Non-Hodgkin Lymphoma: A Primer

Sonali M. Smith, MD
Elwood V. Jensen Professor
Interim Chief, Section of Hematology/Oncology
Department of Medicine
Director, Lymphoma Program
The University of Chicago
DISCLOSURES
Sonali M. Smith, MD

- I have the following relevant financial relationships to disclose:
  - Consultant for: Genentech/Roche, Celgene, TGTX, Karyopharm, Janssen, Bantam
  - Speaker’s Bureau for: none
  - Stockholder in: none
  - Honoraria from: none
  - Employee of: none
  - Institutional research funding: Portola, Genentech, Acerta, Pharmacyclics, Celgene, Curis, BMS, TG Therapeutics, Merck, Forty-Seven, Novartis

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What is lymphoma?

Lymphoma is a family of blood cancers derived from mature lymphocytes

- B-cells
- T-cells
- NK-cells

- Lymphocytes normally fight viruses, bacteria, fungi, and foreign organisms
- Lymphocytes travel in lymphatic system
- These cells can grow in nodal and extranodal locations
NHL: US Burden of Disease 2020

Estimated New Cases

<table>
<thead>
<tr>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>Breast</td>
</tr>
<tr>
<td>191,930</td>
<td>276,480</td>
</tr>
<tr>
<td>21%</td>
<td>30%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>Lung &amp; bronchus</td>
</tr>
<tr>
<td>116,300</td>
<td>112,520</td>
</tr>
<tr>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>Colon &amp; rectum</td>
</tr>
<tr>
<td>78,300</td>
<td>69,650</td>
</tr>
<tr>
<td>9%</td>
<td>8%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Uterine corpus</td>
</tr>
<tr>
<td>62,100</td>
<td>65,620</td>
</tr>
<tr>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Thyroid</td>
</tr>
<tr>
<td>60,190</td>
<td>40,170</td>
</tr>
<tr>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>Melanoma of the skin</td>
</tr>
<tr>
<td>45,520</td>
<td>46,100</td>
</tr>
<tr>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>Non-Hodgkin lymphoma</td>
</tr>
<tr>
<td>42,380</td>
<td>34,860</td>
</tr>
<tr>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>Kidney &amp; renal pelvis</td>
</tr>
<tr>
<td>58,380</td>
<td>28,900</td>
</tr>
<tr>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>Pancreas</td>
</tr>
<tr>
<td>35,470</td>
<td>27,200</td>
</tr>
<tr>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Leukemia</td>
</tr>
<tr>
<td>30,400</td>
<td>25,060</td>
</tr>
<tr>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>All sites</td>
<td>All sites</td>
</tr>
<tr>
<td>893,660</td>
<td>912,930</td>
</tr>
</tbody>
</table>

80,000 new cases/year
20,000 deaths/year

662,789 people living with lymphoma

Etiology

- Increasing age
- Abnormalities of the immune system
  - Inherited
  - Related to treatment of another condition
  - Acquired (HIV)
- Viruses
  - Hepatitis B and C
  - Human herpes virus 6
- Exposure to certain chemicals
- Bacteria
  - Helicobacter pylori
Age Distribution of NHL vs. HL

- NHL: ~80,000 cases/year
- HD: ~9000 cases/year
DIAGNOSIS
"Tissue is the issue," and "more is better"

<table>
<thead>
<tr>
<th></th>
<th>PRO</th>
<th>CON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fine needle aspirate</td>
<td>• can distinguish lymphoma from other cancers</td>
<td>• Unable to give architectural detail</td>
</tr>
<tr>
<td></td>
<td>• Quick, easy, office-based</td>
<td>• Insufficient for most prognostic tests</td>
</tr>
<tr>
<td>Core needle biopsy</td>
<td>• Can be done in hard to reach places (stomach, spinal cord)</td>
<td>• Unable to give architectural detail</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insufficient for most prognostic tests</td>
</tr>
<tr>
<td>Incisional or excisional biopsy</td>
<td>• Gold standard</td>
<td>• May be more invasive</td>
</tr>
<tr>
<td></td>
<td>• Allows architectural evaluation</td>
<td>• May require surgery and anesthesia</td>
</tr>
<tr>
<td></td>
<td>• Allows tests for prognosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can be used for research</td>
<td></td>
</tr>
</tbody>
</table>
Excisional lymph node biopsy

nodular

diffuse
NHL Classification Systems

• 1970’s:
  – Rappaport classification
  – Kiel classification
  – Lukes & Collins classification
  – British National Lymphoma classification
  – Dorfman classification

