Aggressive B and T cell lymphomas: Treatment paradigms in 2018

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Disclosures

Consulting advice:

Gilead, Juno, Celgene, Sutro, BMS, Genentech/Roche, Pfizer, Bayer, ADC Therapeutics, AstraZeneca, United Therapeutics, Biotest, Karyopharm, MEI Pharma, Novartis
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%)**

- **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%)**
Comparison of CHOP-R and EPOCH-R

**R-CHOP**

- Rituximab 375 mg/m² d1
- Cyclophosphamide 750 mg/m² d1
- Doxorubicin 50 mg/m² d1
- Vincristine 1.4 mg/m² (2 mg cap) d1
- Prednisone 40 mg/m² d1-5
- q3w × 6

**DA*-R-EPOCH**

- Rituximab 375 mg/m² d1
- Etoposide 50 mg/m²/d CI d1-4*
- Doxorubicin 10 mg/m²/d CI d1-4*
- Vincristine 0.4 mg/m²/d CI d1-4
- Cyclophosphamide 750 mg/m² d5*
- Prednisone 60 mg/m² bid d1-4
- G-CSF 5 μg/kg d6-ANC recovery
- q3w × 6
Prognostic factors (APLES)

- Age >60 years
- Performance status >1
- LDH >1× normal
- Extranodal sites >1
- Stage III or IV

Risk Category

- Low (L): 0 or 1
- Low intermediate (LI): 2
- High intermediate (HI): 3
- High (H): 4 or 5

International Prognostic Index (IPI) in aggressive NHL

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>75</td>
<td>2</td>
</tr>
<tr>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td>6</td>
</tr>
<tr>
<td>0</td>
<td>8</td>
</tr>
</tbody>
</table>

What does the physician need or want to know when approaching a new DLBCL patient?

- Clinical features
  - International Prognostic Index
  - Primary mediastinal (R-EPOCH)
  - CNS, testicular (variations of rx)

- Pathological and molecular features
  - BM involvement (variations of rx)
  - Double hit (FISH) > Double protein (R-EPOCH)
  - Cell of origin (Germinal Center/Activated B Cell)
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
Caveats in understanding clinical characteristics and outcomes in “double hit and double protein” lymphoma

- Clinical features of the subtype are less favorable
- Selection biases of series
- Variability in molecular testing
- Challenges and changes in morphologic/pathologic classification
- Non-uniform therapy
- Single vs multicenter
- Retrospective
FISH DH DLBCL and treatment with R-CHOP

Green et al, JCO 2012
DA-EPOCH-R in double hit lymphoma

Petrich et al Blood 2014
Oki et al BJH 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/CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL

- Primary endpoints: EFS, molecular predictors of outcome for each regimen
- Secondary endpoints: RR, OS, toxicity, use of molecular profiling

Bartlett et al, ASH 2016

Alliance 50303: Design

- N = 524; enrolled 2005 – 2013; Data cutoff November 2016
  - Analysis planned after 242 events, but due to low event rate DSMB released data July 2016 with 167 events

<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 3/4</td>
<td>73</td>
<td>77</td>
<td>0.641</td>
</tr>
<tr>
<td>IPI 0-2</td>
<td>65</td>
<td>61</td>
<td>0.405</td>
</tr>
</tbody>
</table>

**GRADE ≥ 3 TOXICITY**

| Treatment related deaths     | 2          | 2              | 0.975   |
| Platelets                    | 11         | 65             | <0.001  |
| Febrile neutropenia          | 17         | 35             | <0.001  |
| Infection                    | 11         | 14             | 0.169   |
| Neuropathy – sensory/motor   | 2/1        | 14/8           | <0.001  |
**Alliance 50303: Outcomes**

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

**Event Free Survival**

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

**Overall Survival**

HR = 1.18 (0.79-1.77)
DA-EPOCH-R without RT for PMBCL

DA-EPOCH-R in children and adults with PMBCL: A retrospective multicenter analysis

Objectives:
- Describe outcomes in a large number of patients with PMBCL treated with DA-EPOCH-R
- Compare pediatric and adult experience

Methods:
- Collected data from 24 academic medical centers on patients treated from 2005-2015
- No age restriction
- Excluded pediatric patients enrolled on ANHL1131

