Aggressive B and T cell lymphomas: Treatment paradigms in 2019

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Disclosures

Consulting advice:

Gilead, Celgene, Sutro, BMS, Genentech/Roche, Bayer, ADC Therapeutics, AstraZeneca, Biotest, Karyopharm, MEI Pharma, Novartis, Merck, Morphosys, Beigene, Nordic Nanovector, Karyopharm
Diffuse large B cell lymphoma

- Median age 60, usually with advanced stage disease
  - LAN, extranodal disease, symptoms
- Practical objective of treatment – cure (70%)
- Reasonably good clinical prognostic tools
- Most patients treated same (R-CHOP)
- Unmet need – more cures, reduce toxicity
- Who should we treat differently?
- If refractory to second-line therapy, prognosis is poor
Treatment algorithm for DLBCL

- **CHOP-R (100%)** (DA-R-EPOCH)
  - Cure (60-70%)
  - Relapsed/Refractory (30-40%)

- **2nd line therapy**
  - R-ICE, R-DICE, R-DHAP, etc

- Transplant eligible (20-25%)
  - ASCT + HDC
    - Cure (5%)
    - Relapse (15-20%)

- Transplant ineligible (10-15%)
  - Relapse (10-15%)

- 3rd line or later therapy (25-35%)
When do I treat patients with DLBCL today with something other than R-CHOP x 6?

Double hit subtype

Data not robust in double protein subtype

Primary mediastinal

HIV associated

Testicular

Limited stage (?)

CNS

Elderly
Double hit vs Double protein DLBCL
10-25% of DLBCL

- Double-hit lymphoma: High-grade B-cell lymphoma with translocations of MYC as well as BCL2, BCL6, or both ("triple-hit")
  - Histologically classified as DLBCL or B-cell lymphoma unclassifiable with intermediate features between DLBCL and Burkitt Lymphoma
  - Cell of origin: Virtually always germinal center subtype
  - Outcome poor with standard therapies

- Double-expressing lymphomas: DLBCL with dual immunohistochemical expression of MYC (≥40%) and BCL2 (≥70%) in the absence of translocations
  - Cell of origin: Usually activated B cell subtype
  - Outcome inferior to other DLBCLs, but not as poor as DHL
FISH DH DLBCL and treatment with R-CHOP

Green et al, JCO 2012
Prognostic Significance of MYC Single, Double, Triple Hit and MYC-Translocation Partner Status in Diffuse Large B-Cell Lymphoma

Andreas Rosenwald, Laurie H. Sehn and Delphine Maucort-Boulch on behalf of the Lunenburg Lymphoma Biomarker Consortium (LLBC)

60th ASH Annual Meeting
December 2018, San Diego
**MYC Translocation Partner (IG vs non-IG) is Prognostically Relevant in Double/Triple-Hit**

**Progression Free Survival Probability (%)**

0 10 20 30 40 50 60 70 80 90 100

**Time (months)**

0 12 24 36 48 60 72 84 96 108 120

**Overall Survival Probability (%)**

0 10 20 30 40 50 60 70 80 90 100

**Time (months)**

0 12 24 36 48 60 72 84 96 108 120

**HR= 2.8 [1.9-4.2] before 24 months**

**HR= 0.3 [0.1-1.3] after 24 months**

**HR= 3.5 [2.4-5.3] before 24 months**

**HR= 0.5 [0.2-1.7] after 24 months**

**Legend**

- **negative**
- **DH&TH/lg**
- **DH&TH/non-lg**
- **SH/lg**
- **SH/non-lg**
DA-EPOCH-R in double hit lymphoma

Petrich et al Blood 2014
Oki et al BJH 2014
MYC rearrangement positive large B-cell lymphoma patients can be treated successfully with R-CHOP plus lenalidomide

results of the multicenter phase II HOVON 130 trial


HOVON

Stichting Haematolo-Oncologie voor Volwassenen Nederland • www.hovon.nl
R2CHOP: Rituximab-CHOP + lenalidomide

<table>
<thead>
<tr>
<th>Day</th>
<th>Agent</th>
<th>Dose/day</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Cyclophosphamide</td>
<td>750 mg/m²</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
<td>1.4 mg/m²</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>Doxorubicin</td>
<td>50 mg/m²</td>
<td>i.v.</td>
</tr>
<tr>
<td></td>
<td>Rituximab</td>
<td>375 mg/m²</td>
<td>i.v.</td>
</tr>
<tr>
<td>Day 1-5</td>
<td>Prednisone</td>
<td>100 mg</td>
<td>orally</td>
</tr>
<tr>
<td>Day 1-14</td>
<td>Lenalidomide</td>
<td>15 mg</td>
<td>orally</td>
</tr>
</tbody>
</table>

R2CHOP regimen, every 3 weeks

- 6 cycles of R-CHOP + 2 cycles of rituximab
- 6 cycles of lenalidomide (C2-C7)