• 1981:
  – Working formulation

• 1990’s:
  – Updated Kiel classification
  – REAL classification

• **2001, 2008, 2017**: WHO classification

1. Overall pattern
2. Cell size
3. Nuclear shape
Working formulation

1. Overall pattern
2. Cell size
3. Nuclear shape

Overall architectural pattern

Cell size

Shape of the nucleus

Follicular (or nodular)
Diffuse

Small  Intermediate  Large

Cleaved  Non-cleaved
Conceptual approach to lymphomas

- Clinical behavior
- B-cell development
- WHO classification
Conceptual approach to lymphomas: clinical behavior

Low grade/indolent lymphoma
1. Slow growing
2. Incurable
3. More common in elderly

Intermediate grade/aggressive lymphoma
1. Fast growing
2. Potentially curable
3. Occurs in all age groups

High grade/highly aggressive lymphoma
1. Very fast growing
2. Highly curable
3. Bimodal peak (i.e. Burkitt lymphoma)

MCL?

T-NHL?
Conceptual approach to B-NHL: normal B-cell development

Mantle zone

Conceptual approach to B-NHL: normal B-cell development

Lymph Node

Ig gene rearrangements, V-region gene recombination

B-cell precursor

Naïve B cell

No BCR

Apoptosis

Somatic hypermutation

Clonal expansion

Mutations that increase antigen affinity

Class switching

Mutations that reduce antigen affinity

Clonal expansion

Selection

Differentiation

Apoptosis

Plasma cell

Memory B cell

Light zone

FDC

T cell

Cellular Origin of B-Cell Lymphomas

Most B-Cell Lymphomas Are Derived From the Germinal Center

Conceptual approach to lymphoma: WHO classification

• Lineage is the starting point of disease definition
  – B, T, or NK cells

• Each disease is a distinct entity based on a constellation of clinical and laboratory features
  – Morphology
  – Immunophenotype
  – Genetic features
  – Clinical presentation and course

• Site of involvement is often a signpost for important biological distinctions

Use of clinical features is a novel aspect; diagnosis is not made in vacuum
There are nearly 100 types of lymphoma

Goals of therapy vary by histology and expected clinical behavior:
- Curative intent
- Palliative intent

WHO Classification of Lymphoid Malignancies 2008, 2016 update
There are many ways to slice the “lymphoma pie”

- B-cell
- T-cell
- NK-cell

- Hodgkin lymphoma
- Non-Hodgkin lymphoma
Treatment: General Principles

• Accurate histologic diagnosis essential
• Treatment decisions based primarily on HISTOLOGY rather than STAGE
  – Age
  – Pace of illness
  – Systemic symptoms
Goal of treatment depends on the disease

- **DLBCL**: Goal is CURE
- **Hodgkin**: Goal is symptom management
- **FL**: Goal is symptom management
- **TCL**: Goal is palliation, prolongation of survival
- **MCL**: Goal is palliation, prolongation of survival
Type of treatment depends on the disease

- **DLBCL**
  - Combination chemotherapy, stem cell transplant

- **Hodgkin**
  - Observation, monoclonal antibodies, targeted agents, chemoimmunotherapy

- **FL**

- **TCL**

- **MCL**
  - Aggressive chemotherapy, stem cell transplant
Most common NHL, peak incidence 6th decade
Large cells with loss of follicular architecture of node
May present as extranodal disease (stomach, CNS, testis, skin)
Median survival, weeks to months if not treated
Immunophenotype: CD19+, CD20+, CD22+, CD79a+
Cytogenetics: t(14;18) in 20-30%; 3q27 in 30%
Curable in 30-90%
DLBCL: a study in clinical and biologic heterogeneity

Clinicopathologic subtypes (PMBL, PCNSL, 1⁰ testicular lymphoma, IVL, PEL)

Genomic variants
Gene expression profiling subtypes

Morphologic variants

Neoplasm of large B lymphoid cells with a diffuse growth pattern

Altered protein expression
2002+: Rituximab plus CHOP-like regimens improves overall survival
CAN WE MOVE BEYOND R-CHOP?
Challenging R-CHOP

