Program will begin shortly

Welcome & Introductions
NHL: Update on Slow-Growing Lymphomas

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Disclosure

Owen A. O’Connor, MD, PhD
Consulting: Millennium Takeda, Spectrum Pharmaceuticals and Mundipharma
Research Support: Celgene and Acetlyon
THE INDOLENT LYMPHOMAS
AN OVERVIEW

- Just what is lymphoma?
- How do we classify different types of lymphoma
- Lymphoma epidemiology: A relatively rare disease
- New “targeted” treatments
- Trying to put maintenance therapy in perspective
- Emerging biological agents
- Some principles of treatment
Where do lymphomas come from?

**The Human Body is a Highly Organized Network of Interacting Systems**

- **Atoms**
  - Carbon
  - Hydrogen
  - Oxygen
  - Nitrogen
  - Sulfur

- **Biomolecules**
  - Proteins
  - Lipids
  - Nuclei Acids
  - Carbohydrates

- **Organelles**
  - Mitochondria, nucleus

- **Cells**
  - 50,000,000,000,000
  - Over 100 different kinds of cell

- **Tissues**
  - 4 different kinds of tissue

- **Organs & Organ Systems**
The Collection of Blood Cells is a Type of Connective Tissue

Blood is considered connective tissue because:
1. It is embryologically derived from the same origins as other connective tissue (bone, muscle, cartilage)
2. It 'connects' the body systems together

Hematopoietic System includes:
- Bone marrow
- Spleen
- Tonsils
- Lymph nodes
- Peyers Patches


~ 70 Types of Lymphoma
B- AND T- LYMPHOCYTES NATURALLY UNDERGO “CONTROLLED” RECOMBINATION SHM, LEADING TO IMMUNOGLOBULIN DIVERSITY

A HIERARCHY OF HOW HETEROGENEITY CAN BE VIEWED IN LYMPHOPROLIFERATIVE MALIGNANCIES
Gene expression array demonstrates that the stromal microenvironment has profound prognostic influence.

<table>
<thead>
<tr>
<th>Expression Signature</th>
<th>Relative Risk of Death</th>
<th>P Value</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune response 1</td>
<td>0.15</td>
<td>&lt; .0001</td>
<td>Favorable</td>
</tr>
<tr>
<td>Immune response 2</td>
<td>9.35</td>
<td>&lt; .0001</td>
<td>Unfavorable</td>
</tr>
</tbody>
</table>

**Expression Signature (Prognosis)**

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<th>Expression Signature</th>
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</tr>
</thead>
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<tr>
<td>Immune response 1 (favorable)</td>
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<td>&lt; .0001</td>
</tr>
<tr>
<td>Immune response 2 (unfavorable)</td>
<td>9.35</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

Clonal Expansion

The 4 Major Defects That Drive Every Cancer – Corrupting Normal Cell Functions

Growth Defects: (1) The drivers of cell growth are left on; (2) the brakes don't work
Survival Defects: (3) Drivers of cell death lost; (4) Drivers of immortality turned on
How do we classify lymphomas?

or

What kind of lymphoma do I have?

Organizing 70 Types of Lymphoma

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially curable</td>
<td>Requires some form of chemotherapy</td>
</tr>
<tr>
<td>Relapsed disease can potentially be cured</td>
<td>Side effects of chemotherapy</td>
</tr>
<tr>
<td>Responds quick to treatment</td>
<td>Fast growing can produce symptoms quickly</td>
</tr>
<tr>
<td>4 to 6 months of treatment if cured</td>
<td>Relapse can be hard to manage</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very slow growing</td>
<td>Not curable – rare exceptions</td>
</tr>
<tr>
<td>Watching could be option</td>
<td>May require some form of lifelong therapy</td>
</tr>
<tr>
<td>Treatments less and less rely on chemotherapy</td>
<td>Can transform to aggressive</td>
</tr>
<tr>
<td>Can be relatively asymptomatic even with disease</td>
<td>Treatment side effects</td>
</tr>
</tbody>
</table>
**HISTORY OF NHL CLASSIFICATION**

