. Leonard, M.D.
Richard T. Silver Distinguished Professor of Hematology and Medical Oncology
Professor of Medicine
Associate Director, Weill Cornell Cancer Center
Chief, Lymphoma/Myeloma Service
Center for Lymphoma and Myeloma
Topics for Discussion

- **Non-Hodgkin Lymphoma**
  - Upfront DLBCL – moving beyond R-CHOP
  - Relapsed DLBCL – limited progress
  - Indolent lymphoma
    - Vaccines
    - New Combinations and Novel Agents
  - T-Cell Lymphoma
Phase III R-CHOP14 vs. R-CHOP21 regimen in newly diagnosed DLBCL

Eligibility criteria:
- Newly diagnosed CD20+ DLBCL

R-CHOP14
CHOP14 x 6 cycles
Rituximab x 8 cycles
Lenograstim d 4-12 each cycle
N-540

R-CHOP21
CHOP21 x 8 cycles
Rituximab x 8 cycles
N=540

Stratification:
- IPI (0-1, 2, 3, 4-5)
- Age <60 vs. ≥60 years
- Treatment center

- Primary: Overall Survival
- Secondary: Failure free survival
  - Toxicity
  - Response

R-CHOP-21 vs R-CHOP-14 in DLBCL

Strengths
- 1000+ patients, 119 sites, 3.5 years
- All ages, mostly advanced stage, balanced IPI
- Powered for overall survival
- Waiting for sufficient followup for full presentation (current median f/u 17 months)

Weaknesses (debatable)
- 8 cycles of therapy
- GCSF in roughly 50% of R-CHOP-21, all R-CHOP-14
## Toxicity during treatment

<table>
<thead>
<tr>
<th>Toxicity grade ≥ 3</th>
<th>R-CHOP21</th>
<th>R-CHOP14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia*</td>
<td>58</td>
<td>31</td>
</tr>
<tr>
<td>Thrombocytopenia*</td>
<td>4</td>
<td>9</td>
</tr>
<tr>
<td>Anaemia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Febrile neutropenia*</td>
<td>13 (2 deaths)</td>
<td>5</td>
</tr>
<tr>
<td>Infection</td>
<td>22 (1 death)</td>
<td>18 (2 deaths)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>0.4</td>
<td>2</td>
</tr>
<tr>
<td>Neurological</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Other grade 5 toxicities</td>
<td>n=4</td>
<td>n=4</td>
</tr>
</tbody>
</table>

*p< 0.01* (considered significant due to multiple testing)

R-CHOP-21 vs R-CHOP-14 in DLBCL

Key points – dosing/toxicity

- More early stopping in R-CHOP-21
  - R-CHOP-21 19% stopped early (6% NR/PD/death)
  - R-CHOP-14 10% stopped early (2% NR/PD/death)
  - Importance vs artifact of regimen
    - 8 cycles, Shorter duration of therapy with 14d cycle, Less GCSF, MD choice

- Similar % dose delays

- More thrombocytopenia with R-CHOP-14

- More neutropenia, FN with R-CHOP-21 (less GCSF)
## Overall response rates

<table>
<thead>
<tr>
<th>Based on end of treatment scan n=831</th>
<th>R-CHOP21 n= 405 %</th>
<th>R-CHOP14 n=426 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>49</td>
<td>40</td>
</tr>
<tr>
<td>CRu</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>PR</td>
<td>24</td>
<td>32</td>
</tr>
<tr>
<td>SD</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>PD/relapse</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>p=0.183</td>
<td>63</td>
</tr>
<tr>
<td>CR/CRu/PR</td>
<td>p=0.139</td>
<td>88</td>
</tr>
</tbody>
</table>

249 patients not evaluable or data missing

Failure-free survival: Entire cohort

2-year FFS: 74%; 95% CI: 71%-77%

R-CHOP-21 vs R-CHOP-14 in DLBCL

Key points – efficacy

• End of treatment ORR and CR rates similar
• 2 year FFS – 74% (seems good for “all comers”)

• Bottom line
  - More time will tell (? late 2010)
  - R-CHOP-21 remains current standard
Phase II trial of R-ACVBP with up-front autotransplantation in patients with poor risk DLBCL NHL : LNH 2003-3

- Doxorubicin 75 mg/m² D1
- Cyclophosphamide 1200 mg/m² D1
- Vindesine 2mg/m² D1, D5
- Bleomycin 10 mg D1, D5
- Prednisone 60mg/m² D1-D5
- MTX intrathecal 15 mg D2
- G-CSF 5 µg/kg D6-D13