DA-EPOCH-R

Add biologic agents

Obinutuzumab

Consolidation

2020: R-CHOP-21 remains the standard of care
Possible reasons for equivalent outcomes

• Trials enrolled all-comers with DLBCL
  – Not stratified for GC and non-GC
  – Inadvertent inclusion of double hit lymphomas
  – Mixture of DEL and non DEL
• Not powered to detect differences based on outcomes of subgroups
• Unexpectedly good outcomes for the control arm

ABBREVIATIONS: DLBCL, diffuse large B-cell lymphoma; GC, germinal center; DEL, dual expression lymphoma
Retrospective data identifies high-risk groups unlikely to be cured with R-CHOP

<table>
<thead>
<tr>
<th>SUBSET</th>
<th>FREQ</th>
<th>R-CHOP</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CR</td>
<td>PFS</td>
<td>OS</td>
</tr>
<tr>
<td>ABC DLBCL</td>
<td>30-50%</td>
<td>NR</td>
<td>2-yr 28%</td>
<td>2-yr 46%</td>
</tr>
<tr>
<td>Double hit lymphoma</td>
<td>3-12%</td>
<td>40%</td>
<td>1-yr %</td>
<td>&lt;1yr</td>
</tr>
<tr>
<td>Dual expression of MYC/BCL2</td>
<td>21%</td>
<td>NR</td>
<td>5-yr 27%</td>
<td>5-yr 30%</td>
</tr>
<tr>
<td>Elderly DLBCL&gt;60y</td>
<td>50%</td>
<td>70-80%</td>
<td>5-yr 50%</td>
<td>5-yr 58%</td>
</tr>
<tr>
<td>High IPI</td>
<td>45%</td>
<td>NR</td>
<td>4-yr 53%</td>
<td>4-yr 55%</td>
</tr>
</tbody>
</table>

*DPL: dual protein expression of MYC and BCL2
Cell-of-origin (COO) model: there are two biologic subgroups in DLBCL


Two molecular subtypes with disparate outcomes
Cell of origin Subtypes of DLBCL: Immunophenotypic Classification

**Figure 4.** Immunohistochemical algorithm to identify germinal center B-cell like DLBCL (GCB) from non-germinal center B-cell like DLBCL.

- **CD10**
  - pos
  - neg

- **GCB**
  - pos

- **BCL6**
  - pos
  - neg

- **Non-GCB**
  - neg

- **MUM1/IRF1**
  - pos
  - neg

- **GCB**

Approximately 20% error rate

Beyond Cell of Origin: 
*MYC* and *BCL2* abnormalities

- Either the GENES or the PROTEINS can be abnormal
- If it’s the GENES/CHROMOSOMES: “Double Hit Lymphoma”
- If it’s the PROTEINS WITHOUT THE GENES: DLBCL with dual expression “dual expressor lymphoma”
Diffuse large B-cell lymphoma, NOS

- Distinction of GCB vs ABC/non-GC type required with use of immunohistochemical algorithm acceptable, may affect therapy.
- Coexpression of MYC and BCL2 considered new prognostic marker (double-expressor lymphoma).
- Mutational landscape better understood but clinical impact remains to be determined.

### Approximately 25-30% of DLBCL have dual protein expression

- **BCL2 ≥ 50%**
- **MYC ≥ 40%**
Double-hit lymphoma vs. DLBCL, not otherwise specified with dual expression of MYC and BCL2

Double-hit lymphoma
- High grade B-cell lymphoma with translocations of MYC, BCL2, +/- BCL6
- Accounts for 5-7% of all DLBCL
- New category:
  - 2016 WHO category: “High grade B-cell lymphoma, with rearrangements of MYC and BCL2 and/or BCL6”
- Outcome poor with standard therapies

Double-expressing lymphomas
- DLBCL with immunohistochemical expression of MYC (≥40%) and BCL2 (≥50% recommended in 2016 WHO revision) in the absence of translocations
- Accounts for 20-30% of all DLBCL
- Not a distinct entity but an adverse prognostic factor
- Outcome inferior to other DLBCLs treated with R-CHOP, but not as poor as DHL

Majority are germinal center DLBCL

Majority are non-germinal center DLBCL
R-CHOP is insufficient in DHL

R-CHOP was inferior to intensive treatment: HR 0.53 (95% CI 0.29-0.98, P 5 .042).
R-CHOP is insufficient in DHL

CNS PROPHYLAXIS
Who needs CNS prophylaxis?