- NHL classification schemes have evolved based on growing understanding of cancer cell characteristics
- Subclassifications are driving more specific clinical trials and therapeutic approaches

### WHO CLASSIFICATION OF LYMPHOID NEOPLASMS

**PARTIAL LIST – APPROXIMATELY 68 TYPES**

<table>
<thead>
<tr>
<th>Precursor Cell Lymphoma</th>
<th>Peripheral T and NK Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoblastic lymphoma, T cell</td>
<td>T-prolymphocytic leukemia</td>
</tr>
<tr>
<td>Lymphoblastic lymphoma, B cell</td>
<td>Granular Lymphocytic leukemia</td>
</tr>
<tr>
<td><strong>Peripheral B-cell Lymphoma</strong></td>
<td>NK cell leukemia</td>
</tr>
<tr>
<td>SLL/CLL type**</td>
<td>Mycosis fungoides/Sezary*</td>
</tr>
<tr>
<td>B-prolymphocytic leukemia</td>
<td>Peripheral T cell lymphoma, NOS</td>
</tr>
<tr>
<td>Lymphoplasmacytic lymphoma*</td>
<td>Angioimmunoblastic lymphoma</td>
</tr>
<tr>
<td>Mantle cell lymphoma*+/-</td>
<td>NK/T cell, nasal</td>
</tr>
<tr>
<td>Follicular lymphoma*</td>
<td>Enteropathy associated lymphoma</td>
</tr>
<tr>
<td>Marginal zone lymphoma, MALT*</td>
<td>Hepatosplenic γδ lymphoma</td>
</tr>
<tr>
<td>Marginal zone lymphoma, Nodal*</td>
<td>Subcutaneous panniculitis-like</td>
</tr>
<tr>
<td>Marginal zone lymphoma, Splenic*</td>
<td>Anaplastic large cell lymphoma, system</td>
</tr>
<tr>
<td>Hairy cell leukemia</td>
<td>Anaplastic large cell lymphoma, cutan.*</td>
</tr>
<tr>
<td>Diffuse large cell lymphoma</td>
<td>Adult T-cell lymphoma/leukemia</td>
</tr>
<tr>
<td>Burkitt’s lymphoma</td>
<td>PTLD</td>
</tr>
</tbody>
</table>
# WHO/REAL Classification of Lymphoma

## Features of Some Common Diseases

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Frequency (%)</th>
<th>Immunophenotype</th>
<th>Molecular Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLCL</td>
<td>31</td>
<td>CD20+</td>
<td>BCL2, BCL6, CMYC</td>
</tr>
<tr>
<td>FL</td>
<td>22</td>
<td>CD20+, CD10+, CD5-</td>
<td>BCL2</td>
</tr>
<tr>
<td>SLL/CLL</td>
<td>6</td>
<td>CD20 weak, CD5+, CD23+</td>
<td>+12, del(13q)</td>
</tr>
<tr>
<td>MCL</td>
<td>6</td>
<td>CD20+, CD5+, CD23-</td>
<td>CYCLIN D1</td>
</tr>
<tr>
<td>PTCL</td>
<td>6</td>
<td>CD20-, CD3+</td>
<td>Variable</td>
</tr>
<tr>
<td>MZL (MALT)</td>
<td>5</td>
<td>CD20+, CD5-, CD23-</td>
<td>BCL10, +3, +18</td>
</tr>
<tr>
<td>Mediastinal LCL</td>
<td>2</td>
<td>CD20+</td>
<td>Variable</td>
</tr>
<tr>
<td>ALCL</td>
<td>2</td>
<td>CD20-, CD3+, CD30+, CD15-, EMA+</td>
<td>ALK</td>
</tr>
<tr>
<td>LL (T/B)</td>
<td>2</td>
<td>T cell CD3+, B cell CD19+</td>
<td>Variable, TCL1-3</td>
</tr>
<tr>
<td>Burkitt-like</td>
<td>2</td>
<td>CD20+, CD10-, CD5-</td>
<td>CMYC, BCL2</td>
</tr>
<tr>
<td>MZL (Nodal)</td>
<td>1</td>
<td>CD20+, CD10-, CD23-, CD5-</td>
<td>+3, +18</td>
</tr>
<tr>
<td>SLL, PL</td>
<td>≤1</td>
<td>CD20+, cdg+, CD5-, CD23-</td>
<td>PAX-5</td>
</tr>
<tr>
<td>BL</td>
<td>≤1</td>
<td>CD20+, CD10+, CD5-</td>
<td>CMYC</td>
</tr>
<tr>
<td>TOTAL</td>
<td>88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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**The epidemiology of lymphoma**
LYMPHOMA, LIKE MOST CANCERS, IS A DISEASE OF THE ELDERLY