Progression free survival

Mounier et al. *J Clin Oncol* 2009; 27(suppl):793s (abstract 8507)
R-ACVBP + AuSCT in DLBCL

Strengths
- Multicenter study, 200+ pts (2 years)
- 75% received AuSCT
- aaIPI 2 or 3 (targeting high risk)

Weaknesses
- Phase II, with historical comparison
- Under age 60 only
R-ACVBP + AuSCT in DLBCL

Key points

- 75% PFS, 81% OS (at 3 years f/u)
- PFS 15% better than non-rituximab similar regimen (historical comparison)

Bottom line

- Effective regimen for high risk, younger patients
- Needs comparative study
- Do you need the SCT?
- Do you need the ACVBP (vs CHOP)?
Epratuzumab (anti-CD22) + R-CHOP-21 in DLBCL

**Strengths**
- Multicenter study
- Representative by age, IPI
- Definitions and reporting of both EFS and PFS

**Weaknesses**
- Phase II, comparisons to other groups
- 80 eligible patients (107 enrolled)
### Phase II Trial of Anti-CD22 MoAb Epratuzumab Plus R-CHOP in Previously Untreated DLBCL: Response

<table>
<thead>
<tr>
<th>Response by CT (n = 80)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>94%</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>71%</td>
</tr>
<tr>
<td>PR</td>
<td>23%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PET Response (n=77)</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Response Rate</td>
<td>96%</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>87%</td>
</tr>
<tr>
<td>PR</td>
<td>9%</td>
</tr>
<tr>
<td>EFS at 12 months (n = 80)</td>
<td>79%</td>
</tr>
<tr>
<td>PFS at 12 months (n = 80)</td>
<td>87%</td>
</tr>
<tr>
<td>OS at 12 months (n = 80)</td>
<td>89%</td>
</tr>
</tbody>
</table>

Overall Survival
Progression-Free Survival
Event-Free Survival

Epratuzumab (anti-CD22) + R-CHOP-21 in DLBCL

Key points

- Toxicity similar to R-CHOP except 70% gr 4 neutropenia, 17% FN
  - Use of GCSF
- Efficacy
  - 94% ORR (71% CR/CRU), 87% PET negative
  - 2 year PFS 79%, OS 79%
  - IPI 3-5 2 year PFS 78%
- Bottom line
  - Compares favorably, randomized study needed
Lining up these 3 studies w/ respect to “higher risk” patients (apples to oranges to plums)

- **CHOP-R (21 or 14)**
  - 2 year FFS - IPI 2-3 72%, IPI 4-5 60%

- **R-ACVBP + AuSCT**
  - 3 year PFS - aalPI 2-3 75%

- **CHOP-E-R**
  - 2 year PFS – IPI 3-5 78%
  - 2 year FFS – IPI 3-5 67%

**Bottom line – cautious optimism**
R-CHOP-21 or 14
FFS and OS by response*

50 % of failures and deaths occur within 6 months

*Based on end of treatment scan (n=831)

To make progress beyond R-CHOP-21, new approaches need to be used earlier.

- New strategies need to be implemented at or near the start of therapy in order to reduce progression within the first 6 months.
Possible new strategies beyond R-CHOP-21 in DLBCL

- New chemotherapy regimen from day 1
  - Different agents, dose, schedule
    - DA-EPOCH-R vs CHOP-R, CALGB 50303
- Addition of novel agents from day 1
- Changing regimens midstream (PET)
- AutoSCT or other “consolidation” in first remission
- “Maintenance therapies” after R-CHOP
Possible new strategies beyond R-CHOP-21 in DLBCL

- New chemotherapy regimen from day 1
  - Different agents, dose, schedule
    - DA-EPOCH-R vs CHOP-R, CALGB 50303
- Addition of novel agents from day 1
- Changing regimens midstream (PET) "??????"
- AutoSCT or other “consolidation” in first remission
- “Maintenance therapies” after R-CHOP
R-ICE vs. R-DHAP Followed by ASCT and Maintenance Rituximab or Observation in Relapsed DLBCL (CORAL): Study Design

- Relapsed/refractory, CD20+ DLBCL
- Aged ≤ 65 years

R-ICE Versus R-DHAP Followed by ASCT and Maintenance Rituximab or Observation in Relapsed DLBCL (CORAL): Grade 3/4 Adverse Events