Additionally:
- CNS prophylaxis, pegfilgrastim, PJP and DVT prophylaxis
Pathology review results

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
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<tbody>
<tr>
<td><strong>Morphology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>65</td>
<td>79%</td>
</tr>
<tr>
<td>BCL-u</td>
<td>12</td>
<td>15%</td>
</tr>
<tr>
<td>Indecisive DLBCL/BCL-U</td>
<td>5</td>
<td>6%</td>
</tr>
<tr>
<td><strong>N=82</strong></td>
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<td></td>
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<tr>
<td><strong>FISH</strong></td>
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<td></td>
</tr>
<tr>
<td>Single hit</td>
<td>20</td>
<td>24%</td>
</tr>
<tr>
<td>Double hit</td>
<td>44</td>
<td>54%</td>
</tr>
<tr>
<td>• MYC+/BCL2+</td>
<td>31</td>
<td>38%</td>
</tr>
<tr>
<td>• MYC+/BCL6+</td>
<td>13</td>
<td>16%</td>
</tr>
<tr>
<td>Triple hit</td>
<td>9</td>
<td>11%</td>
</tr>
<tr>
<td>MYC+ (BCL2 and BCL6 status unknown)</td>
<td>9</td>
<td>11%</td>
</tr>
<tr>
<td><strong>N=82</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>GEP (nanostring)</strong></td>
<td></td>
<td></td>
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<tr>
<td>GCB subtype</td>
<td>29</td>
<td>76%</td>
</tr>
<tr>
<td>ABC subtype</td>
<td>7</td>
<td>18%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>5%</td>
</tr>
</tbody>
</table>
Median FU of 15.9 months, 1-year estimates

**R2CHOP**

- **PFS**
  - Cumulative percentage
  - N=82
  - Log rank p=0.001
  - 66% vs 55%

- **OS**
  - Cumulative percentage
  - N=82
  - Log rank p=0.564
  - 85% vs 60%

**Historical R-CHOP and intensive regimens**

- Log rank p=0.001
- Intensive Induction (N=136)
- R-CHOP (N=63)
- Intensive Induction (N=171)
- R-CHOP (N=100)

Petrich Blood 2014
Planned Intergroup Trial in DH/DE DLBCL
Phase I then Phase II-III
BCL-2 inhibitor Venetoclax

Untreated DHL/DPL

DA-EPOCH-R (DH)
CHOP-R (DE)

DA-EPOCH-R (DH)
CHOP-R (DE) + Venetoclax (ABT199)

Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)
**Alliance 50303: Outcomes**

<table>
<thead>
<tr>
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<th>R-CHOP</th>
<th>DA-EPOCH-R</th>
<th>P-value</th>
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<tbody>
<tr>
<td>ORR</td>
<td>89%</td>
<td>89%</td>
<td>0.983</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>62%</td>
<td>61%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>27%</td>
<td>27%</td>
<td></td>
</tr>
</tbody>
</table>

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

**Event Free Survival**

**Overall Survival**

HR = 1.18 (0.79-1.77)
Excellent outcome of young patients (18-60 years) with favourable-prognosis diffuse large B cell lymphoma (DLBCL) treated with 4 cycles CHOP plus 6 applications of rituximab: Results of the 592 patients of the FLYER trial of the DSHNHL/GLA. (ASH 2018 Abstract 781)

Viola Poeschel¹, Gerhard Held¹, Marita Ziepert², Bettina Altmann², Mathias Witzens-Harig³, Harald Holte⁴, Lorenz Thurner¹, Andreas Viardot⁵, Peter Borchmann⁶, Lothar Kanz⁷, Ulrich Keller⁸, Christian Schmidt⁹, Rolf Mahlberg¹⁰, Bernd Metzner¹¹, Reinhard Marks¹², Heinz-Gert Hoeffkes¹³, Konstantinos Christofyllakis¹, Josif Amam¹, Christian Berdel¹⁴, Stephan Stilgenbauer¹, Norbert Schmitz¹⁵, Lorenz Truemper¹⁶, Niels Murawski¹, Markus Löffler², Michael Pfreundschuh¹