- Kidney and/or adrenal involvement
- Age > 60 years
- LDH > normal
- PS > 1
- Stage III/IV disease
- EN involvement

Schmitz JCO 2016
Who needs CNS prophylaxis?

Double hit lymphoma

Median OS 45 months


Double expression lymphoma

Median OS 14 months

Savage et al. Blood 2016.127.2182-2188
Suggested treatment approach for aggressive B-cell lymphomas: 2017

• Diffuse large B-cell lymphoma
  – Cell of origin
    • GCB vs. non-GCB
  – Double expressor
    • MYC and BCL2 protein overexpression

• High grade B-cell lymphoma with MYC, BCL2 and/or BCL6 rearrangements
  – Double/Triple hit lymphoma

R-CHOP

❑ Intensive therapy
❑ Consider CNS prophylaxis

Slide courtesy of Paul Barr
WHAT IF THE DISEASE DOES NOT RESPOND OR COMES BACK?
“Treatment Algorithm” for DLBCL

“R-CHOP”

CR

Cure

Relapse

Salvage regimen

chemoresistant

chemosensitive

HDT/AutoSCT

Cure

Relapse

Primary refractory

?
Autologous stem cell transplant is based on the concept that “more is better”

There are 4 main parts:
- “Salvage” chemotherapy
- Stem cell collection (“mobilization”)
- Delivery of high dose chemotherapy with autologous stem cell rescue
- Post transplant recovery and immunizations

It works best if:
- Disease responds to salvage chemotherapy
- There is no bone marrow involvement
- Patient is in good condition to receive high doses of chemotherapy

CORAL: outcome by prior rituximab exposure and time to relapse

Outcome by prior rituximab AND relapse < 12 months

Outcome by prior rituximab AND relapse > 12 months
Expected survival for rel/ref DLBCL

Patients unable to undergo autologous stem cell transplant have median survivals < 1 year

Crump Blood Aug 3, 2017, pre-pub
CAR-T cell therapy

- Uses a patient’s own T-cells instead of stem cells
- Does not require the disease to be in remission
- Uses less chemotherapy than an autologous stem cell transplant
- A “living drug”
- Has different risks:
  - Cytokine release syndrome (CRS)
  - Neurotoxicity
CAR-T cell process

CAR T-cell Therapy

Remove blood from patient to get T cells

Make CAR T cells in the lab
- Insert gene for CAR

CAR T cell
- Chimeric antigen receptor (CAR)

CAR T cells bind to cancer cells and kill them

Grow millions of CAR T cells

Infuse CAR T cells into patient

CD19 Directed CAR T Cell Products in Clinical Development

- **NCI**
  - Gene transfer: Retrovirus
  - CD19 Ab, Hinge, Transmembrane, Signal 2, Signal 1
  - Kite Pharma KTE-C19
  - Axicabtagene ciloleucel
  - Axi-cel

- **U Penn**
  - Gene transfer: Lentivirus
  - CD28, CD8a
  - Novartis CTL-019
  - Tisagenlecleucel

- **FHCRC / SCH**
  - Gene transfer: Lentivirus
  - CD28, CD8
  - Juno Therapeutics JCAR017 (CD4:CD8 = 1:1)
  - Lisocabtagene maraleucel
  - Liso-cel

Adapted from van der Steeg et al. Nat Rev Drug Discov, 2015
2-year follow up of ZUMA-1

Progression-Free Survival

Median PFS (95% CI), months
5.9 (3.3 – 15.0)

- The 6-month plateau was largely maintained, with only 10 patients progressing beyond the 6-month follow-up

NR, not reached; PFS, progression-free survival.
JULIET: Median Duration of Response

- No relapses were observed beyond 11 months after infusion
- 54% (15/28) of patients who had achieved a PR converted to CR
Response and Durability by IRC Assessment

Efficacy-Evaluable Patients (N=256)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (95% CI)</td>
<td>73% (67–78)</td>
</tr>
<tr>
<td>CR rate (95% CI)</td>
<td>53% (47–59)</td>
</tr>
<tr>
<td>Time to first CR or PR, median (range), months</td>
<td>1.0 (0.7–8.9)</td>
</tr>
<tr>
<td>DOR at 6 months (95% CI), %</td>
<td>60.4 (52.6–67.3)</td>
</tr>
<tr>
<td>DOR at 12 months (95% CI), %</td>
<td>54.7 (46.7–62.0)</td>
</tr>
</tbody>
</table>

Efficacy among patients who received nonconforming product (n=25) was similar to those who received liso-cel

Ci, confidence interval; CR, complete response; DOR, duration of response; IRC, independent review committee; NR, not reached; ORR, objective response rate; PR, partial response.

