Aggressive B-Cell Non-Hodgkin Lymphomas

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Disclosures

**Research Funding**
Acerta Pharma BV
Astrazeneca
Bayer
Beigene 11/2019
Ayala (spouse)
Bristol Myers Squibb (spouse)
De Novo Biopharma
Genentech
Ignyta (spouse)
Incyte Corporation
Merck Sharp and Dohme Corp.
Pharmacyclics
Portola Pharmaceuticals
Seattle Genetics

**Consultancy OR Advisory Board**
Astrazeneca
Millenium/Takeda
Beigene
Karyopharm
Outline

• Incidence of B-NHL
• Diffuse Large B-Cell Lymphoma
  • Staging and Pretreatment Evaluation
  • Limited-Stage Disease
  • Advanced-Stage Disease
  • Biologic Risk Stratification
  • Relapsed/Refractory Disease
• Primary Mediastinal Large B-Cell Lymphoma
• High-Grade B-Cell Lymphoma
• Mantle Cell Lymphoma

Total mature NHL = 112,380

- CLL/SLL: 20,980 (19%)
- Follicular lymphoma: 13,960 (12%)
- Marginal zone lymphoma: 7,460 (7%)
- Plasma cell neoplasms: 25,980 (23%)
- Peripheral T-cell lymphoma: 3,950 (4%)
- Mantle cell lymphoma: 3,320 (3%)
- DLBCL: 27,650 (25%)
- Lymphoplasmacytic lymphoma: 2,330 (2%)
- Hairy cell leukemia: 1,910 (2%)
- Mycosis fungoides: 1,620 (1%)
- Burkitt lymphoma/leukemia: 1,480 (1%)
- Others: 1,710 (1%)

DLBCL incidence: 7 per 100k
Table 1  WHO classification of mature large B-cell lymphoid neoplasms

<table>
<thead>
<tr>
<th>Category</th>
<th>Subcategory</th>
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</thead>
<tbody>
<tr>
<td>Diffuse large B-cell lymphoma (DLBCL), NOS</td>
<td>Germinal centre B-cell type&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Activated B-cell type&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>T-cell/histiocyte-rich large B-cell lymphoma</td>
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<tr>
<td>Primary DLBCL of the central nervous system (CNS)</td>
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<tr>
<td>EBV+ DLBCL, NOS&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>EBV+ mucocutaneous ulcer&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>DLBCL associated with chronic inflammation</td>
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<tr>
<td>Lymphomatoid granulomatosis</td>
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<tr>
<td>Primary mediastinal/thymic large B-cell lymphoma</td>
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<tr>
<td>Intravascular large B-cell lymphoma</td>
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<tr>
<td>ALK+ large B-cell lymphoma</td>
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<tr>
<td>Plasmablastic lymphoma</td>
<td></td>
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<tr>
<td>Primary effusion lymphoma</td>
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<tr>
<td>HHV8+ DLBCL, NOS&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>Burkitt lymphoma</td>
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<tr>
<td>Burkitt-like lymphoma with 11q aberration&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma</td>
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</tbody>
</table>

The provisional entities are listed in italics
<sup>a</sup>Changes from the 2008 classification
NOS not otherwise specified, EBV Epstein Barr virus

80% of DLBCL are “NOS”
Diffuse Large B-Cell Lymphoma: Staging and Pretreatment Evaluation
DLBCL: Initial Work-Up

• Diagnosis
  • Incisional or excisional biopsy is preferred
  • Core needle biopsy can be considered if above not feasible

• Patient evaluation
  • B-symptoms: temp > 101°F (38.3°C), drenching NS, unexplained weight loss > 10% over 6 months
  • Comorbidities and functional assessment
  • Laboratory studies (e.g., LDH, Hep B serologies)
  • Consider fertility preservation
  • Consider assessment of LVEF