¹Department of hematology, oncology and rheumatology, Saarland University Medical School, Homburg / Saar, Germany; ²Institute for Medical Informatics, Statistics and Epidemiology, University of Leipzig, Leipzig, Germany; ³Department of Internal Medicine V, University of Heidelberg, Heidelberg, Germany; ⁴Oslo University Hospital, Oslo, Norway; ⁵Department of Internal Medicine III, University Hospital Ulm, Ulm, Germany; ⁶Department of Haematology and Oncology, University Hospital of Cologne, Cologne, Germany; ⁷University Hospital of Tuebingen, Tuebingen, Germany; ⁸Klinikum rechts der Isar der TU München, Munich, Germany; ⁹Department of Medicine III, University Hospital, Munich, Germany; ¹⁰Klinikum Mutterhaus der Borromäerinnen, Trier, Germany; ¹¹Klinikum Oldenburg, Oldenburg, Germany; ¹²Department of Hematology and Oncology, University Medical Center, Freiburg, Germany; ¹³Klinikum Fulda TumorKlinik, Fulda, Germany; ¹⁴Department of radiooncology, Saarland University Medical School, Homburg / Saar, Germany; ¹⁵Medizinische Klinik A, University Hospital Münster, Münster, Germany; ¹⁶Georg August University, Goettingen, Germany
• Front-line treatment of aggressive B-cell lymphoma
• 18-60 years, stage I/II, aaIPI = 0, no bulk (max. diameter < 7.5 cm)
## Demographics

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 588)</th>
<th>6 x R-CHOP (n = 295)</th>
<th>4 x R-CHOP (n = 293)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>234 (40 %)</td>
<td>116 (39 %)</td>
<td>118 (40 %)</td>
<td>0.814</td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>48 (18, 60)</td>
<td>47 (19, 60)</td>
<td>49 (18, 60)</td>
<td>0.438</td>
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<tr>
<td>LDH &gt; UNV</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td>-</td>
</tr>
<tr>
<td>ECOG &gt; 1</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td>0 (0 %)</td>
<td>-</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
<td></td>
<td>0.953</td>
</tr>
<tr>
<td>I</td>
<td>346 (59 %)</td>
<td>172 (58 %)</td>
<td>174 (59 %)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>236 (40 %)</td>
<td>119 (40 %)</td>
<td>117 (40 %)</td>
<td></td>
</tr>
<tr>
<td>III/IV</td>
<td>6 (1 %)</td>
<td>4 (1 %)</td>
<td>2 (1 %)</td>
<td></td>
</tr>
<tr>
<td>aaIPI</td>
<td></td>
<td></td>
<td></td>
<td>0.686</td>
</tr>
<tr>
<td>0</td>
<td>582 (99 %)</td>
<td>291 (99 %)</td>
<td>291 (99 %)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>6 (1 %)</td>
<td>4 (1 %)</td>
<td>2 (1 %)</td>
<td></td>
</tr>
<tr>
<td>Extralymph. involvement</td>
<td></td>
<td></td>
<td></td>
<td>0.975</td>
</tr>
<tr>
<td></td>
<td>191 (32 %)</td>
<td>96 (32 %)</td>
<td>95 (32 %)</td>
<td></td>
</tr>
<tr>
<td>Bulky disease</td>
<td>2 (0.3 %)</td>
<td>1 (0.3 %)</td>
<td>1 (0.3 %)</td>
<td>1.000</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>36 (6 %)</td>
<td>9 (3 %)</td>
<td>27 (9 %)</td>
<td>0.002</td>
</tr>
</tbody>
</table>
Response Rates

- **CR/CRu**: 92% (n = 295)
- **PR**: 2%
- **NC**: 1%
- **PRO**: 3%
- **Therapy-associated death**: 1%
- **Unknown**: 1%
- **CR/CRu and additional treatment**: 2%

**Treatment Regimens**

- **6 x R-CHOP-21** (n = 295)
- **4 x R-CHOP-21 + 2 x R** (n = 293)
Primary Endpoint: PFS

At 36 months:

- **6 x R-CHOP-21**
  - 94% (95% CI: 91%; 97%)
  - (n = 295)

- **4 x R-CHOP-21 + 2 x R**
  - 96%, (95% CI: 94%; 99%)
  - (n = 293)

Median follow-up: 66 months
Overall Survival (OS)

At 36 months:

- **6 x R-CHOP-21**
  - 98% (95% CI: 96 %; 99 %)
  - (n = 295)

- **4 x R-CHOP-21 + 2 x R**
  - 99 % (95 % CI: 98 %; 100 %)
  - (n = 293)

Median follow-up: 67 months
Outcome by GCB vs ABC gene signatures in DLBCL
N=233 patients treated with R-CHOP

# Oncogenic mechanisms and potential therapeutic targets in GCB and ABC DLBCLs

<table>
<thead>
<tr>
<th>DLBCL subtype</th>
<th>Cell of origin</th>
<th>Oncogenic mechanisms</th>
<th>Potential targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCB</td>
<td>Germinal centre B-cell</td>
<td>BCL2 translocation* EZH2 mutations‡ PTEN deletions§ Loss of PTEN expression</td>
<td>BCL6 EZH2 PI3K/Akt</td>
</tr>
<tr>
<td>ABC</td>
<td>Post-germinal centre B-cell</td>
<td>NF-κB activation¶ CARD11 mutations MYD88 mutations CD79B mutations A20 deletions</td>
<td>BCR CBM complex IRAK-4 JAK–STAT</td>
</tr>
</tbody>
</table>

