Updates in Diffuse Large B-cell Lymphoma

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Outline

1. Updates in Stratification and Prognostication
2. Updates in Frontline Treatment
3. Updates in CNS relapse prevention
4. Updates in R/R Setting
Most Common Subtypes of NHL

- Mantle cell (6%)
- Follicular (25%)
- SLL/CLL (7%)
- MALT-type marginal-zone B cell (7.5%)
- Nodal-type marginal-zone B cell (<2%)
- Lymphoplasmacytic (<2%)
- Burkitt (2.5%)
- Other subtypes (9%)
- T and NK cell (12%)
- Diffuse large B-cell (30%)

WHO 2016: Refinements of aggressive B-cell lymphomas classification

- DLBCL: Distinction between ABC and GCB subtypes (IHC algorithms acceptable)
- DLBCL double expressor (MYC and BCL2)
- High grade B-cell lymphomas with MYC-R, BCL2-R and/or BCL6-R
- High grade B-cell lymphomas NOS (replaces BCLU)

DLBCL is a molecularly heterogeneous disease; certain patient subsets do worse

Patients with ABC DLBCL are less likely to be cured by R-CHOP

“Double-Hit” (Myc + Bcl-2) carries worst prognosis

Additional Unmet Need
- Primary refractory or first relapse within 12 months
- High IPI score at relapse
- Transformed lymphoma
- Relapse post ASCT or not ASCT eligible
Evolving role of NGS in aggressive B-cell lymphomas classification

![Diagram showing the role of NGS in aggressive B-cell lymphomas classification.](image)
### Implications of DLBCL subtypes and potential therapies

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Prevalence</th>
<th>5-yr overall survival</th>
<th>Genetic themes</th>
<th>Genetically related lymphomas</th>
<th>Gene expression signatures</th>
<th>Potential therapeutic targets</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>8.7%</td>
<td>40% (All) 37% (ABC)</td>
<td>Myc-T-Bcl-dependent NF-κB dependent</td>
<td>BM-Maturation</td>
<td>B cell activation</td>
<td>BCR-dep. NF-κB, PI3 kinase, mTORC1, BCL2, BCL6, MCL1, JAK1, IRAK4, IRF4</td>
</tr>
<tr>
<td>N1</td>
<td>1.7%</td>
<td>27% (All) 22% (ABC)</td>
<td>NOTCH1 signaling</td>
<td>Altered B cell differentiation</td>
<td>NOTCH1-mutant CLL</td>
<td>NOTCH1 Quiescence, Plasma cell, T cell-myeloid-FDC</td>
</tr>
<tr>
<td>A53</td>
<td>5.8%</td>
<td>63% (All) 33% (ABC) 100% (GCB)</td>
<td>TP53 inactivation/DNA damage Aneuploidy Immunodeficiency</td>
<td>B cell activation</td>
<td>p53 low</td>
<td>BCR-dep. NF-κB</td>
</tr>
<tr>
<td>BN2</td>
<td>13.3%</td>
<td>67% (All) 76% (ABC) 100% (GCB) 38% (UC)</td>
<td>NOTCH2 signaling</td>
<td>Altered B cell differentiation BCR-dependent NF-κB</td>
<td>MZL Transformed MZL</td>
<td>B cell activation</td>
</tr>
<tr>
<td>ST2</td>
<td>6.4%</td>
<td>84% (All) 81% (GCB)</td>
<td>JAK/STAT3 signaling</td>
<td>NF-κB activation</td>
<td>NLPHD THRLBCL</td>
<td>GC B cell PI3K signaling, JAK2 signaling, Glycosylation, Stromal</td>
</tr>
<tr>
<td>GCB</td>
<td>5.9% (MYC+) 17.6% (MYC-) 48% (MYC+) 82% (MYC-)</td>
<td>Chromatin modification Anti-apoptosis</td>
<td>STIP1 – GNA13 inactivation</td>
<td>B cell activation</td>
<td>P13 kinase JAK2</td>
<td></td>
</tr>
<tr>
<td>MYC+</td>
<td></td>
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<tr>
<td>MYC-</td>
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<tr>
<td>MYC</td>
<td></td>
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</tr>
</tbody>
</table>
Double-Hit Signature With TP53 Abnormalities Predicts Poor Survival in Patients With Germinal Center B-Cell Like (GCB) DLBCL Treated With R-CHOP

Background
Genomic analysis of cases of de novo GCB DLBCL, including those patients with DH lymphoma (presence of MYC and BCL2 and/or BCL6 translocations)
The objective was to develop a molecular subtyping schema to risk-stratify patients with GCB DLBCL treated with R-CHOP

Results
87 non GCB DLBCL cases divided into 4 groups:
- GCB1 (DH positive, TP53 inactivation): poor survival
- GCB2 (DH positive, TP53 wildtype): good survival
- GCB3 (DH negative, EZH2 mutation and/or BCL2 translocation): intermediate survival
- GCB4 (DH negative, without EZH2 mutation or BCL2 translocation): excellent survival

