Aggressive B and T cell lymphomas: Treatment paradigms in 2017

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Associate Director, Meyer Cancer Center
Disclosures

Consulting advice:

Teva, Gilead, Juno, Celgene, Kite, Genmab, Nanostring, Biotest, Regeneron, Abbvie, Sutro, Sunesis, BMS
WHO Lymphoma Classification 2016

100 + entities

Table 1. 2016 WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

<table>
<thead>
<tr>
<th>Mature B-Cell Neoplasms</th>
<th>Mature T- and NK neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>T-cell prolymphocytic leukemia</td>
</tr>
<tr>
<td>B-cell prolymphocytic leukemia</td>
<td>Chronic lymphoproliferative disorder of NK cells</td>
</tr>
<tr>
<td>Monoclonal B-cell lymphocytosis</td>
<td>Aggressive NK-cell leukemia</td>
</tr>
<tr>
<td>Splenic marginal zone lymphoma</td>
<td>Systemic EBV T-cell lymphoma of childhood</td>
</tr>
<tr>
<td>Lymphoplasmacytoid lymphoma</td>
<td>HIV-associated lymphoid interstitial pneumonitis</td>
</tr>
<tr>
<td>Waldenström macroglobulinaemia</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>Monoclonal gammopathy of undetermined significance (MGUS), IgM</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Primary monoclonal gammopathy</td>
<td>Multiple myeloma</td>
</tr>
<tr>
<td>Primary immunodeficiency</td>
<td>Primary immunodeficiency</td>
</tr>
<tr>
<td>Sjögren syndrome</td>
<td>Primary immunodeficiency</td>
</tr>
<tr>
<td>Primary cutaneous CD30+ T-cell lymphoma</td>
<td>Primary cutaneous CD30+ T-cell lymphoma</td>
</tr>
<tr>
<td>Mycosis fungoides</td>
<td>Primary cutaneous NK/T-cell lymphoma</td>
</tr>
<tr>
<td>Sarcoid syndrome</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Peripheral T-cell lymphoma, NOS</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Angioimmunoblastic T-cell lymphoma</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Follicular T-cell lymphoma</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Nodal peripheral T-cell lymphoma with TFR rearrangements</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, ALK+</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Anaplastic large cell lymphoma, ALK-</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
<tr>
<td>Blastic plasmacytoid dendritic cell neoplasm</td>
<td>Primary cutaneous CD8+ T-cell lymphoma</td>
</tr>
</tbody>
</table>

Table 1. (continued)

| 100 + entities |

Table 1. (continued)

| Malignant epithelial-derived T-cell lymphoma |
| Primary T-cell lymphoma of the GI tract |
| Hodgkin lymphoma |
| Classical Hodgkin lymphoma |
| Nodular sclerosis classical Hodgkin lymphoma |
| Mixed cellularity classical Hodgkin lymphoma |
| Lymphocyte-rich classical Hodgkin lymphoma |
| Post-transplant lymphoproliferative disorders (PTLD) |
| Plasmacytic hypergamia PTLD |
| Infectious mononucleosis PTLD |
| Follicular hypergamia PTLD |
| Polylymphocytic PTLD |
| Malignant PTLD (B- and T-cell types) |
| Classical Hodgkin lymphoma PTLD |
| Histiocytic and dendritic cell neoplasms |
| Histiocytic sarcoma |
| Langhan cell histiocytosis |
| Erdheim-Chester disease |

Swerdlow et al, Blood 2016

small population, but in others associated with a lymphocytosis. In 2008 it was unknown whether MBL was a precursor of CLL, we now know that MBL precedes virtually all cases of CLL/small lymphocytic lymphoma (SLL). The updated WHO will retain the current criteria for MBL, but it will emphasize that “low-count” MBL, defined as a PB CLL count of <0.5 x 10^9/L, must be distinguished from “high-count” MBL because low-count MBL has significant differences from CLL, an extremely limited, if any, chance of progression, and up to new evidence provided does not require routine follow-up outside of standard medical care. In contrast, high-count MBL requires routine yearly follow-up, and has very similar phenotypic and genotypic features as the stage 0 CLL, although immunoglobulin heavy chain variable region (IGHV)- mutated cases are more frequent in MBL. Also impacting our diagnostic criteria, the new criteria will eliminate the option to diagnose CLL with <5 x 10^9/L PB CLL cells in the absence of extramedullary
Less precision in practice