Alliance 51301 Study Schema

Relapsed/Refractory DLBCL-ABC Salvage ≥PR, stem cells collected

Randomization Stratify by time to relapse, conditioning regimen

Arm A

ASCT: CBV or BEAM + Ibrutinib 560 mg

Ibrutinib x 12 months Follow Up

Arm B

ASCT: CBV or BEAM

Placebo x 12 months Follow Up

Crossover if Progression

ASCT: CBV or BEAM
A Global, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib Plus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone in Patients With Previously Untreated Non-Germinal Center B-Cell-Like Diffuse Large B-Cell Lymphoma

Anas Younes,1 Laurie H Sehn,2 Peter Johnson,3 Pier Luigi Zinzani,4 Xiaonan Hong,5 Jun Zhu,6 Olga Samoilova,7 Cheolwon Suh,8 Itaru Matsumura,9 Andres Lopez-Hernandez,10 Ulrich Dührsen,11 Catherine Thieblemont,12 Jodi Carey,13 Grace Liu,14 S. Martin Shrieve,15 Steven Sun,14 Jessica Vermeulen,16 Louis Staudt,17 and Wyndham Wilson,18 on behalf of the PHOENIX investigators

1Memorial Sloan Kettering Cancer Center, New York, NY, USA; 2BC Cancer Centre for Lymphoid Cancer, Vancouver, BC, Canada; 3Cancer Research UK Clinical Centre, University of Southampton, Southampton, UK; 4Institute of Hematology, “Seràgnoli” University of Bologna, Bologna, Italy; 5Fudan University Shanghai Cancer Center, Shanghai, China; 6Department of Lymphoma, Peking University Cancer Hospital & Institute, Beijing, China; 7Regional Clinical Hospital, Nizhniy Novgorod, Russian Federation; 8Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; 9Department of Hematology and Rheumatology, Kindai University Faculty of Medicine, Osaka City, Japan; 10Department of Hematology, University Hospital Vall d’Hebron, Barcelona, Spain; 11Department of Hematology, University Hospital Essen, Essen, Germany; 12APHP, Hôpital Saint-Louis, Hematologic Oncology, Paris, France; 13Diderot University, Sorbonne Paris-Cité, Paris, France; 14Janssen R&D, Spring House, PA, USA; 15Janssen Research & Development, Raritan, NJ, USA; 16Janssen Research & Development, San Diego, CA, USA; 17Lymphoid Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA; 18National Cancer Institute, National Institutes of Health, Bethesda, MD, USA
Key eligibility criteria

- Untreated non-GCB DLBCL
  - Determined by Hans-based IHC at a central laboratory
  - Retrospectively analyzed for ABC subtype using GEP
- Stage II to IV measurable disease
- R-IPI ≥ 1
- ECOG performance status ≤ 2

End points

- Primary end point: EFS† in ITT (non-GCB) and ABC subgroup
- Secondary end points: PFS, CR rate, OS, safety
  - Response assessed per Revised Response Criteria for Malignant Lymphoma¹

Study Design: Double-Blind, Placebo-Controlled Study

N = 838

Randomize

1:1

R-CHOP (6-8 cycles*) + placebo

*As prespecified by site

R-CHOP (6-8 cycles*) + 560 mg ibrutinib

R-CHOP (6-8 cycles*) + placebo

R-CHOP (6-8 cycles*) + 560 mg ibrutinib

¹Stratified by R-IPI, region, and number of prespecified treatment cycles (6 vs 8 cycles).
- Prophylactic antibiotics and G-CSF were not mandated but were permitted at the investigator’s discretion per local or other standard guidelines

¹EFS: time from randomization to PD, relapse from CR, initiation of subsequent disease-specific therapy for PET-positive or biopsy-proven residual disease after ≥ 6 cycles of R-CHOP, or any-cause death.

Patient Disposition (ITT)