Song et A. ASH Meeting Abstracts 2020: 533
Updates in Frontline DLBCL Treatment
<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>ORR (CR) %</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>**PYRAMID (bortezomib- non GCB)**1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VR-CHOP (n=92)</td>
<td>96 (56)</td>
<td>2-yr: 82%</td>
<td>2-yr: 93%</td>
</tr>
<tr>
<td>R-CHOP (n=91)</td>
<td>98 (49)</td>
<td>2-yr: 78% p=0.611</td>
<td>2-yr: 88%; p= 0.763</td>
</tr>
<tr>
<td><strong>CALGB/Alliance 50303</strong>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CHOP (n= 233)</td>
<td>89.3 (62.3)</td>
<td>3-yr: 81%</td>
<td>3-yr: 85%</td>
</tr>
<tr>
<td>DA-EPOCH-R (n= 232)</td>
<td>88.8 (61.1)</td>
<td>3-yr: 79%; p= 0.438</td>
<td>3-yr: 85%; p= 0.420</td>
</tr>
<tr>
<td>**GOYA (obinutuzumab)**3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CHOP (n=712)</td>
<td>77.9 (59.5)</td>
<td>3-yr: 66.5%</td>
<td>3-yr: 81.4%</td>
</tr>
<tr>
<td>G-CHOP (n=706)</td>
<td>77.4 (56.7)</td>
<td>3-yr: 69.9%; p= 0.92</td>
<td>3-yr: 81.2%; p= 1.0</td>
</tr>
<tr>
<td>**PHOENIX (ibrutinib)**4</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IR-CHOP (n=419)</td>
<td>89.3 (67.3)</td>
<td>HR: 0.949 (0.704–1.279) (p= 0.731)</td>
<td>HR: 0.991 (0.712-1.183) (p= 0.959)</td>
</tr>
<tr>
<td>R-CHOP (n=419)</td>
<td>93.1 (68.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>**ROBUST (lenalidomide)**5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R2-CHOP (n=285)</td>
<td>91 (65)</td>
<td>HR: 0.85 (0.63-1.14) (p = 0.29)</td>
<td>2-yr: 79%</td>
</tr>
<tr>
<td>R-CHOP (n= 285)</td>
<td>91 (64)</td>
<td></td>
<td>2-yr: 80%; p= NS</td>
</tr>
<tr>
<td>**REMARC (lenalidomide maintenance)**6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R-CHOP → Len (n= 323)</td>
<td></td>
<td>2-yr: 80%</td>
<td>2-yr: 89%</td>
</tr>
<tr>
<td>R-CHOP → Px (n= 327)</td>
<td></td>
<td>2-yr: 75%, p= 0.0135)</td>
<td>2-yr: 87%, p= NS</td>
</tr>
</tbody>
</table>

Does lenalidomide + R-CHOP improve outcomes in DLBCL?

**ROBUST: R2-CHOP vs R-CHOP**

- 2-y PFS: 67%
- Placebo/R-CHOP

**ECOG E1412: R2-CHOP vs R-CHOP**

- 2-y PFS: 76%
- 2-y PFS: 69%

Does lenalidomide + R-CHOP improve outcomes in DLBCL?

**ROBUST: R2-CHOP vs R-CHOP**

- Phase III (Only ABC by GEP (NanosTring))
- N= 570 (R-CHOP: 285, R2-CHOP= 285). Primary endpoint: PFS
- Median age 65 (21 – 83)
- IPI 3 – 5: 58%, Stage III/IV: 87%
- Median time from Dx to treatment: 31 days
- Lenalidomide dose: 15 mg d1-d14 every three weeks

**ECOG E1412: R2-CHOP vs R-CHOP**

- Phase II (all DLBCL but stratified by COO [also using GEP-NanosTring])
- Median age 66 (24 – 92)
- IPI 3-5: 66%, Stage III/IV: 97%
- Median time from Dx to treatment: 21 days
- Lenalidomide dose: 25 mg d1-d10 every three weeks

SENIOR trial: SQ rituximab-mini CHOP +/- lenalidomide in DLBCL in older than 80

- Multicenter, randomized, double-blind, placebo-controlled phase III study

**Primary endpoint**: PFS, defined as first documented relapse or progression assessed by blinded independent review, or all-cause death

**Secondary endpoints**: safety, OS, efficacy by R-CHOP response

Pts aged $\geq$ 80 yrs with untreated CD20+ DLBCL, stages II-IV, IPI $\geq$, CrCl $\geq$ 40

R2-mini CHOP*  
(n = 122)

R-mini CHOP  
(n = 127)

*Lenalidomide given 10 mg days 1-14

Follow up  
End points:  
PFS, OS, AEs

Oberic L et al J Clin Oncol 2021
SENIOR trial: Outcomes and Prognostic Factors

![Progression-free survival by arm-ABC set (Lymph2CX)](image1)

![Overall survival by arm-ABC set (Lymph2CX)](image2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPI (0-2 v 3-5)</td>
<td>0.94 (0.43 to 2.04)</td>
<td>.871</td>
</tr>
<tr>
<td>Non-ABC v ABC (Lymph2CX)</td>
<td>1.14 (0.68 to 1.92)</td>
<td>.614</td>
</tr>
<tr>
<td>IADL scale</td>
<td>0.72 (0.44 to 1.18)</td>
<td>.193</td>
</tr>
<tr>
<td>MNA (normal v malnourished)</td>
<td>1.16 (0.67 to 2.03)</td>
<td>.596</td>
</tr>
<tr>
<td>Ann Arbor stage (I-II v III v IV)</td>
<td>2.01 (0.94 to 4.32)</td>
<td>.073</td>
</tr>
<tr>
<td>Lymphocyte count (&lt; 1 v ≥1 G/L)</td>
<td>0.80 (0.50 to 1.30)</td>
<td>.373</td>
</tr>
<tr>
<td>Albumin (≤35 v &gt; 35 g/L)</td>
<td>2.08 (1.25 to 3.57)</td>
<td>.005</td>
</tr>
</tbody>
</table>