## DLBCL Pathology - Key testing

**Question 1- Adequacy of sample for Dx? Morphology, clonality, other**

<table>
<thead>
<tr>
<th>Assay</th>
<th>Role</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow</td>
<td>Clonality, cell surface markers</td>
<td>DLBCL can be flow negative</td>
</tr>
<tr>
<td>IHC</td>
<td>Biologic risk stratification</td>
<td>Hans criteria for Cell of Origin (COO) Double Expressor: MYC &gt;40% and BCL2 &gt;50%</td>
</tr>
<tr>
<td>FISH</td>
<td>Diagnosis - MYC breakapart, then BCL2/6</td>
<td>(&quot;Double hit&quot; is now high-grade B-cell lymphoma)</td>
</tr>
</tbody>
</table>
Pretreatment evaluation

- Echo/MUGA (especially if cardiac risk factors, HTN)
- Fertility evaluation and preference
- Laboratory workup (Hep B, HIV, LDH)
- Imaging and other staging
- Venous access
Defining “nodal sites” ; benefit of PET

PET-CT vs CT- in roughly 20%:
- Detection of more extranodal sites (GI, head+neck, skin+soft tissue most common)
- Upstaging: stage migration in light of IPI shift

Image -Dr Maciej Debowksi, Radiopaedia.org, rID: 65530
Is BM Bx necessary in the PET era?

Guidelines still say yes, but:

- BM Bx utilization in staging is decreasing in practice*
- PET-CT sensitivity high (meta-analysis: 88%)**
- Impact on Px debatable (marrow often detects low-grade dz)

Consider marrow for:

- Key treatment decisions (stage/therapy change)
- Required in clinical trials
- Baseline cytopenias
- Uncertain PET result

*Bischin PMID 31993568
**Adams E J Nuc Med 2014
DLBCL: Role of Lumbar Puncture

- **CNS IPI:**
  - Risk factors: same as standard IPI plus kidney or adrenal involvement
  - Low (0-1) or intermediate (2-3) risk: defer LP
    - Risk of CNS relapse < 5%
  - High (4-6) risk: intervene
    - Risk of CNS relapse > 10%

**ALSO**
- HIV-associated
- Testicular involvement
- Breast DLBCL
- MYC and BCL2 over-expression (i.e., “double-expressor lymphoma”) - not a validated risk factor (Klanova Blood 2019)

Diffuse Large B-Cell Lymphoma: Limited Stage Disease
Limited stage DLBCL: Long-Term Risk of Relapse

Not your “typical” DLBCL relapse curve?
40 M previously healthy male developed R armpit swelling

**R axillary Bx Path- GCB DLBCL**

**Flow cytometry:** negative  
**Morphology:** Diffuse sheets of large atypical cells  
**IHC:** CD10+ (GCB subtype), MYC 5%

**FISH:** BCL6 rearrangement (only)

**PET:** 1. FDG avid right axillary LAD, Deauville 5. Size 4.5 cm  
2. No other sites.

**BM Bx - negative**
## Therapy for Limited Stage DLBCL: Short-course options

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Population/findings</th>
<th>Downsides</th>
<th>Consider In (presenter opinion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCHOP x 3 + IFRT</td>
<td><em>Int-High grade NHL</em>&lt;br&gt;Miller NEJM 1998, Persky JCO 2008, Stephens JCO 2016</td>
<td>RT acute/late effects (40-46 Gy)</td>
<td>IPI risks present; elderly/frail with optimal XRT field-</td>
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### OPTIONS WITHOUT RADIOTHERAPY -