Roth et al. BJH 2017
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Total Cohort n=156</th>
<th>Pediatrics (age &lt;21) n=38</th>
<th>Adult (age ≥21) n=118</th>
<th>p value peds vs. adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age in yrs: median (range)</strong></td>
<td>31y (9-70)</td>
<td>16y (9-20)</td>
<td>34y (21-70)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td><strong>Female sex: number (%)</strong></td>
<td>100 (64.1%)</td>
<td>21 (55.3%)</td>
<td>79 (66.9%)</td>
<td>0.243</td>
</tr>
<tr>
<td><strong>ECOG performance status: median (range)</strong></td>
<td>1 (0-4)</td>
<td>N/A</td>
<td>1 (0-4)</td>
<td>N/A</td>
</tr>
<tr>
<td><strong>Stage: number (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>26 (16.8%)</td>
<td>1 (2.6%)</td>
<td>25 (21.4%)</td>
<td>N/A*</td>
</tr>
<tr>
<td>II</td>
<td>68 (43.9%)</td>
<td>9 (23.7%)</td>
<td>59 (50.4%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>30 (19.4%)</td>
<td>23 (60.5%)</td>
<td>7 (6.0%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>31 (20.0%)</td>
<td>5 (13.2%)</td>
<td>26 (22.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>B symptoms: number (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>61 (39.9%)</td>
<td>11 (30.6%)</td>
<td>50 (42.7%)</td>
<td>0.244</td>
</tr>
<tr>
<td>II</td>
<td>58 (37.3%)</td>
<td>15 (40.0%)</td>
<td>38 (32.2%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>31 (20.0%)</td>
<td>11 (28.9%)</td>
<td>19 (16.0%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>30 (19.4%)</td>
<td>9 (23.7%)</td>
<td>26 (22.2%)</td>
<td></td>
</tr>
<tr>
<td><strong>Bulky tumor &gt;10cm: number (%)</strong></td>
<td>95 (62.9%)</td>
<td>29 (78.4%)</td>
<td>66 (57.9%)</td>
<td>0.031</td>
</tr>
<tr>
<td>LDH &gt; ULN: number (%)</td>
<td>125 (82.8%)</td>
<td>30 (85.7%)</td>
<td>95 (81.9%)</td>
<td>0.799</td>
</tr>
<tr>
<td>Extranodal disease: number (%)</td>
<td>51 (32.9%)</td>
<td>15 (39.5%)</td>
<td>36 (30.8%)</td>
<td>0.328</td>
</tr>
<tr>
<td>Pleural effusion: number (%)</td>
<td>73 (48.0%)</td>
<td>20 (58.8%)</td>
<td>53 (44.9%)</td>
<td>0.176</td>
</tr>
<tr>
<td>Pericardial effusion: number (%)</td>
<td>82 (53.9%)</td>
<td>19 (55.9%)</td>
<td>63 (53.4%)</td>
<td>0.847</td>
</tr>
<tr>
<td>CD20+ malignant cells: number (%)</td>
<td>146 (98.6%)</td>
<td>30 (100%)</td>
<td>116 (98.3%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

Roth et al, BJH 2017
## DA-R-EPOCH in PMBCL

### Event Free Survival

- **Adult**: 3 yr EFS: 87.4%
- **Pediatrics**: 3 yr EFS: 81.0%

### Overall Survival

- **Adult**: 3 yr OS: 97.1%
- **Pediatrics**: 3 yr OS: 90.7%

### Total Cohort (n=156)

<table>
<thead>
<tr>
<th>Metric</th>
<th>Pediatric (age&lt;21) n=38</th>
<th>Adult (age ≥ 21) n=118</th>
<th>P value for peds vs. adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 yr EFS (95% CI)</td>
<td>81.0 (68.3-93.7)</td>
<td>87.4 (81.2-93.6)</td>
<td>0.338</td>
</tr>
<tr>
<td>3 yr OS (95% CI)</td>
<td>90.7 (80.6-100.0)</td>
<td>97.1 (94.0-100.0)</td>
<td>0.170</td>
</tr>
<tr>
<td>Follow up in mo: Median (range)</td>
<td>24.0 (6.0-83.3)</td>
<td>22.6 (2.7-101.0)</td>
<td>0.780</td>
</tr>
</tbody>
</table>