Oberic L et al *J Clin Oncol* 2021
SENIOR trial: Outcomes and Safety

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>R-miniCHOP (n=124)</th>
<th>R2-miniCHOP (n=117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3-4 (%patients)</td>
<td>71 (74%)</td>
<td>95 (81%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (18%)</td>
<td>38 (35%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (0.8%)</td>
<td>9 (7.6%)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 (0.8%)</td>
<td>3 (3.4%)</td>
</tr>
<tr>
<td>Infections</td>
<td>10 (8%)</td>
<td>16 (13.5%)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>1 (0.8%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Grade 5 (fatal)</td>
<td>7 (5.6%)</td>
<td>8 (6.8%)</td>
</tr>
</tbody>
</table>

- Lenalidomide did not improve outcomes in > 80 DLBCL
- Lenalidomide was associated with higher toxicity
- Low dosing (10mg) might have prevented efficacy
- Mini-RCHOP is well tolerated in older patients but with good PS, nutritional status and functionality.

Oberic L et al J Clin Oncol 2021
Single agent Mosunetuzumab (bi-specific antibody) for elderly/unfit patients with untreated DLBCL

- Mini R-CHOP is SOC with PFS and OS 47 and 69%, respectively
- About 30% of DLBCL pts older than 75 are unable to receive standard R-CHOP
- Frailty and comorbidities affects outcomes
- Other regimens such as BR or R-CVP, while better tolerated, have suboptimal outcomes

Olzewski A et al. ASH Meeting Abstracts 2020
GO40554: Phase I/II of mosunetuzumab for elderly/unfit 1L DLBCL

Key inclusion criteria
- Treatment naïve DLBCL or HGBL
- Age ≥80 years or 60–79 years with impairment in:
  - ≥1 ADL or
  - instrumental ADL or
  - inability to tolerate full dose CIT

Study design (1L DLBCL elderly/unfit)
- Optional pre-phase treatment with prednisone ± vincristine
- Step-up dosing of mosunetuzumab during Cycle (C) 1 D1/D8/D15
- Response assessments: at interim (C4; IRA) primary (C8; PRA), and every 6 months

Dosing schedule
- First safety cohort dose:
  C1D1: 1mg; C1D8: 2mg; C2–C8D1: 13.5mg
- Second safety cohort dose:
  C1D1: 1mg; C1D8: 2mg; C2–C8D1: 30mg
- Expansion cohort dose:
  C1D1: 1mg; C1D8: 2mg; C2–C8D1: 30mg

Olzewski A et al. ASH Meeting Abstracts 2020
GO40554: Phase I/II of mosunetuzumab for elderly/unfit 1L DLBCL

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DLBCL (n= 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age</td>
<td>82 (67 – 100)</td>
</tr>
<tr>
<td>Age &gt; 80</td>
<td>21 (72)</td>
</tr>
<tr>
<td>IPI score ≥ 3</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>ECOG/PS ≥ 2</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Stage III/IV</td>
<td>18 (62%)</td>
</tr>
<tr>
<td>DLBCL subtype</td>
<td></td>
</tr>
<tr>
<td>non GCB</td>
<td>16 (55%)</td>
</tr>
<tr>
<td>GCB</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>15 (52%)</td>
</tr>
</tbody>
</table>

- 29 patients with DLBCL enrolled (8 pts younger than 80)
- DL 1 mg → 2 mg → 13mg (n=8 pts)
- DL 1 mg → 2 mg → 30mg (n= 21 pts)
- N=7 safety cohort, N=14 expansion cohort
- 16 pts had a median of 6 cycles
- CRS: 47% (all grade 1)
GO40554: Phase I/II of mosunetuzumab for elderly/unfit 1L DLBCL

Olzewski A et al. ASH Meeting Abstracts 2020
**Mosunetuzumab + CHOP (M-CHOP) for untreated DLBCL**

**✓ N= 43**
- R/R NHL: 7 pts
- DLBCL: 43 pts

**✓ Schedule:**
- C1 Mosun step up C1D1(1mg), D8(2mg), D15(30mg). Mosun 30 mg on D1 C2-C6
- PR/SD were allowed Mosun for additional 11 cycles

**✓ General characteristics**
- Stage II-IV, median IPI 3 (2-4), median age 66

**✓ Adverse events:**
- CRS grade 1-2 53%. 1 pt received tocilizumab. No vasopressor
- No ICANS

<table>
<thead>
<tr>
<th></th>
<th>M-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Best objective response</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>R/R NHL (n=7)</td>
</tr>
<tr>
<td>Overall response</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>Complete response</td>
<td>5 (71.4)</td>
</tr>
<tr>
<td>Partial response</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>-</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1 (14.3)</td>
</tr>
<tr>
<td>Data not available (discontinued)</td>
<td>-</td>
</tr>
</tbody>
</table>

Phillips T et al. ASH Meeting Abstracts 2020
PD-1 inhibition in NHL: Potential effect on priming