Permission for Celgene to distribute these slides was granted by the lead author.
# Efficacy of CAR T-Cell Therapy in B-NHL

<table>
<thead>
<tr>
<th></th>
<th>Axicabtagene Ciloleucel</th>
<th>Tisagenlecleucel</th>
<th>Lisocabtagene Maraleucel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median follow-up</td>
<td>24 months</td>
<td>18 months</td>
<td>12 months</td>
</tr>
<tr>
<td>Best ORR</td>
<td>74%</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>Best CR Rate</td>
<td>54%</td>
<td>32%</td>
<td>59%</td>
</tr>
<tr>
<td>Median PFS</td>
<td>5.9 months</td>
<td>2.9 months</td>
<td>_______</td>
</tr>
<tr>
<td>Median OS</td>
<td>NR</td>
<td>12 months</td>
<td>NR</td>
</tr>
<tr>
<td>Durable ORR</td>
<td>36%</td>
<td>34%</td>
<td>49%</td>
</tr>
<tr>
<td>Durable CR Rate</td>
<td>35%</td>
<td>29%</td>
<td>46%</td>
</tr>
</tbody>
</table>

KYMRIAH [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2017/2018
YESCARTA [package insert]. Santa Monica, CA: Kite Pharma, Inc.; 2017
Neelapu SS, et al. Presented at 59th American Society of Hematology Annual Meeting; December 9-12, 2017; Atlanta, GA. Abstract 578.
Abramson JS, et al. Presented at 2018 American Society of Clinical Oncology Annual Meeting; June 1-5, 2018; Chicago, IL. Abstract 7505.
No standard of care—goal is palliation

- **Clinical trials**
- Chemoimmunotherapy
  - Gemcitabine-based regimens
  - Pola-BR
- Non-chemotherapy options
  - Selinexor
  - Tafasitamab-lenalidomide (FDA-approved 7/31/2020)
    - *Ibrutinib (preferential activity in non-GC DLBCL)*
    - *Len/rituximab (preferential activity in non-GC DLBCL)*
- Best supportive care

*not FDA-approved*
Pola-BR: anti CD79b ADC plus BR

- Primary endpoint CR rate at EOT
- Med f/u 22.3 months
### RP2: Pola-BR vs. BR

<table>
<thead>
<tr>
<th></th>
<th>Pola-BR (n=40)</th>
<th>BR (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>67y (33-86)</td>
<td>71y (30-84)</td>
</tr>
<tr>
<td>Male</td>
<td>70%</td>
<td>62.5%</td>
</tr>
<tr>
<td>PS 0-1</td>
<td>83%</td>
<td>78%</td>
</tr>
<tr>
<td>ABC-DLBCL</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>GCB-DLBCL</td>
<td>38%</td>
<td>43%</td>
</tr>
<tr>
<td>Med prior Rx</td>
<td>2 (1-7)</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>Ref to last Rx</td>
<td>75%</td>
<td>85%</td>
</tr>
<tr>
<td>DOR to last Rx &lt;12 m</td>
<td>45%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Main reasons for transplant ineligibility include advanced age and insufficient response to prior salvage therapy.

Sehn *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507.
# Pola-BR vs. BR Results

<table>
<thead>
<tr>
<th></th>
<th>Pola-BR (n=40)</th>
<th>BR (n=40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOT Response % (ORR/CR)</td>
<td>45/40</td>
<td>18/18</td>
</tr>
<tr>
<td>Best response % (ORR/CR)</td>
<td>63/50</td>
<td>25/23</td>
</tr>
<tr>
<td>Med DR</td>
<td>12.6</td>
<td>7.7m</td>
</tr>
<tr>
<td>Med PFS</td>
<td>9.5m</td>
<td>3.7m</td>
</tr>
<tr>
<td>Med OS</td>
<td>12.4m</td>
<td>4.7m</td>
</tr>
</tbody>
</table>