- Similar number of patients with ABC subtype in both arms (77.0% vs 74.8%)
- Median follow-up 34.8 months
- Median time from diagnosis to treatment approximately 27 days
## Patient Demographics and Disease Characteristics (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib + R-CHOP (n = 419)</th>
<th>Placebo + R-CHOP (n = 419)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>63.0</td>
<td>61.0</td>
</tr>
<tr>
<td>&gt; 65 years, n (%)</td>
<td>188 (44.9)</td>
<td>160 (38.2)</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>221 (52.7)</td>
<td>226 (53.9)</td>
</tr>
<tr>
<td><strong>Region, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US/Western Europe</td>
<td>131 (31.3)</td>
<td>131 (31.3)</td>
</tr>
<tr>
<td>Rest of world</td>
<td>288 (68.7)</td>
<td>288 (68.7)</td>
</tr>
<tr>
<td><strong>Baseline stage of DLBCL at entry, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>II</td>
<td>101 (24.1)</td>
<td>103 (24.6)</td>
</tr>
<tr>
<td>III</td>
<td>130 (31.0)</td>
<td>118 (28.2)</td>
</tr>
<tr>
<td>IV</td>
<td>188 (44.9)</td>
<td>197 (47.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Ibrutinib + R-CHOP (n = 419)</th>
<th>Placebo + R-CHOP (n = 419)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
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<td></td>
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<tr>
<td>0</td>
<td>190 (45.3)</td>
<td>187 (44.6)</td>
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<tr>
<td>1</td>
<td>191 (45.6)</td>
<td>170 (40.6)</td>
</tr>
<tr>
<td>2</td>
<td>38 (9.1)</td>
<td>62 (14.8)</td>
</tr>
<tr>
<td><strong>Bone marrow involvement, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>50 (11.9)</td>
<td>43 (10.3)</td>
</tr>
<tr>
<td>No</td>
<td>369 (88.1)</td>
<td>376 (89.7)</td>
</tr>
<tr>
<td><strong>Number of planned treatment cycles, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 cycles</td>
<td>246 (58.7)</td>
<td>246 (58.7)</td>
</tr>
<tr>
<td>8 cycles</td>
<td>173 (41.3)</td>
<td>173 (41.3)</td>
</tr>
<tr>
<td><strong>R-IPI score index number, n (%)</strong></td>
<td></td>
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<tr>
<td>1-2</td>
<td>236 (56.3)</td>
<td>238 (56.8)</td>
</tr>
<tr>
<td>3-5</td>
<td>183 (43.7)</td>
<td>181 (43.2)</td>
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Primary End Point EFS in the ITT and ABC Population

<table>
<thead>
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<th>Months</th>
<th>Ibrutinib + R-CHOP</th>
<th>Placebo + R-CHOP</th>
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<td>125</td>
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<tr>
<td>36</td>
<td>125</td>
<td>78</td>
</tr>
<tr>
<td>40</td>
<td>78</td>
<td>41</td>
</tr>
<tr>
<td>44</td>
<td>41</td>
<td>25</td>
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<tr>
<td>48</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>52</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI): 0.949 (0.704-1.279)
p value: 0.7311

ITT (n = 838)

- Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar in the ibrutinib + R-CHOP and placebo + R-CHOP arms in the ITT population
- CNS progression was observed: 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms

ABC (n = 567)

- Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar in the ibrutinib + R-CHOP and placebo + R-CHOP arms in the ABC population
- CNS progression was observed: 10 (2.4%) vs 16 (3.8%) patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms
Ibrutinib + R-CHOP improved EFS and OS vs placebo + R-CHOP in patients < 60 years of age.

Subgroup analyses showed that EFS benefit was consistent across most subgroups for baseline factors.

A similar trend with age was seen in patients with the ABC subtype (HR [95% CI]: 0.532 [0.307-0.922] for EFS; HR [95% CI]: 0.345 [0.138-0.862] for OS).

More patients on the placebo + R-CHOP arm received subsequent antilymphoma therapy (25.2% vs 33.5%).
Treatment-Emergent SAEs,* Overall Population

- TEAE types were consistent with those expected for ibrutinib and R-CHOP
- Prophylactic G-CSF was used in 66.1% vs 63.9% patients in the ibrutinib + R-CHOP and placebo + R-CHOP arms
  - 56.5% vs 56.2% in patients < 60 years
  - 71.8% vs 70.0% in patients ≥ 60 years

*Occurring in ≥ 2% patients in any treatment group.
### Treatment Received by Age < and ≥ 60 Years

<table>
<thead>
<tr>
<th>Age &lt; 60 Years</th>
<th>Age ≥ 60 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ibrutinib + R-CHOP (n = 154)</td>
</tr>
<tr>
<td>R-CHOP* cycles received ≥ 6 cycles</td>
<td>143 (92.9)</td>
</tr>
<tr>
<td>Ibrutinib/placebo cycles received ≥ 6 cycles</td>
<td>138 (89.6)</td>
</tr>
</tbody>
</table>

*Any component.

- In the safety population, ibrutinib/placebo and R-CHOP exposure was reduced in the ibrutinib + R-CHOP arm compared with the placebo + R-CHOP arm.
- The reduced ibrutinib/placebo and R-CHOP exposure was primarily seen in older patients.
Axicabtagene Ciloleucel CAR T-Cell in refractory DLBCL

111 enrolled, 101 received drug

Neelapu et al; NEJM 377;26:2531-44, 2017
Axicabtagene Ciloleucel (Axi-cel) CD19 Chimeric Antigen Receptor (CAR) T-cell Therapy for Relapsed/Refractory Large B-cell Lymphoma: Real World Experience


David B. Miklos**, Sattva S. Neelapu**, Frederick L. Locke**

*LJN and MDJ are co-first authors
**DBM, SSN, and FLL are co-senior authors
Axi-Cel SOC Consort Diagram