- PD-1/PD-L1 inhibition appears to sensitize R/R NHL to subsequent chemotherapy
- Prior PD-1/PD-L1 inhibitor therapy induces higher responses to chemotherapy in treatment naïve solid tumors (many who are not known to be sensitive to PD-1/PD-L1 inhibition)
- There is evidence of PD-1/PD-L1 inhibition synergy with rituximab

Induction and Maintenance Avelumab Plus R-CHOP in Patients with Diffuse Large B-Cell Lymphoma (DLBCL): Phase II Avr-CHOP Study

Hawkes E et al. ASH Meeting Abstracts 2020
Avelumab Plus R-CHOP in Newly Diagnosed DLBCL (Avr-CHOP): Efficacy of priming and combination

Hawkes E et al. ASH Meeting Abstracts 2020
Phase Ib Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab or Tafasitamab + Lenalidomide with R-CHOP in Patients with Newly DLBCL: The First-Mind Trial

Estimated study start date: November 2019

**Study population**
- Treatment naïve
- Histologically confirmed DLBCL (NOS)
- Intermediate- to high-risk disease (IPI 2-5)

**Study design**

**Key eligibility criteria**

**Study countries**

**Background**

**Study rational**

**Study design**

**Arm A:**
- Six 21-day cycles of
  - Tafasitamab (12 mg/kg IV, on Days 1, 8, and 15)
  - R-CHOP
  - Mandatory G-CSF

**Arm B:**
- Six 21-day cycles of
  - Tafasitamab (12 mg/kg IV, on Days 1, 8, and 15)
  - Lenalidomide (25 mg orally, on Days 1-10)
  - R-CHOP
  - Mandatory G-CSF

**Safety run-in phase**
- 12 patients
- Safety confirmed?
- YES (+18 patients)
- Safety review

**Main phase**

**END OF STUDY**
Phase Ib Randomized Study to Assess Safety and Preliminary Efficacy of Tafasitamab or Tafasitamab + Lenalidomide with R-CHOP in Patients with Newly DLBCL: The First-Mind Trial

- 36 patients randomized; results presented for 24 patients (Arm A, n = 13; Arm B, n = 11)
- AEs:
  - Any-grade AEs: 111 in Arm A; 137 in Arm B
  - G≥3 neutropenia: 54% in Arm A; 46% in Arm B
  - G≥3 thrombocytopenia: 8% in Arm A; 18% in Arm B
- 23 SAEs were observed: 11 in Arm A; 12 in Arm B
- 1 SUSAR, *Pneumocystis jirovecii* pneumonia, was reported in Arm B
- No treatment-associated deaths occurred
CNS Relapse Prevention in Aggressive Lymphomas
Background- CNS relapse in DLBCL

- Occurs in 5% overall. It is > 10% in high risk groups (High NCCN-IPI score, high CNS IPI score, double hit lymphoma, double expressor)
- More parenchymal relapses than leptomeningeal relapses
- Current types of CNS prophylaxis:
  - *Intrathecal:* Less toxic, more accessible. CONS: invasive, minimal parenchymal penetration
  - *Intravenous:* usually HD MTX. Potentially better parenchymal penetration but requires hospitalization, could be toxic in older patients or with comorbidities.
- 15-20% of patients will receive either IT or IV CNS prophylaxis

Villa et al Ann Oncol 2010; Schmitz et al JCO 2016
CNS Prophylaxis in Aggressive Non-Hodgkin Lymphoma: A US Multicenter Retrospective Analysis

CNS relapse by prophylaxis route

Overall CNS relapse rate: 7.1%

- CNS relapse after INTRATHECAL prophylaxis: 5.5% (N=808)
- CNS relapse after INTRAVENOUS prophylaxis: 7.1% (N=216)

No significant difference between routes:
- Age
- Stage
- Histology
- Cell of origin (Hans)
- Serum LDH
- Double-hit status
- HIV status
- Number of EN sites
- Individual EN site(s)
- No. prophylaxis doses
- Frontline regimen

N=1024
CNS relapse by route: Propensity score matched analysis

Aim: retrospectively assess impact of prophylaxis route in those who are eligible for either route

Propensity Score Matching Covariates:
- Age >70
- Renal function
- Chemotherapy regimen (RCHOP v REPOCH)

Selected to reflect hypothetical eligibility for HD-MTX

Overall CNS relapse rate
N=1024
5.5%

CNS relapse after INTRATHECAL prophylaxis (N=10)
5.4%

CNS relapse after INTRAVENOUS prophylaxis (N=15)
8.0%

P=0.25

No significant difference seen across routes
Ineffectiveness of IV High-Dose Methotrexate for Prevention of CNS Relapse in Patients with High-Risk DLBCL

University of Calgary & University of Alberta
Alberta, Canada
Alberta Lymphoma Guidelines

Prophylactic HD-MTX
3.5g/m² IV x 3 doses

Intensive chemoimmunotherapy
or consolidative autotransplant

CNS-IPI score 4-6 *
Double hit lymphoma
Testicular lymphoma

High IPI score
Double hit lymphoma

* From 2012-15, HD-MTX recommended if elevated LDH, ECOG >1, and >1 extranodal site
Utilization of prophylactic HD MTX

ALG High-Risk Patients
n=326

HD-MTX
Median 2 doses (range 1-3)
n=115 (35.3%)

HD-MTX use associated with:
- Younger age (median 60 vs. 64 y)
- >1 extranodal site (85% vs. 76%)
- Kidney/adrenals involved (29% vs. 15%)
- Double hit lymphoma (39% vs. 10%)