Sehn *Journal of Clinical Oncology* 36, no. 15_suppl (May 20, 2018) 7507-7507.
Selinexor is an oral selective XPO1 inhibitor; preclinical data support that XPO1 inhibition:

- Reactivates multiple TSPs relevant to NHL, (p53, p21, IκB, FOXO etc.)
- Disrupts localization of eIF4e (overexpressed in most B-cell lymphomas)$^1$
- Reduces c-Myc, Bcl-2, and Bcl-6 levels$^{2-3}$

Exportin 1 (XPO1 or CRM1) mediates the nuclear export of proteins, mRNAs, rRNAs, snRNAs and impacts:

- **Tumor suppressor proteins** (p53, IκB, FOXO etc.)
- **eIF4E** (Translational initiation factor) bound oncogenic mRNAs (c-Myc, Bcl-xL, cyclins etc.)
SADAL: Phase 2b trial of selinexor monotherapy

Objectives:

- **Primary Endpoint:** Overall response rate (ORR): Independent Central Radiological Review (ICRR); Lugano Classification (2014)
- **Secondary Endpoints:** Duration of response (DOR), Overall survival (OS), Safety

**Modified Intent to Treat (mITT) Population:** All patients who were randomized to the 60 mg Arm

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled as of April 3, 2019</td>
<td>127</td>
</tr>
<tr>
<td>Median Age, Years (Range)</td>
<td>67 (35–87)</td>
</tr>
<tr>
<td>Males (%) : Females (%)</td>
<td>75 (59%) : 52 (41%)</td>
</tr>
<tr>
<td>Median Years from DLBCL Diagnosis (Range)</td>
<td>2.6 yrs (&lt;1–26.2)</td>
</tr>
<tr>
<td>De novo DLBCL : Transformed DLBCL : Unknown</td>
<td>96 (76%) : 30 (24%) : 1 (&lt;1%)</td>
</tr>
<tr>
<td>GCB Subtype : Non-GCB Subtype : Unclassified</td>
<td>59 GCB : 63 Non-GCB : 5 Unclassified</td>
</tr>
<tr>
<td>Median Prior Treatment Regimens (Range)</td>
<td>2 (1–6)</td>
</tr>
<tr>
<td>Prior Transplantation</td>
<td>39 (31%)</td>
</tr>
</tbody>
</table>
Selinexor dosing is 60mg BIW with 17% stopping due to A/Es
• ORR 29% (CR 13%)
• Median DOR 9.3 months and for CR 23 months
• Main toxicities: asthenia, nausea, weight loss, cytopenias
Tafasitamab MOA

**MOR208**
Fc-enhanced, anti-CD19 mAb

- ADCC ↑
- ADCP ↑
- Direct Cell Death
- Encouraging single agent activity in NHL patients with long DoR in R/R DLBCL

**Lenalidomide**

- T and NK Cell Activation/Expansion
- Direct Cell Death
- Demonstrated activity as an anti-lymphoma agent, alone or in combination
- Approved for treatment of MCL and FL/MZL

Potentiation of activity by combining Tafasitamab & LEN in vivo and in vitro

Salles et al. ICML 2019. #124.
Horton et al., 2008; Awan et al., 2010; Richter et al., 2013; MorphoSys data on file; Wu et al., 2008; Lapalombella et al., 2008; Zhang et al., 2013, Wiernik et al., 2008; Witzig et al., 2011; Czuczman et al., 2017; Jurczak et al, 2018
L-MIND: Study Design

- **R-R DLBCL**
  - 1-3 prior regimens
  - not eligible for HDCT and ASCT
  - primary refractory patients were to be excluded

- **Cycle 1-3**
  - Tafasitamab
    - 12 mg/kg
    - d 1, 8, 15, 22*
  - Lenalidomide
    - 25 mg/d p.o.
    - d 1-21

- **Cycle 4-12**
  - Tafasitamab
    - 12 mg/kg
    - q4w; d 1, 15

- **Cycle 12+**
  - Tafasitamab
    - 12 mg/kg
    - d 1, 15

  **≥SD**

  Until progression

**Primary endpoint**
- ORR (Central read)

**Secondary endpoints**
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

- Sample size suitable to detect ≥15% absolute increase in ORR for Tafasitamab/LEN combination vs. LEN monotherapy at 85% power, 2-sided alpha of 5%

- **Mature Data:** Primary Endpoint Analysis with data cut-off 30 Nov 2018; minimum Follow-Up 12 months, median Follow-Up 17.3 months

- Primary refractory DLBCL was defined as no response to or progression-relapse during or within 6 months of frontline therapy.
- Response assessment (Cheson 2007 Criteria) was after cycles 2, 4, 6, 9 and 12, thereafter every 3 cycles.
- ASCT, autologous stem cell transplant; HDCT, high-dose chemotherapy; SD, stable disease, p.o., per os.