2012 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>242K</td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>227K</td>
<td>116K</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>73K</td>
<td>110K</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>56K</td>
<td>70K</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>44K</td>
<td>47K</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>40K</td>
<td>32K</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>38K</td>
<td>32K</td>
</tr>
</tbody>
</table>

Source: American Cancer Society, 2012

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
The Good News – Since mid 1990s Cancer Death Rates Dropping

Cancer Death Rates* by Sex, US, 1975-2008

*Age-adjusted to the 2000 US standard population.

Trends in Five-year Relative Survival (%)*, 1975-2007

*5-year relative survival rates based on follow up of patients through 2008.
Source: Surveillance, Epidemiology, and End Results Program, 1975-2008, Division of Cancer Control and Population Sciences, National Cancer Institute, 2011.
New “targeted” treatments for indolent lymphoma

MONOCLONAL ANTIBODIES HAVE CLEARLY CHANGED THE NATURAL HISTORY OF FL

RAPIDLY EMERGING CONCEPTS IN PATHOGENESIS CREATE NEW OPPORTUNITIES IN TREATMENT

The Mergence of Molecular Pathogenesis and Molecular Pharmacology

Distinct mechanisms of action
- Lack cross resistance to other standard agents
- Integration with conventional therapies is currently under study
- Hitting lymphoma at its biological roots

THE B-CELL RECEPTOR LINKS MANY KNOWN DYSREGULATED PATHWAYS IN LYMPHOMA: NF-kB, PI3K/AKT/mTOR AND Bcl2 FOR EXAMPLE

The Axis is Poised for Many Targeted Therapies
- Syk
- AKT
- BTK
- IkB
- mTORC 1 & 2
- PKCβ
- BAFF/BlyS
- NK-κB
- Bcl-2
- XIAP
THE B-CELL RECEPTOR LINKS MANY KNOWN DYSREGULATED PATHWAYS
THE OPPORTUNITIES FOR PRECISION MEDICINE

Fostamatinib
Ibrutinib
AVL-292
Enzastaurin
Bortezomib
Carfilzomib
ABT-737
ABT-199
Obatoclax
Idelalisib
IPI-145
TGR
Perifosine
Everolimus
Temsriolimus
Rapamycin
OSI-027
(dual mTOR)

IBRUTINIB: FIRST-IN CLASS INHIBITOR OF BRUTONS TYROSYNE KINASE (BTK)

- Forms a specific and irreversible bond with cysteine-481 in BTK
- Highly potent BTK inhibition at IC50 = 0.5 nM
- Orally administered with once daily dosing resulting in 24-hr target inhibition
- Blocks mantle cell migration and adhesion
- Blocks pERK, pJNK, and NF-kB pathways in lymphoma lines.

PCI-32765

Modified from P. Perez-Galan et al. Blood. 2011
PATIENT CHARACTERISTICS  
PHASE II OF PCI-32765 IN MCL