No HD-MTX
n=211 (64.7%)

Reason for no HD-MTX:
- Not documented (n=151)
- Toxicity concerns (n=29)
- Other (n=31)
## CNS Relapse Risk By Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CNS relapse risk</th>
<th>Hazard Ratio and P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylactic HD-MTX (n=115)</td>
<td>11.2% vs. 12.2%</td>
<td>0.92 (95% C.I. 0.44-1.9)</td>
</tr>
<tr>
<td>Intensive chemoimmunotherapy (n=35)</td>
<td>5.7% vs. 12.6%</td>
<td>0.64 (95% C.I. 0.20-2.0)</td>
</tr>
<tr>
<td>Consolidative autotransplant (n=68)</td>
<td>6.0% vs. 13.7%</td>
<td>0.55 (95% C.I. 0.24-1.3)</td>
</tr>
<tr>
<td>Intensive chemo or autotransplant (n=102)</td>
<td>6.0% vs. 14.6%</td>
<td>0.47 (95% C.I. 0.19-1.1)</td>
</tr>
</tbody>
</table>
Role of cell free cfDNA as prognostic tool for CNS lymphomas

• Two-part study:
  – N= 6 patients with known CNS involvement by DLBCL
  – N= 19 patients newly diagnosed DLBCL. Underwent NGS MRD assessment

• High risk disease: high CNS-IPI score, epidural mass, histology (DHL, BL, HIV plasmablastic lymphoma)

• NGS-MRD in CSF + in all 6 patients with intraparenchymal disease

• Median follow up 11 months
  – NGS-MRD- → no CNS relapse
  – NGS-MRD+ → 2/10 CNS relapse (12-month incidence of relapse was 29%)

Olszewski et al ASH Meeting 2020
Updates in R/R DLBCL
SCHOLAR-1: Outcomes of patients with refractory DLBCL

- **SCHOLAR-1**: Poor outcomes in patients:
  - Progressive disease to R-CHOP
  - Relapse post autologous HCT < 12 months
  - Refractory to second or later line (N = 636)

- **Outcomes** (N = 636)
  - ORR = 26%
  - CR rate = 7%
  - Median OS = 6.3 mo

ZUMA-1: Axi-Cel for R/R DLBCL - PFS at 27.5 months follow up

The 6-month plateau was largely maintained, with only 10 patients progressing beyond the 6-month follow-up PFS, progression-free survival.


- Median PFS (95% CI), months: 5.9 (3.3 – 15.0)
- ~60% Disease progression after CART

Locke et al. Lancet Oncol 2018
Post CART relapse: Poor Outcomes

- **FHCRC** (n=61)
  - Early PD vs Late PD (≤ 30 days)
  - **OS from PD= 5.3 months**
  - Treatment post CART relapse
    - 2\textsuperscript{nd} CART (14), targeted therapy (14), chemotherapy (5), XRT (4), allo HCT (1), IT therapy (1)
    - No differences in OS for an specific approach

- **US CART Consortium** (n= 136)
  - Early PD vs Late PD (≤ 3 months)
  - **OS from PD= 6 months**
  - Treatment post CART relapse
    - Lenalidomide (30%), CBI (30%), chemotherapy (20%), XRT (10%)
    - ORR: CBI= 24%, Len= 20%, chemotherapy= 11%

Chow et al *Am J Hematol* 2019; Spiegel et al *ASCO Meeting Abstracts* 2019
Current non-CART approved therapies for R/R DLBCL

Lenalidomide + Tafasitamab

Polatuzumab + BR

Selinexor

Median follow up: 17.3 months
Median PFS: 12.1 months

Median follow up: 22.3 months
Median PFS: 9.5 months

Median follow up: 14.7 months
Median PFS: 2.6 months

## Summary of novel approaches for DLBCL

<table>
<thead>
<tr>
<th></th>
<th>Selinexor (N=134)</th>
<th>Polatuzumab + BR (N=40)</th>
<th>Tafasitamab + Lenalidomide (N=81)</th>
<th>Mosunetuzumab (N=274)</th>
<th>REGN1979 (&gt; 80 mg) (N=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age, years (range)</strong></td>
<td>67 (35, 91)</td>
<td>67 (33, 86)</td>
<td>72 (62, 76)</td>
<td>62 (19-96)</td>
<td>67 (30 – 38)</td>
</tr>
<tr>
<td><strong>Study Phase</strong></td>
<td>II</td>
<td>II</td>
<td>II</td>
<td>I/II</td>
<td>I/II</td>
</tr>
<tr>
<td><strong>Prior regimens, median (range)</strong></td>
<td>2 (1 - 5)</td>
<td>2 (1 - 7)</td>
<td>2 (1-4)</td>
<td>3 (1–14)</td>
<td>3 (1 – 11)</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>0</td>
<td>11 (28)</td>
<td>40 (50)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>2, n (%)</td>
<td>84 (63)</td>
<td>11 (28)</td>
<td>35 (43)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>≥3, n (%)</td>
<td>46 (34)</td>
<td>18 (45)</td>
<td>6 (7)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Type of DLBCL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De novo DLBCL, n (%)</td>
<td>101 (75)</td>
<td>38 (95)</td>
<td>74 (91)</td>
<td>117 (65)</td>
<td>61 (87.1)</td>
</tr>
<tr>
<td>Transformed DLBCL, n (%)</td>
<td>31 (23)</td>
<td>0</td>
<td>7 (9)</td>
<td>32 (17.8)</td>
<td>NR</td>
</tr>
<tr>
<td>Missing/Other, n (%)</td>
<td>2 (2)</td>
<td>2 (5)</td>
<td>NR</td>
<td>21 (11.7)</td>
<td>9 (8.2)</td>
</tr>
<tr>
<td><strong>Prior CART therapy</strong></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>30 (11.1)</td>
<td>19 (10.9)</td>
</tr>
<tr>
<td><strong>Responses</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Best ORR (%)</td>
<td>29</td>
<td>45</td>
<td>60*</td>
<td>37.1</td>
<td>57.9</td>
</tr>
<tr>
<td>Complete Response (%)</td>
<td>13</td>
<td>40</td>
<td>43</td>
<td>19.4</td>
<td>42.1</td>
</tr>
<tr>
<td>Partial Response (%)</td>
<td>16</td>
<td>5</td>
<td>18</td>
<td>17.7</td>
<td>15.8</td>
</tr>
<tr>
<td><strong>Duration of Response (median, months)</strong></td>
<td>9.3</td>
<td>12.6</td>
<td>21.7</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>DOR &gt;6 months (%)</strong></td>
<td>38</td>
<td>64</td>
<td>93</td>
<td>NR</td>
<td>100 (4 mo)</td>
</tr>
<tr>
<td><strong>Median Overall Survival, months</strong></td>
<td>9.0</td>
<td>12.4</td>
<td>Not reached</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*LMIND ORR ≥2 prior regimens  50%