Leukapheresed as of 8/31/18 (N=295)

Conditioning Cy 500 mg/m² + Flu 30 mg/m² × 3 d (N=274)

Axi-cel 2 × 10⁶ CAR T cells/kg (N = 274)

• Product did not meet specifications (N=7), enrolled on ZUMA 9
• Died secondary to lymphoma (N=12)
• Non-measurable disease (N=1)
• Infection (N=1)

Median time from leukapheresis to start of conditioning chemotherapy was **21.5 days**

158 (55%) patients received bridging therapy:
- 56% chemotherapy
- 24% steroids
- 13% XRT
- 7% other

• N = 295: ITT Population
• N= 274 mITT* Population (93%)
• Data cutoff: October 31, 2018
• Median follow-up: 3.9 months

*includes 3 patients treated on ZUMA9 with product that was out of spec
Characteristics Differentiating Patients in the Real World from ZUMA-1

- 124 of 286* (43%) patients would not have met eligibility for ZUMA-1 at the time of leukapheresis.

<table>
<thead>
<tr>
<th>Criteria Excluded from ZUMA-1</th>
<th>N=124 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets &lt; 75</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Active DVT/PE</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Prior CD19 or CAR T cell therapy</td>
<td>24 (8)</td>
</tr>
<tr>
<td>GFR &lt; 60</td>
<td>22 (8)</td>
</tr>
<tr>
<td>History of CNS lymphoma</td>
<td>22 (8)</td>
</tr>
<tr>
<td>Symptomatic pleural effusion</td>
<td>11 (4)</td>
</tr>
<tr>
<td>LVEF &lt; 50%</td>
<td>10 (4)</td>
</tr>
<tr>
<td>Prior allogeneic SCT</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>

* Missing data on 7 subjects enrolled on ZUMA 9
## Hospitalization Period and Grade 5 AEs

<table>
<thead>
<tr>
<th></th>
<th>SOC Axi-cel</th>
<th>ZUMA-1(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>N = 274</strong></td>
<td><strong>N = 108</strong></td>
</tr>
<tr>
<td>Tocilizumab usage</td>
<td>63%</td>
<td>45%</td>
</tr>
<tr>
<td>Corticosteroid usage</td>
<td>55%</td>
<td>29%</td>
</tr>
<tr>
<td>Median hospital stay</td>
<td>14 days</td>
<td>N/A</td>
</tr>
<tr>
<td>ICU stay, N (%)</td>
<td>85 (32%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Grade 5 AEs, N (%)</td>
<td>7 (3%)</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
</tr>
</tbody>
</table>

- 7 deaths due to non-relapse mortality after SOC axi-cel
  - Infection (N=5; infection, sepsis, fungemia, candidemia, pneumonia)
  - HLH (N=1)
  - Cerebral Edema (N=1)

\(^1\)Neelapu, Locke et al. *NEJM*. 2017 Dec 28;377(26):2531-2544
Efficacy of Axi-Cel in the Real World

<table>
<thead>
<tr>
<th></th>
<th>SOC Axi-cel Evaluable</th>
<th>SOC Axi-Cel</th>
<th>ZUMA-1&lt;sup&gt;1&lt;/sup&gt; N=108</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow up, months</td>
<td></td>
<td>3.9</td>
<td>15.4</td>
</tr>
<tr>
<td>Day 30 ORR, N (%)</td>
<td>238</td>
<td>191 (80)</td>
<td>N/A</td>
</tr>
<tr>
<td>Day 30 CR, N (%)</td>
<td></td>
<td>113 (47)</td>
<td>N/A</td>
</tr>
<tr>
<td>Best ORR at Day 90, N (%)</td>
<td>248&lt;sup&gt;a&lt;/sup&gt;</td>
<td>201 (81)</td>
<td>89 (82)</td>
</tr>
<tr>
<td>Best CR at Day 90, N (%)</td>
<td></td>
<td>142 (57)</td>
<td>63 (58)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Evaluable patients as of data cut-off date of October 31, 2018

<sup>1</sup>Neelapu, Locke et al. NEJM. 2017 Dec 28;377(26):2531-2544
PFS and OS at Median F/U of 3.9 Months in the Real World

Progression Free Survival

Median PFS time: 6.18 months
95% CI: 4.57 ~ NA months

Overall Survival

6 month OS estimate is 72%
(95% CI 65-80%)

# at risk
242 124 39 7 1

# at risk
242 141 51 11 1

mITT population, OS calculated from time of CAR T infusion until death or last contact.
Axicabtagene Ciloleucel in the Real World: Outcomes and Predictors of Response, Resistance & Toxicity (ASH 2018 Abstract 92)