Distribution of NHL subtypes

- Follicular lymphoma: 22%
- Diffuse large B-cell lymphoma: 31%
- Marginal zone B-cell lymphoma of MALT type: 5%
- Marginal zone B-cell lymphoma of nodal type: 1%
- Small lymphocytic lymphoma: 6%
- Lymphoplasmacytic lymphoma (LPL): 1%
- Composite lymphomas: 13%
- Other subtypes with a frequency of ≤2%: 9%
- Peripheral T-cell: 2%
- pMBLC: 6%
- Mantle cell: 6%
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
Rituximab maintenance after autologous stem cell transplantation prolongs survival in patients with mantle cell lymphoma (final result of the LyMa trial)

Steven Le Gouill, MD, PhD, Catherine Thieblemont, MD, PhD, Anne Moreau, MD, Lucie Oberic, MD, Krimo Bouabdallah, MD, Emmanuel Gyan, MD, PhD, Gandhi Damaj, MD, PhD, Vincent Ribrag, MD, PhD, Pierre Feugier, MD, PhD, Olivier Casasnovas, MD, Hacène Zerazhi, MD, Corinne Haioun, MD, PhD, Hervé Maisonneuve, MD, Eric Van Den Neste, MD, PhD, Olivier Tournilhac, MD, PhD, Katell Ledu, MD, Franck Morschhauser, MD, PhD, Bernard Christian, MD, Guillaume Cartron, MD, PhD, Luc Fornecker, MD, PhD, Danielle Canioni, MD, PhD, Marie-Christine Béné, MD, PhD, Gilles Salles, MD, PhD, Hervé Tilly, MD, PhD, Thierry Lamy, MD, PhD, Remi Gressin, MD, Olivier Hermine, MD, PhD, on behalf of the LYSa group

ClinicalTrials.gov, NCT00921414
**MCL: Role of Maintenance Therapy**

*Inclusion*

\[N=299\]

*Randomization*

\[N=240\]

Induction data presented ASH 2014:

- 82% CR post-induction
- 93% post ASCT

**PFS from time of randomization**

- Rituximab
- Observation

\[p = 0.0032\]
**PFS from Randomization**

**PFS from randomization according to treatment arm - ITT**

With Number of Subjects at Risk and 95% Confidence Limits

<table>
<thead>
<tr>
<th>Time (m)</th>
<th>Observation (95%CI)</th>
<th>Rituximab (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24m</td>
<td>79.8% (71.5-86.0)</td>
<td>93.3% (87.1-96.6)</td>
</tr>
<tr>
<td>36m</td>
<td>72.8% (63.7-79.9)</td>
<td>89.1% (82.0-93.5)</td>
</tr>
<tr>
<td>48m</td>
<td>64.6% (54.6-73.0)</td>
<td>82.2% (73.2-88.4)</td>
</tr>
</tbody>
</table>

**Median Follow up**: 50.2m (46.4-54.2)
OS from Randomization

OS from randomization according to treatment arm - ITT
With Number of Subjects at Risk and 95% Confidence Limits

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</tr>
<tr>
<td>36m:</td>
<td>85.4% (77.5-90.7)</td>
<td>93.3% (87.1-96.6)</td>
</tr>
<tr>
<td>48m:</td>
<td>81.4% (72.3-87.7)</td>
<td>88.7% (80.7-93.5)</td>
</tr>
</tbody>
</table>

Median follow up: 50.2m (46.4-54.2)
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
Intergroup Phase II trial in MCL

Goal: MRD-negative rate in PB 80%

- Bendamustine + Rituximab
- Bendamustine + Rituximab + HiDAC

MRD assessment

MRD- CR

PR or MRD+ CR
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

**RANDOMIZATION**
- Clonal Marker Present?
  - YES
    - Post-induction Restaging (CR, PR, SD/PD)
      - Submit blood to Adaptive for MRD assessment (MRD pos or MRD neg)
  - NO
    - MRD neg PR
    - MRD indeterminate
    - MRD pos CR or PR

**ARM A**
- Auto-HCT + Rituximab

**ARM B**
- Rituximab

**ARM C**
- Auto-HCT + Rituximab

MRD neg CR**

*Post-induction Restaging (CR, PR, SD/PD)*

*Submit blood to Adaptive for MRD assessment (MRD pos or MRD neg)*

*Submit tumor tissue to Adaptive Biotechnologies for clonal marker testing*
Diffuse large B cell lymphoma