Bi-Specific Antibodies
Blinatumomab: T-Cell–Engaging BiTE Antibody

- Blinatumumab is a BiTE antibody designed to direct cytotoxic T-cells to CD19-expressing cancer cells\(^1\)
- Currently indicated for treating Ph-negative relapsed/refractory B-cell precursor ALL (approved December 2014)\(^2\)
  - Administration: 28 μg/day continuous IV infusion over 28 days
- Boxed warnings: CRS and neurological toxicities

T-Cell Engager Antibody Constructs in Clinical Evaluation

Extended half-life (Fc-containing)
- TCE, TCB
- VELOCI-BI/Biclonics
- Duobody
- UniAb/UniRat

Extended half-life (serum albumin binding)
- HLE BiTE
- DART-Fc
- ADAPTIR
- XmAb
- TriTAC

Short half-life
- BiTE
- DART
- TandAb
- ATAC

Anti-tumor–associated antigen
- Anti-CD3

## Bispecific Antibodies vs CAR T-Cell Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bispecific Antibodies</th>
<th>CAR T-Cell Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preparation</td>
<td>“Off the shelf”</td>
<td>In vitro manufacturing (3-4 wks)</td>
</tr>
<tr>
<td>Dosing</td>
<td>Repetitive</td>
<td>Single (following lymphodepleting CT)</td>
</tr>
<tr>
<td>CRS incidence</td>
<td>Less</td>
<td>Greater</td>
</tr>
</tbody>
</table>

**Diagram:**
- **Bispecific antibody** targeting **Tumor cell**
- **Cytotoxic T lymphocyte**
- **CAR T Cell**
GCT3013-01: Epcoritamab (subcutaneous CD20/CD3 bi-specific antibody) for refractory NHL

- Epcoritamab: (DuoBody) BiAbs SQ administration
- Low volume (1 ml)
- Long plasma half life
- T-cell killing occurs at low CD20 expression levels
- RP2D was recommended at 48 mg

Inclusion criteria:
- Adults with R/R CD20+ B-NHL
- Prior treatment with anti-CD20 mAbs
- ECOG PS 0–2
- Measurable disease by CT, MRI, or PET/CT scan
- Adequate renal, liver, and hematologic function

Flat-dose epcoritamab administered in 28-day cycles until disease progression or unacceptable toxicity

Data cut-off: October 19, 2020

## Epcoritamab in R/R B-Cell NHL: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All Patients* (N = 68)</th>
<th>DLBCL/HGBCL (n = 46)</th>
<th>FL (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>68 (21-84)</td>
<td>68 (21-82)</td>
<td>73 (35-84)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>45 (66)</td>
<td>30 (65)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Median time since diagnosis, mos (range)</td>
<td>26.7 (6-330)</td>
<td>22.5 (6-288)</td>
<td>65.6 (14-330)</td>
</tr>
<tr>
<td>Median no. prior therapies (range)</td>
<td>3 (1-18)</td>
<td>3 (1-6)</td>
<td>5 (1-18)</td>
</tr>
<tr>
<td>Prior therapies, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Anti-CD20 mAb</td>
<td>68 (100)</td>
<td>46 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>- Anthracyclines</td>
<td>62 (89.7)</td>
<td>46 (100)</td>
<td>9 (75)</td>
</tr>
<tr>
<td>- Alkylating agents</td>
<td>67 (98.3)</td>
<td>42 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>- ASCT</td>
<td>7 (10)</td>
<td>5 (11)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>- CAR T-cell</td>
<td>6 (9)</td>
<td>5 (11)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Refractory to, n (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Most recent systemic therapy</td>
<td>59 (86)</td>
<td>42 (91)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>- Most recent anti-CD20 mAb (last line)</td>
<td>60 (88)</td>
<td>40 (87)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>- Alkylating agents</td>
<td>56 (82)</td>
<td>42 (91)</td>
<td>9 (75)</td>
</tr>
</tbody>
</table>