- Salles et al. ICML 2019. #124.
**L-MIND: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Specification</th>
<th>n=81 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male, Female</td>
<td></td>
</tr>
<tr>
<td><strong>Age [years]</strong></td>
<td>median (range)</td>
<td>72 (41-86)</td>
</tr>
<tr>
<td>Risk (IPI)*</td>
<td>0-2, 3-5</td>
<td>40 (49), 41 (51)</td>
</tr>
<tr>
<td>Ann Arbor Stage*</td>
<td>I-II, III-IV</td>
<td>20 (25), 61 (75)</td>
</tr>
<tr>
<td>Elevated LDH*</td>
<td>Yes, No</td>
<td>45 (56), 36 (44)</td>
</tr>
<tr>
<td><strong>Prior Lines</strong></td>
<td>median</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>40 (49)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>35 (43)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>5 (6)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Primary Refractory</td>
<td>Yes, No</td>
<td>15 (18), 66 (82)</td>
</tr>
<tr>
<td>Refractory to last prior therapy*</td>
<td>Yes, No</td>
<td>36 (44), 45 (56)</td>
</tr>
<tr>
<td>Prior SCT</td>
<td>Yes, No</td>
<td>9 (11), 72 (89)</td>
</tr>
<tr>
<td>Cell of Origin (Centrally assessed - Hans algorithm)</td>
<td>GCB, Non-GCB, Unknown</td>
<td>37 (46), 20 (25), 24 (30)</td>
</tr>
</tbody>
</table>

*at study entry

--

Salles et al. ICML 2019. #124.
### L-MIND: Treatment-Emergent AEs

<table>
<thead>
<tr>
<th>Hematologic TEAEs in ≥10% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Anaemia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Leukopenia</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Non-hematologic TEAEs in ≥10% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Asthenia</td>
</tr>
<tr>
<td>Cough</td>
</tr>
<tr>
<td>Oedema peripheral</td>
</tr>
<tr>
<td>Pyrexia</td>
</tr>
<tr>
<td>Rash</td>
</tr>
<tr>
<td>Decreased appetite</td>
</tr>
<tr>
<td>Hypokalemia</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Back pain</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Nausea</td>
</tr>
<tr>
<td>Muscle spasm</td>
</tr>
<tr>
<td>Bronchitis</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>Dyspnoea</td>
</tr>
</tbody>
</table>

- 37 patients (43%) required LEN dose reduction
- 62/80 patients (78%) were able to stay at dose ≥20mg/d

5 infusion-related reactions in 5 patients (6%) were reported for Tafasitamab (all grade 1)
- Treatment-related SAEs occurred in 15 (18.5%) patients (primarily infections [10%] or neutropenic fever [5%])
- 4 treatment-emergent deaths (sudden death, respiratory failure, cerebrovascular accident, PML) were reported as unrelated to study drugs

N=81. TEAEs, treatment-emergent adverse events, numbers represent % patients

- Salles et al. ICML 2019. #124.
L-MIND: Efficacy

**Key Outcomes:**

- ORR 60%**
- CR 42.9%
- Med DR 21.7m
- Med PFS 12.1m
- 12m OS 73.7%

Treatment considerations in relapsed aggressive B-cell lymphomas

Initial Treatment

- Relapse
  - Early Relapse
  - Late relapse

- Refractory

Candidate for aggressive treatment

Chemosensitive:
- AutoHCT

Chemo-resistant:
- CAR-T

Not candidate for aggressive treatment

- Chemotherapy
- Pola-BR
- Selinexor
- Tafasitamab LENALIDOMIDE
- CLINICAL TRIAL!!

*not FDA-approved
The University of Chicago Lymphoma Program

Not pictured: Rachel Kraft, Michelle Rainer, Amy Wang
Questions?