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

CHOP-R (100%) (DA-R-EPOCH)

- Cure (60-70%)
- Relapsed/Refractory (30-40%)

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

- Transplant eligible (20-25%)
- Transplant ineligible (10-15%)

Transplant eligible

- ASCT + HDC

  - Cure (5%)
  - Relapse (15-20%)

Transplant ineligible

- 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
**International Prognostic Index (IPI) in aggressive NHL**

**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

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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)
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/DP DLBCL
Phase I then Phase II-III
BCL-2 inhibitor Venetoclax

Untreated DHL/DPL

DA-EPOCH-R

DA-EPOCH-R + Venetoclax (ABT199)

Ph I Investigator-initiated study (Alliance Foundation) WCM/NYP Coordinating Site (Rutherford)
Phase II/III NCI/Alliance/Intergroup (Abramson MGH)
What about new approaches in DLBCL?

- Strategies under investigation independent of cell of origin
- Strategies targeting specific cell of origin subtype
Roche GOYA Phase III: Study Design

Previously untreated DLBCL (N = 1,400)

Randomize

- GA101 x 8 cycles + CHOP x 6 or 8
- Rituximab x 8 cycles + CHOP x 6 or 8

GA101: 1,000 mg d1, d8, d15, cycle 1; d1, cycles 2–8, every 21 days
Rituximab: 375 mg/m² d1, cycles 1–8, every 21 days

Other studies of “unselected” DLBCL patients
R-CHOP + (maintenance) enzastaurin, everolimus, lenalidomide
GOYA investigator-assessed PFS (ITT pop)

KM plot of INV-assessed PFS by treatment arm

R-CHOP, n=712
G-CHOP, n=706

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP</th>
<th>G-CHOP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts with event, n (%)</td>
<td>215 (30.2)</td>
<td>201 (28.5)</td>
</tr>
<tr>
<td>1-yr PFS, %</td>
<td>79.8</td>
<td>81.6</td>
</tr>
<tr>
<td>2-yr PFS, %</td>
<td>71.3</td>
<td>73.4</td>
</tr>
<tr>
<td>3-yr PFS, %</td>
<td>66.9</td>
<td>69.6</td>
</tr>
</tbody>
</table>

HR (95% CI), stratified p-value: 0.92 (0.76, 1.11), p=0.3868

Median follow-up: 29 months

Vitolo et al, ASH 2016
**Alliance/CALGB 50303: R-CHOP vs R-EPOCH in Newly Diagnosed DLBCL**

Untreated patients with newly diagnosed DLBCL  
(N = 478)

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

R-CHOP
- every 3 wks for 6 cycles

R-EPOCH
- Doxorubicin, etoposide, vincristine Days 1-4; cyclophosphamide Day 5; prednisone Days 1-5

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**

<table>
<thead>
<tr>
<th></th>
<th>R-CHOP (%)</th>
<th>DA-EPOCH R (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment related deaths</td>
<td>2</td>
<td>2</td>
<td>0.975</td>
</tr>
<tr>
<td>Platelets</td>
<td>11</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>17</td>
<td>35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Infection</td>
<td>11</td>
<td>14</td>
<td>0.169</td>
</tr>
<tr>
<td>Neuropathy – sensory/motor</td>
<td>2/1</td>
<td>14/8</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Alliance 50303: Outcomes

### Event Free Survival

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

**Median follow-up 5.0 y**

**HR=1.14 (0.82-1.61)**

**p = 0.4386**

### Overall Survival

**HR=1.18 (0.79-1.77)**
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

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

DLBCL

Subset 1
CHOP-R

Subset 2
Other regimen

→ CHOP-R

→ Other regimen

→ CHOP-R

→ Other regimen
ABC DLBCL-associated signaling

Ibrutinib in relapsed DLBCL patients with ABC versus GCB subtype

<table>
<thead>
<tr>
<th></th>
<th>ABC subtype (N=29)</th>
<th>GCB subtype (N=20)</th>
<th>Unclassifiable (N=16)</th>
<th>Unknown (N=5)</th>
<th>Total (N=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Evaluable for Response</td>
<td>4</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>PP ORR(^4) (CR + PR)</td>
<td>10 (40%)</td>
<td>1 (5.3%)</td>
<td>0</td>
<td>2 (66.7%)</td>
<td>13 (21.7%)</td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>2 (8%)</td>
<td>0</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>8 (32%)</td>
<td>1 (5.3%)</td>
<td>0</td>
<td>1 (33.3%)</td>
<td>10 (16.7%)</td>
</tr>
<tr>
<td>PFS (months)</td>
<td>2.5</td>
<td>1.28</td>
<td>0.95</td>
<td>NR(^3)</td>
<td>1.64</td>
</tr>
</tbody>
</table>