<table>
<thead>
<tr>
<th></th>
<th>Bortezomib-Naïve (N=41)</th>
<th>Bortezomib-Exposed (N=27)</th>
<th>Total (N=68)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median:</td>
<td>66 (76)</td>
<td>69 (85)</td>
<td>67 (79)</td>
</tr>
<tr>
<td>Range:</td>
<td>47 – 83</td>
<td>54 – 83</td>
<td>47 – 83</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31 (76)</td>
<td>23 (85)</td>
<td>54 (79)</td>
</tr>
<tr>
<td><strong>Time from Initial Diagnosis, # (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 3 yrs to 1st dose</td>
<td>20 (49)</td>
<td>6 (22)</td>
<td>26 (38)</td>
</tr>
<tr>
<td>≥ 3 yrs to 1st dose</td>
<td>21 (51)</td>
<td>21 (78)</td>
<td>42 (62)</td>
</tr>
<tr>
<td><strong>ECOG Status:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (59)</td>
<td>13 (48)</td>
<td>37 (54)</td>
</tr>
<tr>
<td>1</td>
<td>12 (29)</td>
<td>12 (44)</td>
<td>24 (35)</td>
</tr>
<tr>
<td>2</td>
<td>5 (12)</td>
<td>2 (7)</td>
<td>7 (10)</td>
</tr>
<tr>
<td><strong>Prior regimens, # (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Range</td>
<td>1 – 5</td>
<td>1 – 5</td>
<td>1 – 5</td>
</tr>
<tr>
<td>&lt; 3 regimens</td>
<td>28 (68)</td>
<td>11 (41)</td>
<td>39 (57)</td>
</tr>
<tr>
<td>≥ 3 regimens</td>
<td>13 (32)</td>
<td>16 (59)</td>
<td>29 (43)</td>
</tr>
</tbody>
</table>

Approved and Anticipated Uses of Ibrutinib

- FDA approved for patients with relapsed or refractory chronic lymphocytic leukemia
- FDA approved for patients with 17p deletion as front line therapy
- FDA approved for patients with relapsed or refractory mantle cell lymphoma
- Approved in Waldenstroms Macroglobulinemia
- Combination with R-CHOP highly effective in ABC DLBCL
THREE PI3K INHIBITORS IN CLINICAL DEVELOPMENT

- Idelalisib is a first-in-class PI3Kd inhibitor, and has shown promising activity in indolent lymphoma, producing an objective response (OR) rates in the range of 72-85% when used in combination with rituximab and/or bendamustine.
- IPI-145 is a PI3Kg/d inhibitor that has demonstrated promising activity in both B- and T-cell lymphoma.
- Idelalisib and IPI-145 display high structural similarity and contain nitrogen based heterocyclic backbones known to induce hepatotoxicity (increased LFTs).
- TGR-1202 has a different backbone designed to potentially minimize toxicity while preserving delta specificity. In vivo studies have shown no hepatotoxicity.

<table>
<thead>
<tr>
<th>TGR-1202</th>
<th>Idelalisib</th>
<th>IPI-145</th>
</tr>
</thead>
</table>

IDELALISIB PHASE 1 STUDY NHL DEMONSTRATES MARKED ACTIVITY IN PATIENTS WITH MCL AND Indolent NHL

**Best On-Treatment Change in Tumor Size (ITT Analysis)**

<table>
<thead>
<tr>
<th>% Change in Lymph Node Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>-100</td>
</tr>
</tbody>
</table>

**MCL** (N=38*)

**DNL** (N=50*)

- Inevaluable (patients without a follow-up tumor assessment)
- Inevaluable (patients without a follow-up tumor assessment; includes 6 patients with LPL with no adenopathy)
- Criterion for response (Cheson 2007)
- Tumor assessments for 2 patients have not been recorded
- Tumor assessments for 4 patients have not been recorded

Reference: Kahl, ICML 2011, #330
**DOUBLE REFRACTORY (RITUXIMAB + ALKYLATOR) iNHL: WATERFALL PLOT LYMPH NODE RESPONSE**

- 90% had improvement in lymphadenopathy
- 57% had ≥50% decrease from baseline

**PHASE 1B IDELALISIB IN NHL: BEST OVERALL RESPONSE**
**Approved and Anticipated Uses of Idelalisib**

- FDA approved for patients with indolent lymphomas with rituximab
- FDA approved for patients with relapsed CLL
RESULTS FROM THE PHASE 1/2A STUDY OF NAVITOCLAX (ABT-263) IN PATIENTS WITH RELAPSED OR REFRACTORY LYMPHOID MALIGNANCIES