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<th>Population/findings</th>
<th>Downsides</th>
<th>Consider In (presenter opinion)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCHOP-14 x 4-6</td>
<td><em>Lower risk DLBCL</em>; PET-CR after 4 cycles&lt;br&gt;89% 5 yr EFS w/RCHOP alone&lt;br&gt;XRT vs observation</td>
<td>q14 day RCHOP needs GCSF</td>
<td>No IPI risks + desire a brief treatment course could do RCHOP-14 x 4</td>
</tr>
<tr>
<td>RCHOP-21 x 4 + 2 R</td>
<td><em>Lowest risk DLBCL</em>&lt;br&gt;(stage 2 OK / no IPI risks, no bulk 7.5cm)&lt;br&gt;96% 3 yr PFS w/4 RCHOP</td>
<td>May undertreat stage II? Extra 2 R needed?</td>
<td>Young/no IPI risks</td>
</tr>
<tr>
<td>R-CHOP-21 x 4</td>
<td><em>All limited stage DLBCL</em>&lt;br&gt;(nonbulky 10 cm)&lt;br&gt;89% 5 yr PFS in PET neg w/4 RCHOP</td>
<td>Too few PET + pts to judge that arm. Inferior for non-GCB and double expressor</td>
<td>PET-3 negative - May be best in low biologic risk pts</td>
</tr>
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**Notes:**
- **RCHOP x 3 + IFRT**
  - *Int-High grade NHL*
  - RT acute/late effects (40-46 Gy)
  - Considered in elderly/frail with optimal XRT field.

- **RCHOP-14 x 4-6**
  - Lower risk DLBCL
  - PET-CR after 4 cycles
  - 89% 5 yr EFS w/RCHOP alone
  - q14 day RCHOP needs GCSF
  - No IPI risks + desire a brief treatment course could do RCHOP-14 x 4

- **RCHOP-21 x 4 + 2 R**
  - Lowest risk DLBCL
  - (stage 2 OK / no IPI risks, no bulk 7.5cm)
  - 96% 3 yr PFS w/4 RCHOP
  - May undertreat stage II? Extra 2 R needed?

- **R-CHOP-21 x 4**
  - All limited stage DLBCL
  - (nonbulky 10 cm)
  - 89% 5 yr PFS in PET neg w/4 RCHOP
  - Too few PET + pts to judge that arm. Inferior for non-GCB and double expressor
  - PET-3 negative - May be best in low biologic risk pts
Diffuse Large B-Cell Lymphoma: Advanced-Stage Disease
Randomized trials for 1L DLBCL - Outcome of "typical" studies

DA-EPOCH+R vs R-CHOP
Bartlett JCO 2019

GCHOP vs R-CHOP
Sehn J Hem Onc 2020
Benefits to NCCN IPI
- DLBCL pt specific
- High LDH elevations represented
- Slightly wider range/better discrimination of groups

Table 3. The NCCN-IPI

<table>
<thead>
<tr>
<th>NCCN-IPI</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Age, y</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, normalized</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>1</td>
</tr>
</tbody>
</table>

*Disease in bone marrow, CNS, liver/GI tract, or lung.
MYC dysregulation: protein and translocation

Double expressor (protein) ≈ 30%
Double hit ≈ 10%

![Graph showing overall survival](image)

Yellow line: protein overexpression
MYC > 40%
BCL2 > 50%
Double expression of MYC and BCL2

≈ 30% of new DLBCL

“double positive” = DP
IHC cutoffs
40% for MYC
70% for BCL2 (50% in 1 study)
How urgent is DLBCL treatment?

Accelerated workup and treatment:

- SVC syndrome
- Neurologic compromise or involvement
- Tumor lysis syndrome
- Poor PS, disease-related or unclear
- Very high (3x or greater) LDH elevations
- Metabolic- lactic acidosis, hyperCa
Randomized First-Line DLBCL Trials vs R-CHOP

- RCH-P with polatuzumab (Polarix): Fully accrued
- RCHOP + Enzastaurin (ENGINE): IPI 3-5
- RCHOP + tafasitamab (MOR208, CD19 MoAb)
- RCHOP + acalabrutinib for non-GCB

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- Nonrandomized- RCHOP + checkpoint blockade
DLBCL: Post-Treatment Surveillance