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Roth et al, BJH 2017
Outcome by end of therapy FDG-PET

Patients evaluated by PET or PET/CT at end of therapy:

<table>
<thead>
<tr>
<th>Deauville score : number (%)</th>
<th>Total Cohort n=156</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤3</td>
<td>149 (96.1%)</td>
<td>94 (75.2%)</td>
<td>95.4%</td>
</tr>
<tr>
<td>4</td>
<td>17 (13.6%)</td>
<td>75.4%</td>
<td>100%</td>
</tr>
<tr>
<td>5</td>
<td>14 (11.2%)</td>
<td>28.6%</td>
<td>74.1%</td>
</tr>
</tbody>
</table>

Roth et al, BJH 2017
Approach to testicular DLBCL
IELSG10 – 53 patients

Stage I
- RCHOP × 3*

Stage II
- RCHOP × 3*

+ 4 doses IT MTX

CR/PR
- RCHOP × 3
- Testicular RT†

CR
- RCHOP × 3
- Testicular RT + IF-RT†

PR
- RCHOP × 5
- Testicular RT + IF-RT†

Vitolo et al, JCO 2011
Approach to testicular DLBCL
IELSG10 – 53 patients

Vitolo et al, JCO 2011
Approach to limited stage DLBCL

S0014 – R-CHOP x 3 + IFRT

Persky et al, JCO 2008
Approach to limited stage DLBCL

Is RT needed?

Sehn, Cancer Journal, 2012
Long term F/U limited stage DLBCL

S8736 – CHOP x 3 + IFRT vs CHOP x 8

Stephens et al, JCO 2016
Who is at risk for CNS involvement in DLBCL?

CNS-IPI

Table 2. Factors Defining the CNS International Prognostic Index: Results of Multivariable Analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney and/or adrenal glands involved</td>
<td>2.8</td>
<td>1.3 to 5.8</td>
<td>.006</td>
</tr>
<tr>
<td>Age &gt; 60 years</td>
<td>2.5</td>
<td>1.3 to 4.5</td>
<td>.001</td>
</tr>
<tr>
<td>LDH &gt; normal</td>
<td>2.4</td>
<td>1.3 to 4.5</td>
<td>.005</td>
</tr>
<tr>
<td>ECOG PS &gt; 1</td>
<td>2.2</td>
<td>1.3 to 3.9</td>
<td>.006</td>
</tr>
<tr>
<td>Stage III/IV disease</td>
<td>2.0</td>
<td>1.0 to 3.8</td>
<td>.039</td>
</tr>
<tr>
<td>Extramedullary involvement &gt; 1</td>
<td>1.0</td>
<td>0.5 to 1.8</td>
<td>.935</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase.

Schmitz et al, JCO 2016
What CNS prophylaxis or treatment do I use in high risk patients?

R-CHOP + d14 MTX 3.5 g/m2 x 3-4 cycles

Retrospective analysis
65 “high risk” patients
2 CNS recurrences

CNS Risk Factor | No. | %
--- | --- | ---
> 1 extranodal site | 40 | 62
> 1 extranodal site and elevated LDH | 30 | 46
Hollender score of 4-5 | 11 | 17

**High-risk sites**
- Bone marrow
- Testis
- Paranasal sinus
- Orbit
- Breast
- Renal/adrenal
- Liver
- Epidural disease

CNS indicates central nervous system; LDH, lactate dehydrogenase.

Abramson et al, Cancer 2010
R-mini CHOP for age 80 and over

- Rituximab 375 mg/m\(^2\) day 1
- Cyclophosphamide 400 mg/m\(^2\) day 1
- Doxorubicin 25 mg/m\(^2\) day 1
- Vincristine 1 mg day 1
- Prednisone 40 mg/m\(^2\) days 1-5

R-mini CHOP for age 80 and over

What about new approaches in DLBCL?