*Histology: DLBCL, 67.2% (de novo, 34.5%; transformed, 29.3%; unknown, n = 2); HGBCL, 5.2%; FL, 19.0%; MCL, 5.2%; MZL, 1.7%; SLL, 1.7%. Hutchings. ASH Meeting Abstracts 2020.
## Epcoritamab in R/R B-Cell NHL: Baseline Characteristics

### Median follow up (DLBCL): 7 months
- 4 pts post CART relapse: 2 CR and 2 PR

### Safety
- CRS G1-2 59%. No G ≥ 3 CRS
- No ICANS

### The RP2D was determined at 48 mg

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DLBCL (N= 46)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>12 – 60 mg</td>
</tr>
<tr>
<td></td>
<td>(n= 23)</td>
</tr>
<tr>
<td>Evaluable pts</td>
<td>22</td>
</tr>
<tr>
<td>ORR</td>
<td>15 (68%)</td>
</tr>
<tr>
<td>CR</td>
<td>10 (46%)</td>
</tr>
<tr>
<td>PR</td>
<td>5 (23%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>5 (23%)</td>
</tr>
</tbody>
</table>

Hutchings. ASH Meeting Abstracts 2020.
### Odonextamab CD20/CD3 BiAbs in B-NHL: Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odonextamab (N = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, yrs (range)</td>
<td>67 (27-89)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>96 (70.6)</td>
</tr>
<tr>
<td>ECOG PS 0/1, n (%)</td>
<td>57 (41.9)/79 (58.1)</td>
</tr>
<tr>
<td>Ann Arbor stage, n (%)</td>
<td></td>
</tr>
<tr>
<td>I-II</td>
<td>18 (13.2)</td>
</tr>
<tr>
<td>III-IV</td>
<td>118 (86.8)</td>
</tr>
<tr>
<td>Bulky disease, n (%)</td>
<td>46 (33.8)</td>
</tr>
<tr>
<td>B-NHL, n (%)</td>
<td></td>
</tr>
<tr>
<td>DLBCL</td>
<td>78 (57.4)</td>
</tr>
<tr>
<td>FL grade 1-3a</td>
<td>38 (27.9)</td>
</tr>
<tr>
<td>MCL</td>
<td>12 (8.8)</td>
</tr>
<tr>
<td>MZL</td>
<td>6 (4.4)</td>
</tr>
<tr>
<td>Other*</td>
<td>2 (1.5)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Odonextamab (N = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median prior lines of therapy, n (range)</td>
<td>3 (1-11)</td>
</tr>
<tr>
<td>Prior ASCT, n (%)</td>
<td>10 (7.4)</td>
</tr>
<tr>
<td>Prior CAR T-cell therapy,† n (%)</td>
<td>35 (25.7)</td>
</tr>
<tr>
<td>Refractory to last line of therapy, n (%)</td>
<td>109 (80.1)</td>
</tr>
<tr>
<td>Refractory to anti-CD20 antibody, n (%)</td>
<td>113 (83.1)</td>
</tr>
<tr>
<td>Refractory to alkylator therapy, n (%)</td>
<td>92 (67.6)</td>
</tr>
<tr>
<td>Double refractory to alkylator therapy and anti-CD20 antibody, n (%)</td>
<td>91 (66.9)</td>
</tr>
</tbody>
</table>

DLBCL, n = 30; FL, n = 2; MCL, n = 3. No response or relapse within ≤ 6 mos.

Odronetamab in B-NHL: Antitumor Activity in R/R DLBCL With Doses 80-320 mg (No Prior CAR T-Cells)

- **ORR**: 55% (6/11); **CR rate**: 55% (6/11); median duration of CR: not reached
  - 83% of CRs durable (ie, lasting ≥ 3 mos), ongoing up to 21 mos

Median duration follow-up: 6 mos (range: 1-24).

Odronextamab in B-NHL: Antitumor Activity in R/R DLBCL (relapse post CART) Doses 80-320 mg

- ORR: 33% (8/24); CR rate: 21% (5/24); median duration of CR: not reached
  - 100% of CRs ongoing at last tumor assessment, up to 20 mos


Median duration follow-up: 3 mos (range: 0-22).

**Odronextamab in B-NHL: Cytokine-Release Syndrome**

<table>
<thead>
<tr>
<th>CRS, n (%)</th>
<th>DLBCL (n = 78)</th>
<th>FL Grade 1-3a (n = 38)</th>
<th>Other B-NHL‡ (n = 20)</th>
<th>All Patients (N = 136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>31 (39.7)</td>
<td>13 (34.2)</td>
<td>4 (20.0)</td>
<td>48 (35.3)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>14 (17.9)</td>
<td>11 (28.9)</td>
<td>0</td>
<td>25 (18.4)</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td><strong>4 (5.1)</strong>*</td>
<td><strong>1 (2.6)</strong>†</td>
<td><strong>4 (20.0)</strong></td>
<td><strong>9 (6.6)</strong></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>1 (5.0)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>All cases</td>
<td>49 (62.8)</td>
<td>25 (65.8)</td>
<td>9 (45.0)</td>
<td>83 (61.0)</td>
</tr>
</tbody>
</table>

*Occurred during step-up dosing, n = 2 in Wk 1 (including after 1-mg initial dose), n = 2 in Wk 2. †Occurred during full-dose period (ie, Wk 3 onwards). Includes MCL, MZL, FL grade 3b, and Waldenström macroglobulinemia.