N=70  
Median age=63  
Median prior treatments=3 (range 1-7)  
IPI high-intermediate/high risk 59%

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

Study design

- DLBCL
  - GCB
    - CHOP-R
  - Non-GCB
    - CHOP-R
    - Other regimen
    - Ibrutinib + CHOP-R

CHOP-R
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
Ibrutinib in Relapsed or Refractory CNS Lymphoma

- Meaningful ibrutinib concentrations in CSF at 560 mg/day

- Interim analysis of the French iLOC phase 2 study, PCNSL:
  - Disease control rate 15/18 (83%); ORR 10/18 (55%) @ 2 months
  - Responses in 3 compartments: Brain, IO, CSF
  - Two aspergillosis cases
  - Final analysis is pending (n=52)

- MSKCC Phase 1B/2 Study, PCNSL and isolated CNS relapse:
  - Ibrutinib at 560 and 840mg with manageable toxicities, no DLTs, one case of aspergillosis
  - 15/20 (75%) ORR; mPFS of 5.4 month
  - Combination trial of Ibrutinib + methotrexate (-/+ rituximab) ongoing

- Single-agent Ibrutinib has therapeutic efficacy in recurrent/refractory PCNSL, and possibly SCNSL

- Need to define role of ibrutinib in therapeutic strategy of PCNSL
ABC DLBCL-associated signaling

Response to Lenalidomide in Relapsed and Refractory DLBCL Based on Subtype

- Retrospective analysis of patients with relapsed DLBCL treated with lenalidomide as a single agent or in combination with rituximab/steroids at several institutions (N=56) suggests activity in the non-GCB subset.

Hernandez-Illizaliturri et al. Cancer 2011
Upfront DLBCL – Novel agent/regimen in specific clinical or molecular patient subsets

Study design

DLBCL

- GCB
  - CHOP-R
- Non-GCB
  - CHOP-R
  - Lenalidomide + CHOP-R

Other regimen
- CHOP-R
Comparison of R-CHOP in ABC/Non-GCB Retrospective vs Prospective studies

- **Retrospective (Lenz, NEJM 2008)**
  - 2-year PFS 40% ABC by GEP with R-CHOP, GCB > ABC subtype

- **Prospective**
  - 2-year PFS 80% non-GCB by IHC with R-CHOP

Spectrum of ABC/Non-GCB DLBCL patients

Less Favorable  More Favorable

Excluded due to concerns about delays/risk

Randomized in a selected patient population (patients who could wait for screening/enrollment)

“Favorable outcome”
Phase 1b Study of Pembrolizumab in Patients with Relapsed/Refractory PMBCL: Results from the Ongoing KEYNOTE-013 Trial

Pier Luigi Zinzani,1 Vincent Ribrag,2 Craig H. Moskowitz,3 Jean-Marie Michot,2 John Kuruvilla,4 Arun Balakumaran,5 Yayan Zhang,5 Patricia Marinello,5 Sabine Chlost,5 Eric Gustafson,5 Margaret A. Shipp,6 Philippe Armand6

1Institute of Hematology “L. e A. Seràgnoli”, University of Bologna, Bologna, Italy; 2Institut Gustave Roussy, Villejuif, France; 3Memorial Sloan Kettering Cancer Center, New York, NY, USA; 4Princess Margaret Cancer Centre, Toronto, ON, Canada; 5Merck & Co., Inc., Kenilworth, NJ, USA; 6Dana-Farber Cancer Institute, Boston, MA, USA
Phase 1b KEYNOTE-013 Study

Overall Study
- MDS
- MM
- Classical HL
- NHL
- PMBCL
  - Relapsed/refractory
  - ASCT failure/ineligible
  - ECOG PS 0-1
  - Adequate organ function
  - No autoimmune disease
  - No pneumonitis

Pembrolizumab IV
- 10 mg/kg Q2W
- OR
- 200 mg Q3W

CR
Discontinuation allowed after ≥24 wk

PR or SD
Treat for 24 mo
or
PD
or
Intolerable toxicity
Discontinue
(option to continue until PD confirmed)