- Strategies under investigation independent of cell of origin
- Strategies targeting specific cell of origin subtype
Germinal Center vs Activated B Cell DLBCL

Dissecting a Cancer into Molecularly and Clinically Distinct Subgroups by Gene Expression Profiling

Diffuse Large B Cell Lymphoma

Activated B Cell-like, Germinal Center B Cell-like, Primary Mediastinal B Cell Lymphoma

Germinal Center vs Activated B Cell DLBCL

IHC surrogate (Hans) - CD10, bcl-6, MUM-1
GCB vs “non-GCB”

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*</td>
<td>BCL6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EZH2 mutations\‡</td>
<td>EZH2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTEN deletions\§</td>
<td>PI3K/Akt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Loss of PTEN expression</td>
<td></td>
</tr>
<tr>
<td>ABC</td>
<td>Post-germinal centre B-cell</td>
<td>NF-κB activation\‖</td>
<td>BCR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CARD11 mutations</td>
<td>CBM complex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MYD88 mutations</td>
<td>IRAK-4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CD79B mutations</td>
<td>JAK–STAT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A20 deletions</td>
<td></td>
</tr>
</tbody>
</table>

Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets

Study design

- Subset 1
  - CHOP-R

- Subset 2
  - Other regimen
Agents under evaluation based on cell of origin

- Bortezomib
- Ibrutinib
- Lenalidomide
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
Axicabtagene Ciloleucel CAR T-Cell in refractory DLBCL

111 enrolled, 101 received drug

Neelapu et al; NEJM 377;26:2531-44, 2017
Axicabtagene Ciloleucel CAR T-Cell in refractory DLBCL

111 enrolled, 101 received drug

Neelapu et al; NEJM 377;26:2531-44, 2017
### Axicabtagene Ciloleucel CAR T-Cell in refractory DLBCL

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 1 or 2</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>65 (64)</td>
<td>37 (37)</td>
<td>28 (28)</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>34 (34)</td>
<td>13 (13)</td>
<td>21 (21)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>29 (29)</td>
<td>20 (20)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Tremor</td>
<td>29 (29)</td>
<td>28 (28)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Aphasia</td>
<td>18 (18)</td>
<td>11 (11)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15 (15)</td>
<td>8 (8)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Agitation</td>
<td>9 (9)</td>
<td>5 (5)</td>
<td>4 (4)</td>
</tr>
<tr>
<td>Memory impairment</td>
<td>7 (7)</td>
<td>6 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Mental-status change</td>
<td>6 (6)</td>
<td>4 (4)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

### Cytokine release syndrome

<table>
<thead>
<tr>
<th>Event</th>
<th>Any Grade</th>
<th>Grade 1 or 2</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>94 (93)</td>
<td>81 (80)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>77 (76)</td>
<td>66 (65)</td>
<td>11 (11)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>41 (41)</td>
<td>32 (32)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>22 (22)</td>
<td>13 (13)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>21 (21)</td>
<td>20 (20)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Neelapu et al; NEJM 377;26:2531-44, 2017
CTCL: Background

- Chronic T-cell lymphoma primarily involving skin
- Mycosis fungoides (MF) and primary cutaneous anaplastic large cell lymphoma (pcALCL) are the most common CD30 expressing CTCL
- Brentuximab vedotin, a CD30 targeting antibody-drug-conjugate, has clinical activity in CTCL
  - Duvic et al. ORR, MF 54%, pcALCL 100%;
  - Kim et al. ORR, MF/Sézary syndrome 70%