- **Relapses** occur mostly in the first 2 years
- **Limited utility** of surveillance imaging\(^1\)
  - Most relapses (60%) identified BEFORE a schedule follow up visit
    - **Imaging detects** few relapses in asymptomatic pts
  - **Survival** no different in relapses detected in planned follow up vs not

---

Diffuse Large B-Cell Lymphoma: Relapsed/Refractory Disease
**CONCLUSION:** For relapse < 12 mo from diagnosis, salvage therapy followed by auto transplant yields relatively poor outcome.
Strategy in Treating Relapsed DLBCL

1. Goal setting: Bridge to cellular therapy vs. Stand-alone tx)
   - Fitness for auto, Car T-cell; allo
   - Address high risk: early relapse, high sIPI, MYC+

2. Select specific therapy
   - Expected toxicities (organ/hematologic)
   - preferences/logistics
Strategy in Treating Relapsed DLBCL: ASCT and Car-T therapy

Adapted from Chow/Gopal Blood 2018
Chimeric antigen receptor T (CAR-T) Therapy

Approved for relapsed/ref DLBCL failing ≥2 lines:

• Yescarta (axicabtagene ciloleucel, axi-cel): Kite, Oct 2017

• Kymriah (tisagenlecleucel): Novartis, May 2018
CD19 CAR-T cells: CR’s appear to be cured

A Duration of Response

<table>
<thead>
<tr>
<th>Response (%)</th>
<th>100</th>
<th>90</th>
<th>80</th>
<th>70</th>
<th>60</th>
<th>50</th>
<th>40</th>
<th>30</th>
<th>20</th>
<th>10</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since First Response</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

Complete response
Objective response
Partial response

Median (95% CI)

- Complete Response: NR (NE-NE)
- Objective Response: 11.1 (3.9-NE)
- Partial Response: 1.9 (1.4-2.1)

Axi-cel

Tisagenlecleucel

A Duration of Response

- Patients with complete response
- All patients

Median duration among all patients not reached (95% CI, 10.0 months to not reached)

No. at Risk
- Patients with complete response
- All patients

DLBCL Relapsed After, or Ineligible for, auto/Car-T

- Polatuzumab + BR- approved 6/2019
- Selinexor- approved 6/23/20 (after 2 prior tx)
- Lenalidomide+ Tafasitamab- approved 7/31/20
Polatuzumab vedotin: CD79b-targeted Ab with MMAE payload

**CD79b**
- A component of the B-cell receptor
- Expressed on mature B cells

Published data for pola in B-NHL
- Single agent phase I
- Randomized phase 2:
  - Pola+R vs pina+R
  - Pola + RCHOP phase I/II
- Randomized phase II
  - Pola BR vs BR
Polatuzumab vedotin + BR

Pivotal trial design/accrual: (phase Ib/expansion) +
- Randomized phase 2: Pola BR vs BR, 40 pts per arm
- Objective: 65% CR rate w/pola BR (c/w 40%)

Dose: 1.8 mg/kg polatuzumab + BR (90 mg/m2)

Notable eligibility criteria:
- No transformed disease
- “Ineligible for second-line stem cell transplant (SCT)”
- 6 month life expectancy
- No car T-cells within 100 days, no prior allo
Polatuzumab vedotin + BR

**Efficacy:** CR 40% with pola BR vs. 18%
- Median PFS: 9.5 months in pola BR vs 3.7 in BR
- OS 12.4 vs 4.7 mo

- Toxicity: 23% grade 3-4 infection
- 42% received all 6 cycles
- 33% d/c therapy due to AE
- 54% had a treatment delay

**Limitations**
- BR as a backbone
- Uncertain impact if bridging for future car T-cell therapy

Sehn JCO 2019
Selinexor: Oral small molecule targeting nuclear export (exportin)

Pivotal trial design/Accrual: Single arm phase 2. Accrued 267 over 4 yrs @ 59 sites

Dose: 60 mg PO, Days 1 and 3 of each week

Notable eligibility criteria
- 60 day “washout” from prior therapy
Selinexor: Oral small molecule targeting nuclear export (exportin)

**Efficacy**
- 28% ORR; 2.6 mo PFS/9 mo OS
- 12% CR (15 pts)

**Toxicity**: fatigue/nausea (mostly grade 1-2); cytopenias (plts) most common grade 3 or higher AE

**Limitations**: Efficacy and durability limited. Pt selection.
Tafasitamab (CD19 Mo Ab) + lenalidomide:

Design/accrual: single arm phase 2; 156 screened/81 treated over 23 mo.