- Most CRS events mild or moderate, resolved within median 2 days (range: 1-41) with supportive care

# Bi-Specific Antibodies currently studied in DLBCL: Efficacy

<table>
<thead>
<tr>
<th>Ab type</th>
<th>CD20/CD3</th>
<th>CD20/CD3 sq</th>
<th>CD19/CD3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glofitamab</td>
<td>Mosunetuzumab</td>
<td>Odonextamab</td>
<td>Epcoritamab</td>
</tr>
<tr>
<td>Phase</td>
<td>1</td>
<td>1/1b</td>
<td>1</td>
</tr>
<tr>
<td>N</td>
<td>98</td>
<td>131</td>
<td>68</td>
</tr>
<tr>
<td>Histology</td>
<td>FL, DLBCL, TFL, other</td>
<td>DLBCL, TFL, FL, other</td>
<td>DLBCL, FL, WM, MCL, MZL</td>
</tr>
<tr>
<td>Prior Therapies</td>
<td>3 (1-13)</td>
<td>3 (1-14)</td>
<td>3 (1-11)</td>
</tr>
<tr>
<td>ORR</td>
<td>aNHL: 60.9%, DLBCL: 55%</td>
<td>DLBCL/TFL: 34%</td>
<td>DLBCL: 60%</td>
</tr>
<tr>
<td>CR</td>
<td>aNHL: 49.3%, DLBCL: 42%</td>
<td>DLBCL/TFL: 19%</td>
<td>DLBCL: 60% (&gt; 80 mg)</td>
</tr>
</tbody>
</table>

ORR, overall response rate; CR, complete response; TFL, transformed follicular lymphoma

## Bi-Specific Antibodies currently studied in DLBCL: Safety

<table>
<thead>
<tr>
<th>Antibody</th>
<th>CD20/CD3</th>
<th>CD19/CD3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CD20-TCB</td>
<td>Mosunetuzumab</td>
</tr>
<tr>
<td>N</td>
<td>64 ( &gt; 600 ug)</td>
<td>131</td>
</tr>
<tr>
<td>DLTs</td>
<td>1 at 220 ug (MI)</td>
<td>Not reported</td>
</tr>
<tr>
<td>MTD</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Grade ≥ 3AEs</td>
<td>56% (27% related)</td>
<td>55% (26% related)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>0</td>
<td>2%</td>
</tr>
<tr>
<td>CRS any</td>
<td>39%</td>
<td>23%</td>
</tr>
<tr>
<td>CRS ≥3</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>NT any</td>
<td>30% (6% related)</td>
<td>49%</td>
</tr>
<tr>
<td>NT ≥3</td>
<td>5%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Glofitamab CD20/CD3 TCD BiAbs: Duration of response and PFS in aggressive and indolent R/R NHL

Median DOR aNHL: 5.5 months
Median DOR iNHL: 10.8 months
Median duration of CR: Not reached

Median PFS aNHL: 2.9 months
Median PFS iNHL: 11.8 months

Phase II: Loncastuximab tesirine anti-CD19 ADC in R/R DLBCL
Loncastuximab for R/R DLBCL: responses by histology and DoR

- **ORRs in high-risk subgroups**: transformed disease (44.8%), aged 65–74 (45.8%), aged ≥75 (52.4%), double- or triple-hit DLBCL (33.3% [all CRs]), and prior **CAR T therapy (46.2%)**
- Any-grade TEAEs: GGT increased (40.7%), neutropenia (39.3%), thrombocytopenia (33.1%), and fatigue (27.6%)
- **G≥3 TEAEs**: neutropenia (25.5%), thrombocytopenia (17.9%), GGT increased (16.6%), and anemia (10.3%)

Carlo-Stella. EHA 2020 Abstract S233; Caimi et al. ASH Meeting Abstracts 2020
Combination studies in R/R DLBCL

• **1ViPOR (NCI study):** Phase Ib/II of venetoclax, ibrutinib, prednisone, lenalidomide and obinutuzumab. Limited duration therapy- 6 months. (n= 53 pts; 23% prior CART):
  – Non GCB → ORR: 64%, CR: 57%
  – GCB → ORR: 47%, CR: 18%

• **2Ph Ib/II Polatuzumab, venetoclax and rituximab (n= 48 pts):**
  – ORR: 65%, CR: 31%

• **3LOTIS: Loncastuximab + ibrutinib (n= 28 pts)**
  – ORR: 73.7%, CR: 45.5 %.

---

1 Melani et Al. ASH Meeting Abstracts 2020: 598; 2 Gritti et Al. ASH Meeting Abstracts 2020: 599; 3 Depaus et Al. ASH Meeting Abstracts 2020: 2099
Conclusions

• Better knowledge on the molecular and genetic aspects of DLBCL. Therapeutic implications?
• R-CHOP remains as standard of care in the DLBCL frontline setting. Future studies ongoing: POLARIX, First-MIND. ZUMA-12
• DLBCL CNS relapses represent an unmet need. The best preventive strategy remains unknown. Role of cfDNA in prognostication and treatment?
• DLBCL post CART failure has a very poor prognosis. Improving CAR-T efficacy and/or best treatment at relapse. Bi-specific antibodies and combinatorial targeted agents seem active