Caron A. Jacobson, MD 1, Bradley Hunter, MD, MPH1, Philippe Armand, MD, PhD1, Yusuke Kamihara, MD, PhD1, Jerome Ritz, MD, PhD1, Scott J Rodig, MD2, Kyle Wright, M.D., Ph.D.2, Mikel Lipschitz, M.S.2, Robert A. Redd, MS1, Joseph Maakaron, MD3, Samantha Jaglowski, MD, MPH3, Marcela V. Maus, MD, PhD4, Yi-Bin Chen, MD4, Jeremy S. Abramson, MD, MMSc4, Justin Kline, MD5, Jonathon B. Cohen, MD, MS6, Stephen D. Smith, MD7, David G. Maloney, MD, PhD8, Ajay K. Gopal, MD8, Matthew J. Frigault, MD* and Utkarsh H. Acharya, DO7,8*

1Dana Faber Cancer Institute, Boston, MA, 2Brigham and Women’s Hospital, Boston, MA, 3Ohio State University, Columbus, OH, 4Massachusetts General Hospital Cancer Center, Boston, MA, 5University of Chicago, Chicago, IL, 6Emory University, Atlanta, GA, 7Seattle Cancer Care Alliance, University of Washington, Seattle, WA, 8University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA

*Contributed equally to this work
ZUMA-1 Eligibility and Bridging Therapy: Outcomes

Progression-free Survival

Overall Survival

- **ZUMA-1 Ineligible: Other (+/- Bridging)**
- **ZUMA-1 Ineligible: Bridging only**
- **ZUMA-1 Eligible**
Outcomes of Patients with Large B-Cell Lymphomas and Progressive Disease Following CD19-Specific CAR T-cell Therapy (ASH 2018 Abst 94)

Poor OS after progressive disease

Survival Probability

Time After Progression (months)

MEDIAN = 5.3 MONTHS

Number at risk

Strata

0 10 20 30 40 50

58 17 7 4 3 1
Impact of bridging therapy and type of progression on survival

Survival Probability

Time After Progression (months)

No Bridging + Delayed PD
No Bridging + Initial PD
Bridging + Delayed PD
Bridging + Initial PD

MEDIAN OS (MONTHS)

13.55
5.20
3.19
2.34

P = 0.19

Number at risk
The Phase 3 ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Previously Untreated Subjects with CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Steven Horwitz, Owen A O’Connor, Barbara Pro, Tim Illidge, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper

American Society of Hematology Annual Meeting; San Diego, California, December 1-4, 2018, Abstract #997
ECHELON-2 Study Design (NCT01777152)

**Key Eligibility Criteria**
- Age ≥18 years
- CD30-expression (≥10% cells)
- Previously-untreated PTCL:
  - Systemic ALCL (sALCL)* including ALK(+) sALCL with IPI ≥2, ALK(-) sALCL
  - PTCL-NOS, AITL, ATLL, EATL, HSTCL
- *targeting 75% (±5%) ALCL per EU regulatory commitment

**Stratification Factors**
- IPI score (0-1 vs. 2-3 vs. 4-5)
- Histologic subtype (ALK-positive sALCL vs. all other histologies)

**Treatment Arms**
- A+CHP
  - (A) brentuximab vedotin 1.8 mg/kg +
  - (C) cyclophosphamide 750 mg/m² +
  - (H) doxorubicin 50 mg/m² +
  - (P) prednisone 100 mg (Days 1-5)
  - + placebo vincristine
  - Q3W for 6 to 8 cycles
- CHOP
  - (C) cyclophosphamide 750 mg/m² +
  - (H) doxorubicin 50 mg/m² +
  - (O) vincristine 1.4 mg/m² +
  - (P) prednisone 100 mg (Days 1-5)
  - + placebo brentuximab vedotin
  - Q3W for 6 to 8 cycles

**Per investigator discretion:**
GCSF primary prophylaxis, consolidative RT and SCT

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukaemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; GCSF, granulocyte-colony stimulating factor; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index
### Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>A+CHP (N=226)</th>
<th>CHOP (N=226)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>133 (59)</td>
<td>151 (67)</td>
</tr>
<tr>
<td>Age in years, median</td>
<td>58 (18-85)</td>
<td>58 (18-83)</td>
</tr>
<tr>
<td>IPI score, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>53 (23)</td>
<td>48 (21)</td>
</tr>
<tr>
<td>2-3</td>
<td>140 (62)</td>
<td>144 (64)</td>
</tr>
<tr>
<td>4-5</td>
<td>33 (15)</td>
<td>34 (15)</td>
</tr>
<tr>
<td>Stage III/IV, n (%)</td>
<td>184 (81)</td>
<td>180 (80)</td>
</tr>
<tr>
<td>Disease diagnosis, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sALCL</td>
<td>162 (72)</td>
<td>154 (68)</td>
</tr>
<tr>
<td>ALK+</td>
<td>49 (22)</td>
<td>49 (22)</td>
</tr>
<tr>
<td>ALK-</td>
<td>113 (50)</td>
<td>105 (46)</td>
</tr>
<tr>
<td>PTCL-NOS</td>
<td>29 (13)</td>
<td>43 (19)</td>
</tr>
<tr>
<td>AITL</td>
<td>30 (13)</td>
<td>24 (11)</td>
</tr>
<tr>
<td>ATLL</td>
<td>4 (2)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>EATL</td>
<td>1 (0)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
Progression-free Survival