PD

PET/CT scans at weeks 6 and 12
then Q9W per IHP 2007 criteria

Primary endpoints: Safety; Objective response rate

N = 18 (13 women), median age 30.5 (22-62) yrs, all ECOG PS 0-1
Median prior lines of therapy 3 (range 2-6)

Clinicaltrials.gov NCT01953692

*aThe first 11 patients received 10 mg/kg Q2W with first response assessment at 12 weeks; the next 8 received 200 mg Q3W with first response assessment at 6 weeks. The two doses are equivalent based on PK/PD studies.*
Best Percentage Change From Baseline in Tumor Size (Evaluable Patients)

13/16 (81%) had reduction in target lesions

-50% decrease

Overall response 7/17 (41%)
Complete remission 2/17 (12%)

Best Overall Response
- PD
- SD
- PR
- CR

Median follow-up: 11 mo (range 3-27)
Median response duration: not reached (range 2-23 mo)
6/7 (86%) responses ongoing
2 reached the maximum 2 years of treatment, remain in remission (25.4 mo, 23.8 mo)
KTE-C19 Induces Complete Remissions in Patients with Refractory Diffuse Large B Cell Lymphoma: Interim Results from the Pivotal Phase 2 ZUMA-1


1The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 2H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; 3Washington University, St. Louis, MO, USA; 4University of Miami, Miami, FL, USA; 5Stanford University, Stanford, CA, USA; 6Dana-Farber Cancer Institute, Boston, MA, USA; 7Montefiore Medical Center, Bronx, NY, USA; 8Vanderbilt University Medical Center, Nashville, TN, USA; 9City of Hope, Duarte, CA, USA; 10Mayo Clinic, Rochester, MN, USA; 11University of California at Los Angeles, Los Angeles, CA, USA; 12Loyola University Medical Center, Maywood, IL, USA; 13University of Rochester School of Medicine, Rochester, NY, USA; 14Sarah Cannon Research Institute, Nashville, TN, USA; 15John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; 16Cleveland Clinic, Cleveland, OH, USA; 17Karmanos Cancer Center, Wayne State University, Detroit, MI, USA; 18University of Iowa Carver College of Medicine, Iowa City, IA, USA; 19Banner M.D. Anderson Cancer Center, Gilbert, AZ, USA; 20Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel; 21University of California at San Diego, San Diego, CA, USA; 22Kite Pharma, Santa Monica, CA, USA

*Drs. Neelapu and Locke contributed equally to this work.

This study is supported in part by funding from The Leukemia & Lymphoma Society (LLS) Therapy Acceleration Program®
Eligibility criteria

- Aggressive NHL: DLBCL, PMBCL, TFL
- Chemotherapy-refractory disease: no response to last chemotherapy or relapse ≤ 12 mo post-ASCT
- Prior anti-CD20 mAb and anthracycline
- ECOG PS 0-1

Pre-specified interim efficacy analysis

- Phase 2 cohort 1 (n=50 with ≥3mo follow-up)

Primary endpoint

- Phase 2: ORR

Key secondary endpoints

- DOR, OS, Safety, Levels of CART and cytokines
**ZUMA-1: Phase 2 CONSORT Diagram**

- **Enrolled & Leukapheresed (n=111)**
  - Conditioning: Cy 500 mg/m², Flu 30 mg/m² × 3 days
  - KTE-C19: $2 \times 10^6$ /kg (n=101)
  - No bridging therapy allowed
  - 1 month follow-up (n=93 DLBCL, TFL, PMBCL)
  - ≥3 month follow-up (n=51 DLBCL*, n=11 TFL/PMBCL)
  - Pre-specified interim analysis; data cutoff: Aug 24, 2016

- Not treated:
  - n=5 SAE
  - n=1 Product unavailable
  - n=2 Non-measurable disease
  - n=2 SAE

*Pre-specified interim analysis; data cutoff: Aug 24, 2016*
# ZUMA-1 Pivotal Trial: Response Rates and Toxicity

## Best Overall Response in Patients with ≥3 Month Follow-up

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Age (yrs) Median (range)</th>
<th># prior Rx Median (range)</th>
<th>n</th>
<th>ORR</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLBCL</td>
<td>59 (25-76)</td>
<td>3 (1-7)</td>
<td>51</td>
<td>76%*</td>
<td>47%</td>
</tr>
<tr>
<td>TFL / PMBCL</td>
<td>58 (28-76)</td>
<td>4 (2-12)</td>
<td>11</td>
<td>91%</td>
<td>73%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>62</strong></td>
<td><strong>79%</strong></td>
<td><strong>52%</strong></td>
</tr>
</tbody>
</table>