<table>
<thead>
<tr>
<th>Grade 3/4 AE</th>
<th>R-ICE</th>
<th>R-DHAP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>With neutropenia</td>
<td>33 (17%)</td>
<td>31 (16%)</td>
</tr>
<tr>
<td>Without neutropenia</td>
<td>11 (6%)</td>
<td>15 (8%)</td>
</tr>
<tr>
<td><strong>Renal Toxicity</strong></td>
<td>2 (1%)</td>
<td>11 (6%)</td>
</tr>
<tr>
<td><strong>Platelets transfusions</strong></td>
<td>35%</td>
<td>57%</td>
</tr>
</tbody>
</table>

## R-ICE Versus R-DHAP Followed By ASCT and Maintenance R or Obs in DLBCL (CORAL): Efficacy

<table>
<thead>
<tr>
<th>ORR</th>
<th>%</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients (n = 388)</td>
<td>63%</td>
<td>-</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>R-ICE (n=197)</td>
<td>63.5%</td>
<td>-</td>
</tr>
<tr>
<td>R-DHAP (n=191)</td>
<td>63%</td>
<td></td>
</tr>
<tr>
<td>No Prior Rituximab (n = 122)</td>
<td>83%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Prior Rituximab (n = 124)</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>Relapsed &gt; 12 mo (n = 140)</td>
<td>88%</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>Refractory &lt; 12 mo (n = 106)</td>
<td>46%</td>
<td></td>
</tr>
<tr>
<td>sIPI 0-1 (n = 160)</td>
<td>71%</td>
<td>&lt; .0002</td>
</tr>
<tr>
<td>sIPI 2-3 (n = 76)</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

OVERALL SURVIVAL ACCORDING TO TREATMENT ARM (INDUCTION ITT)

PROGRESSION-FREE SURVIVAL ACCORDING TO TREATMENT ARM (INDUCTION ITT)

Orlando ASCO May 2009 / Coral study  C. Gisselbrecht
PROGRESSION-FREE SURVIVAL ACCORDING TO FAILURE FROM DIAGNOSIS (INDUCTION ITT)

PROGRESSION-FREE SURVIVAL ACCORDING TO PRIOR RITUXIMAB (INDUCTION ITT)

p<0.0001
Phase III BV301 Trial of Idiotype Vaccine (Id-KLH) in Follicular Lymphoma in First CR

**Eligibility criteria:**
- Grade 1-3a follicular lymphoma
- Monoclonal surface IgM or IgG
- Stage III/IV (stage IIx included)
- Achieving CR/CRu after induction cyclophosphamide, doxorubicin, etoposide and prednisone

Primary endpoint: disease-free survival
Secondary endpoints: safety, overall survival, immunologic and molecular responses

* A total of 60 patients failed to maintain CR/CRu and did not receive the study drug.

Results

Enrollment

Assessed for eligibility (n=234)

Excluded from Randomization (n=57)
Did not receive induction therapy (n=6)
Achieved CR (n=2)
Achieved CRu (n=2)
Achieved PD (n=11)
Achieved SD (n=31)
Unknown/Not assessed (n=5)

Randomized (n=177)

Stratify / Randomize

Allocated to Id-KLH (BiovaxID) (n=118)

Failed to Maintain CR/CRu (n=42)

Allocated to KLH (Control) (n=59)

Failed to Maintain CR/CRu (n=18)

Post-Induction Recovery Period (6-12 months)

ITT (n=177)

PD, no vax (n=60)

Vaccination

Vaccinated with Id-KLH + GM-CSF (n=76)
Rec’d 5 immunizations (n=72)
Rec’d 4 immunizations (n=2)
Rec’d 3 immunization (n=2)

Vaccinated with KLH + GM-CSF (n=41)
Rec’d 5 immunizations (n=39)
Rec’d 4 immunizations (n=1)
Rec’d 2 immunization (n=1)

modified ITT (n=117)

Disease Free Survival from Randomization for Id-KLH (BiovaxID) vs. Control Arms (mITT)

Median Follow-up
56.6 mo (range 12.6 – 89.3)

Median DFS
Id-KLH (BiovaxID) = 44.2 mo
Control vaccine = 30.6 mo

N = 117
Id-KLH (BiovaxID) N = 76
Control vaccine N = 41

Events
Id-KLH (BiovaxID) = 44
Control vaccine = 29

Cox PH Model
HR = 0.62; [95% CI: 0.39,0.99]
(p=0.047)