3-yr PFS

A+CHP: 95 (42%)
CHOP: 124 (55%)

Events HR (95% CI) P

A+CHP: 95 (42%) 0.71 (0.54, 0.93) 0.011
CHOP: 124 (55%)

Median PFS (95% CI)

A+CHP: 48.2 mo (35.2, NE)
CHOP: 20.8 mo (12.7, 47.6)

Median Follow-up

36.2 months

N at Risk (Events)

Time (Months)

<table>
<thead>
<tr>
<th>Time (Months)</th>
<th>A+CHP</th>
<th>CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>226(0)</td>
<td>226(0)</td>
</tr>
<tr>
<td>6</td>
<td>211(2)</td>
<td>211(2)</td>
</tr>
<tr>
<td>12</td>
<td>175(9)</td>
<td>175(9)</td>
</tr>
<tr>
<td>18</td>
<td>149(19)</td>
<td>149(19)</td>
</tr>
<tr>
<td>24</td>
<td>124(75)</td>
<td>124(75)</td>
</tr>
<tr>
<td>30</td>
<td>108(82)</td>
<td>108(82)</td>
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<tr>
<td>36</td>
<td>81(85)</td>
<td>81(85)</td>
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<tr>
<td>42</td>
<td>64(88)</td>
<td>64(88)</td>
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<tr>
<td>48</td>
<td>38(93)</td>
<td>38(93)</td>
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<td>54</td>
<td>24(93)</td>
<td>24(93)</td>
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<tr>
<td>60</td>
<td>9(94)</td>
<td>9(94)</td>
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<tr>
<td>66</td>
<td>3(95)</td>
<td>3(95)</td>
</tr>
<tr>
<td>72</td>
<td>0(95)</td>
<td>0(95)</td>
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</tbody>
</table>
Overall Survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Deaths</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>A+CHP</td>
<td>51 (23%)</td>
<td>0.66 (0.46, 0.95)</td>
<td>0.0244</td>
</tr>
<tr>
<td>CHOP</td>
<td>73 (32%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Median Follow-up: 42.1 months

75th Percentile Not reached 17.5 mo
Adverse Events in ≥20% of Subjects

- Nausea
- Peripheral sensory neuropathy
- Neutropenia
- Diarrhea
- Constipation
- Alopecia
- Pyrexia
- Vomiting
- Fatigue
- Anemia

Grade ≥3
A+CHP
CHOP
Grade <3
Mantle cell lymphoma (10%)

Incurable, median survival 5-10 years

Key focus:

- More vs less intensive initial therapies
  - Bendamustine based rx in older pts standard
  - Does SCT improve survival in younger patients?
  - Role of MRD?

- Development of novel agents and translational studies to understand resistance and advance rational combinations
MCL “standard” initial treatment options

- Observation
- R-CHOP
- Modified R-HyperCVAD
- Bortezomib-R-CAP
- R-Bendamustine
  vs
- R-CHOP/DHAP/ASCT
- R-HyperCVAD/MTX/Ara-C
- R-HyperCVAD/MTX/Ara-C/ASCT
- Nordic

Less intensive

More intensive
E1411: Randomized Phase 2 Intergroup Trial: Initial Therapy of Mantle Cell Lymphoma

- **Registration**
  - BR x 6 → Rituximab
  - BVR x 6 → Rituximab
  - BR x 6 → Lenalidomide + Rituximab
  - BVR x 6 → Lenalidomide + Rituximab
E4151: Randomized trial of SCT/R vs R in MRD neg CR MCL patients

Pre-registration

Submit tumor tissue to Adaptive Biotechnologies for clonal marker testing

Clonal Marker Present?

YES

Post-induction Restaging (CR, PR, SD/PD)
- Submit blood to Adaptive for MRD assessment (MRD pos or MRD neg)

MRD neg CR**

ARM A
Auto-HCT + Rituximab

ARM B
Rituximab

MRD neg PR
MRD indeterminate
MRD pos CR or PR

ARM C
Auto-HCT + Rituximab

NO
Key take home points for aggressive lymphoma

- **DLBCL**
  - Modifications to R-CHOP currently based on clinical and pathologic features (not COO)
  - CAR-T cell rx available, undergoing further optimization

- **T cell**
  - CD30-directed therapy of value upfront and relapse

- **MCL**
  - Maintenance rituximab, ? role of MRD-directed therapy
  - BTK inhibitors in relapse