# Brentuximab Vedotin vs Investigator Choice in CD30+ CTCL (Alcanza study)

<table>
<thead>
<tr>
<th></th>
<th>Brentuximab Vedotin (n=64)</th>
<th>Physician’s choice of methotrexate or bexarotene (n=64)</th>
<th>Overall (N=128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 (51-70)</td>
<td>59 (48-67)</td>
<td>60 (48-69)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33 (52%)</td>
<td>37 (58%)</td>
<td>70 (55%)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (48%)</td>
<td>27 (42%)</td>
<td>58 (45%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>56 (88%)</td>
<td>53 (83%)</td>
<td>109 (85%)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (8%)</td>
<td>10 (16%)</td>
<td>15 (12%)</td>
</tr>
<tr>
<td>Not reported</td>
<td>3 (5%)</td>
<td>1 (2%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>43 (67%)</td>
<td>46 (72%)</td>
<td>89 (70%)</td>
</tr>
<tr>
<td>1</td>
<td>18 (28%)</td>
<td>16 (25%)</td>
<td>34 (27%)</td>
</tr>
<tr>
<td>2</td>
<td>3 (5%)</td>
<td>2 (3%)</td>
<td>5 (4%)</td>
</tr>
<tr>
<td>Median CD30 expression*</td>
<td>37.5% (12.5-67.5)</td>
<td>31.3% (12.0-47.5)</td>
<td>31.3% (13.5-50.0)</td>
</tr>
<tr>
<td>Time since initial diagnosis (months)</td>
<td>42.2 (12.6-87.4)</td>
<td>37.0 (12.3-102.7)</td>
<td>40.9 (127-368)</td>
</tr>
<tr>
<td>Time since progression on last therapy (months)</td>
<td>2.4 (1.4-7.9)</td>
<td>1.3 (0.9-37)</td>
<td>1.9 (1.1-38)</td>
</tr>
<tr>
<td>Lines of previous therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>4.0 (2.0-7.0)</td>
<td>3.5 (2.0-5.5)</td>
<td>4.9 (2.0-6.0)</td>
</tr>
<tr>
<td>Skin-directed</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
<td>1.0 (1.0-2.0)</td>
</tr>
<tr>
<td>Systemic</td>
<td>2.0 (1.0-4.0)</td>
<td>2.0 (1.0-4.0)</td>
<td>2.0 (1.0-4.0)</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>48 (75%)</td>
<td>49 (77%)</td>
<td>97 (76%)</td>
</tr>
</tbody>
</table>

Prince et al; Lancet 390: 555-66, 2017
Brentuximab Vedotin vs Investigator Choice in CD30+ CTCL (Alcanza study)

<table>
<thead>
<tr>
<th>ITT Population</th>
<th>Brentuximab Vedotin</th>
<th>Physician's Choice of Methotrexate or Bexarotene</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n=64)</td>
<td>ORR4</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>48 (75%)</td>
<td>24 (50%)</td>
</tr>
<tr>
<td>Stage I/II</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA–IIB</td>
<td>15 (31%)</td>
<td>6 (40%)</td>
</tr>
<tr>
<td>IIB</td>
<td>19 (40%)</td>
<td>12 (63%)</td>
</tr>
<tr>
<td>IIIA–IIIB</td>
<td>4 (8%)</td>
<td>2 (50%)</td>
</tr>
<tr>
<td>IVA</td>
<td>2 (4%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>IVB</td>
<td>7 (15%)</td>
<td>2 (29%)</td>
</tr>
<tr>
<td>pALCL</td>
<td>16 (25%)</td>
<td>12 (75%)</td>
</tr>
</tbody>
</table>

Prince et al; Lancet 390: 555-66, 2017
Brentuximab Vedotin vs Investigator Choice in CD30+ CTCL (Alcanza study)

Prince et al; Lancet 390: 555-66, 2017
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
Bendamustine + Rituximab (+/- maint R) upfront MCL
Median age 71, 84% MIPI int/high risk

PFS (all registered pts)
N = 168
Median: 64.2 months

Pts at risk  168                  133                  110                   94                    70                    38                    11

Rummel et al, ASCO 2016
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**
Maintenance Rituximab after AuSCT in Mantle Cell Lymphoma

Le Gouill et al; NEJM 377;13:1250-60, 2017
Maintenance Rituximab after AuSCT in Mantle Cell Lymphoma

Le Gouill et al; NEJM 377;13:1250-60, 2017
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

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

MRD neg CR*

MRD neg PR
MRD indeterminate
MRD pos CR or PR

ARM A
Auto-HCT + Rituximab

ARM B
Rituximab

ARM C
Auto-HCT + Rituximab
Acalabrutinib in Relapsed/Refractory Mantle Cell Lymphoma

124 pts, median 2 prior rx
81% ORR, 40% CR

Wang et al; Lancet 2017
Acalabrutinib in Relapsed/Refractory Mantle Cell Lymphoma

Wang et al; Lancet 2017
Key take home points for aggressive lymphoma

- **DLBCL**
  - Modifications to R-CHOP currently based on clinical features, COO/molecular directed rx under evaluation
  - CAR-T cell rx available, undergoing further optimization
- **T cell**
  - CD30-directed therapy of value
- **MCL**
  - Maintenance rituximab, role of MRD-directed therapy
  - Novel BTK inhibitors