*P < 0.0001 (exact binomial test comparing observed ORR to historical control assumption of 20%)

## Grade ≥3 Adverse Events, total N = 93 treated

<table>
<thead>
<tr>
<th>Event</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokine release syndrome</td>
<td>12 (13)</td>
</tr>
<tr>
<td>Neurologic event</td>
<td>27 (29)</td>
</tr>
<tr>
<td>Fatal events (excluding PD)</td>
<td>3 (3)</td>
</tr>
</tbody>
</table>

Peak CART cell expansion (day 7-14) associated with ongoing CR at 3 months
Brentuximab Vedotin Demonstrates Significantly Superior Clinical Outcomes in Patients With CD30-Expressing Cutaneous T-Cell Lymphoma Versus Physician's Choice (Methotrexate or Bexarotene): the Phase 3 ALCANZA study

Youn H. Kim,1 Sean Whittaker,2 Steven Horwitz,3 Madeleine Duvic,4 Reinhard Dummer,5 Julia Scarisbrick,6 Pietro Quaglino,7 Pier Luigi Zinzani,8 Pascal Wolter,9 Yinghui Wang,10 Maria Corinna Palanca-Wessels,10 Erin Zagadailov,11 William L. Trepicchio,11 Yi Liu,11 Meredith Little,11 H. Miles Prince12

1Stanford Cancer Institute, Stanford, California, USA; 2Guy's and St Thomas' NHS Foundation Trust, London, UK; 3Memorial Sloan Kettering Cancer Center, New York, USA; 4The University of Texas MD Anderson Cancer Center, Houston, TX, USA; 5University Hospital Zürich, Zurich, Switzerland; 6University Hospital Birmingham, Birmingham, UK; 7University of Turin, Turin, Italy; 8Institute of Hematology “Seràgnoli” University of Bologna, Bologna Italy; 9University Hospitals Leuven, Leuven, Belgium; 10Seattle Genetics, Inc., Bothell, WA, USA; 11Millennium Pharmaceuticals Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA; 12The University of Melbourne, Victoria, Australia
CTCL: Background and rationale

- CTCL, a heterogeneous group of T-cell lymphomas primarily involving skin
- Often a chronic course
- Current systemic therapies for CTCL rarely provide reliable and/or durable responses
- 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 with acceptable safety in CTCL in two phase 2 studies
  - Duvic et al. ORR, MF 54%, pcALCL 100%;
  - Kim et al. ORR, MF/Sézary syndrome 70% \(^4,5\)

ALCANZA: Randomized, open-label, phase 3 trial of brentuximab vedotin vs physician’s choice (methotrexate or bexarotene) in CD30+ CTCL

Screening*

- CD30+ MF or pcALCL with ≥10% CD30+ by central review
- MF ≥1 prior systemic therapy
- pcALCL with prior radiotherapy or ≥1 prior systemic therapy
- Exclusion:
  - Progression on both prior methotrexate and bexarotene

Randomization

- Methotrexate: 5–50 mg PO, weekly
- Bexarotene: 300 mg/m² (target dose) PO, daily
- Brentuximab vedotin: 1.8 mg/kg IV, every 3 weeks

Up to 48 weeks (16x 21-day cycles)

End of treatment visit

- 30 days after last dose of study drug

Post-treatment follow-up

- Every 12 weeks for 2 years and then every 6 months thereafter

N = 128, 64/arm

- Methotrexate or bexarotene was managed as standard of care, targeting maximum tolerated effective dose
- Patients were recruited from 52 centers across 13 countries

Median age 61 yrs; ECOG PS 0-1 in 96%
Median CD30 expression 32% (range 3-100)
Progression-free survival
(ITT population; independent review)

ORR 67% vs 20%
Log-rank test p-value: <0.001
Hazard ratio (95% CI): 0.270 (0.169, 0.430)

Median PFS (months):
B. vedotin: 16.7
MTX or Bex: 3.5

Number of events: BV: 36 ; MTX or Bex: 50
Some reasons why demonstrating benefits of cancer precision medicine may be challenging

- Targeted drug might not be effective
- Assay used to define subsets may not be sufficiently robust or rapid
- Patient selection issues

How do we go forward?

- Control groups
- Improved drugs and better/faster biomarker assays
- Innovative study designs