Dosing: Tafasitamab: 12 mg/kg IV over 2 h, 28 day cycles
- Cycles 1–3 weekly 1, 8, 15, and 22
  - an additional loading dose C1 D4
- Cycle 4 onward: IV q 14 days

Lenalidomide: 25 mg for 3 out of 4 weeks for up to 12 cycles

Notable eligibility:
- Ineligible for transplant (age > 70 or other reasons)
- At MOST, 3 prior regimens
- Primary refractory disease excluded
Tafasitamab (CD19 Mo Ab) + lenalidomide:

**Efficacy:** 13 month follow: ORR 60% including 43 % PR/18 % CR

**Toxicity:** neutropenia/plts, F+N in 12%. 51% of pts had an SAE.

**Limitations:** Small, single arm trial; pt selection (half screened were ineligible). Chronic therapy. PFS needs more follow-up.

Salles Lancet Onc 2020
Primary Mediastinal Large B-Cell Lymphoma
Phase II Study of DA-EPOCH-R (no XRT)

NCI: N = 51
Prospective

Stanford: N = 16
Retrospective

High-Grade B-Cell Lymphomas

• HGBL, with *MYC* and *BCL2* and/or *BCL6* rearrangements
  • Double (DHL) or triple-hit lymphomas (THL)
  • Gene rearrangements by FISH/cytogenetics
  • Copy-number abnormalities DO NOT COUNT
  • Protein over-expression is NOT included

• HGBL, not otherwise specified

• **Treatment**: Intensified regimens are recommended
  • No randomized trials
  • Low IPI patients may be an exception

**DHL in CR1: Role of Auto SCT**

- 159 patients with DHL who achieved CR1
- Compared outcomes by initial regimen and use of stem cell transplant vs observation in CR1
- Median f/u = 26.5 months (range, 0.2-114.6)

Landsburg, Cassaday et al. *J Clin Oncol*. 2017
Mantle Cell Lymphoma

• **Features**
  • Male predominance, EN disease/stage IV usual
  • CD5+ CD23- typical.
  • \textbf{t11;14 by FISH} and /or cyclin D1+ by IHC.

• **Treatment**
  • Initially observe in some cases
  • Young/Fit: Consider intensive induction (Nordic, R+HyperCVAD) → auto SCT
  • Older: BR or VR-CAP (>RCHOP)

• **Special Subgroups**
  • Leukemic Variant: watch/wait
  • TP53 \textit{mutation} : clinical trial and early incorporation of novel agents; ASCT unlikely to benefit
Thank You
DLBCL in First Remission... Maintenance?

• Maintenance rituximab
  • After R-CHOP, no benefit with R maintenance in DLBCL

• Maintenance lenalidomide- REMARC study
  • DLBCL > 60 years old

2Thieblemont J Clin Oncol. 2017 Aug 1
Maintenance with Lenalidomide: REMARC

**Induction**

- R-CHOP
- 6 or 8 cycles

**Maintenance: 24 months**

1:1 random assignment

- Lenalidomide
  - 25 mg/d* for 21 of 28 days
- Placebo

**Registration 1**

- CR
- PR

**Registration 2**

- C6
- C12
- C21

*10 mg lenalidomide for patients with CrCl 30-60 mL/min

Thieblemont J Clin Oncol. 2017
Len Maintenance – REMARC PFS and OS

- Not FDA approved, unclear impact on salvage therapy, NCCN Category 2B