Bortezomib/bendamustine/rituximab (VBR) in rel/ref FL: VERTICAL study

- Bortezomib 1.6 mg/m² days 1, 8, 15, 22 x 5 cycles
- Bendamustine 50, 70, 90 mg/m²/d days 1, 2
- Rituximab 375 mg/m² Days 1, 8, 15, 22 (cycle 1), day 1 thereafter

<table>
<thead>
<tr>
<th>Bendamustine dose level</th>
<th>N (%) (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR</td>
</tr>
<tr>
<td>50 mg/m² (n=3)</td>
<td>3 (100%)</td>
</tr>
<tr>
<td>70 mg/m² (n=6)</td>
<td>3 (50%)</td>
</tr>
<tr>
<td>90 mg/m² (n=6)</td>
<td>6 (100%)</td>
</tr>
</tbody>
</table>

Bortezomib/bendamustine/rituximab (VBR) in rel/ref FL: VERTICAL study

<table>
<thead>
<tr>
<th>Grade 3/4 AE</th>
<th>N (%) (n = 16)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (25%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (31%)</td>
</tr>
</tbody>
</table>

Bendamustine DLT,
70 mg/m² = Gr 4 Dermatitis
90 mg/m² = Gr 3 Thrombocytopenia

Peripheral Neuropathy (all grades) = 7 (44%)

Phase I Trial of SGN-35 in Relapsed/Refractory Hodgkin Lymphoma or Systemic ALCL

- SGN-35: anti-CD30 Ab-drug conjugate (auristatin)
- Previous phase I trial evaluated every 3-week dosing
  - MTD 1.8 mg/kg
  - DLTs at 2.7 mg/kg: febrile neutropenia, hyperglycemia
  - ORR 15/28 (54%); CR 9/28 (32%)
  - Median PFS > 6 months
- Current study evaluating weekly SGN-35
  - DLTs
    - 1/6 patients at 1.0 mg/kg: grade 3 diarrhea
    - 2/6 patients at 1.4 mg/kg: grade 4 hyperglycemia, grade 3 GI
  - Best clinical response
    - All patients (n=27): ORR 48% (13); CR 37% (10)
    - Hodgkin’s Lymphoma (n=22): ORR 41% (9); CR 27% (6)

**PROPEL: Pralatrexate in Patients With Relapsed/Refractory PTCL**

- PDX 30 mg/m²/week I.V., 6 of 7 weeks + vitamin B₁₂ and folic acid supplementation
- Median of 3 prior systemic regimens (range, 1-12)

<table>
<thead>
<tr>
<th>Efficacy (by Central Review, IWC)</th>
<th>All Patients (n = 109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>30 (28%)</td>
</tr>
<tr>
<td>CR</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>CRu</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>PR</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>SD</td>
<td>23 (21%)</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>9.4 months</td>
</tr>
<tr>
<td>Median PFS</td>
<td>108 days</td>
</tr>
<tr>
<td>Median OS</td>
<td>14.7 months</td>
</tr>
</tbody>
</table>

# PROPEL: Pralatrexate in Patients With Relapsed/Refractory PTCL

<table>
<thead>
<tr>
<th>Grade 3/4 Adverse Events</th>
<th>Patients (n = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
</tr>
<tr>
<td>Mucositis</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15 (14%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (15%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>14 (13%)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>4 (4%)</td>
</tr>
</tbody>
</table>

Interim phase II study results of Lenalidomide in recurrent T cell lymphoma

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Number of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best Response</strong></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>CR</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PR</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>SD ≥ 3 months</td>
<td>2 (9%)</td>
</tr>
<tr>
<td><strong>Median PFS</strong></td>
<td>96 days</td>
</tr>
<tr>
<td><strong>Median OS</strong></td>
<td>241 days</td>
</tr>
</tbody>
</table>

**Toxicities,**
- Gr. 4 thrombocytopenia = 33%
- Gr. 3 neutropenia = 21%
- Gr. 3 febrile neutropenia = 17%
- Pain NOS = 17%

Conclusions

- CHOP-R-21 remains current standard for DLBCL
- Relapsed DLBCL remains challenging, particularly for those with short first remission
- Vaccines may improve DFS in FL upfront in certain settings, but overall impact debatable
- Numerous novel agents/regimens under evaluation in various lymphoma subtypes