Best Change in Tumor Size From Baseline

- 10 of 46 assessable patients had PR
- Median PFS 455 days

PHASE 1 STUDY OF ABT-199: BEST PERCENT CHANGE FROM BASELINE IN NODAL SIZE BY CT SCAN

- N = 29 evaluable (at minimum, 6 week assessment)
- Median Time to 50% Reduction = 43 days (range 36 to 113)
**Rationale for Maintenance Therapy in Indolent Lymphoma**

- Maintenance therapy applied in patients responding to induction treatment is effective in hematological malignancies.
- Maintenance therapy can deepen the response and lengthen remission.
- Need to have therapeutic agents with a good efficacy/toxicity ratio:
  - No cumulative toxicity (hematopoietic stem cells)
  - No long term side effects
  - Preserve quality of life
  - Do no compromise subsequent treatment(s) efficacy
FACTORS TO CONSIDER IN EVALUATING THE MERITS OF MAINTENANCE THERAPY

- What is Induction Therapy? \textit{R-Chemotherapy vs Rituximab}
- What is the Extent of Disease? \textit{Low volume vs high volume.}
- What is the Endpoint? \textit{Progression Free Survival (or Event Free Survival) vs Overall Survival}
- Where in the Disease is it Done? \textit{Front-line vs Relapsed Setting}
- Does one Strategy Have More Toxicity? \textit{Low Immunoglobulins and Risk of Infection}

\textit{So Many Factors Difficult to be Dogmatic: Its Not as Simple as You Think?}

UNDERSTANDING TERMINOLOGY
THE DEVIL IS IN THE DETAIL

\textbf{Time to Treatment Failure (TTF)} - the time from randomization to treatment discontinuation for any reason \textit{disease progression, treatment toxicity, patient preference, or death}. From a regulatory point of view, TTF is generally not accepted as a valid endpoint. TTF is a composite endpoint influenced by factors unrelated to efficacy. Discontinuation may be a result of toxicity, patient preference, or a physician's reluctance to continue therapy. \textit{These factors are not a direct assessment of the effectiveness of a drug.}

\textbf{Progression Free Survival} - The progression-free survival (PFS) duration is defined as the time from randomization to \textit{objective tumor progression or death}. Compared with other endpoints, PFS is a preferred regulatory endpoint because it includes death and \textit{may correlate better with OS}. Assessment of either PFS or TTP needs to be conducted in randomized trials. To reduce bias, the same assessment technique should be used at each follow-up, and the same evaluation schedule should be consistently used.

\textbf{Overall Survival} – is defined as time from randomization to \textit{death (all cause)}. It is the \textit{gold standard end-point}, but practically may be difficult because with time patients are doing better and better.
**Preliminary Analysis of Rituximab vs Watch and Wait in Asymptomatic FL Patients**

- **Patients with FL grades 1, 2, and 3a, stage II, III, IV disease, ECOG PS 0-1**
  - (N = 462)

**Arm A**
- Watch and wait

**Arm B**
- Rituximab induction

**Arm C**
- Rituximab induction and maintenance

**Clinic visits**
- R x 4
- Continued follow-up

**PD requiring therapy stops protocol treatment**

**Compulsory CT Scan**
- CT Scan only if clinical CR

**Bone marrow for histology and MRD only if CT shows CR**

---

**Preliminary Analysis of Rituximab vs Watch and Wait in Asymptomatic FL Patients**

- Spontaneous remission observed in 3% of patients on watch and wait vs CR in 45% of patients on rituximab
- 93 patients required new therapy during follow-up period:
  - 84 patients (90%) had PD
  - 78 patients (84%) received chemotherapy as new treatment

- **PFS**
  - **3-Yr PFS**
    - W + W: 33%
    - R4: 60%
    - R4 + RM: 81%

- **HR** (rituximab vs W + W): 0.46; 95% CI: 0.33-0.65; \( P < .001 \)
- **HR** (rituximab + M vs W + W): 0.21; 95% CI: 0.15-0.29; \( P < .001 \)
- **HR** (rituximab + M vs rituximab): 0.43; 95% CI: 0.24-0.72; \( P = .001 \)

Ardesha K, et al.
RITUXIMAB MAINTENANCE THERAPY IN FL
THE FIRST STUDY (SAKK TRIAL)

Untreated or relapsed/refractory FL
grade I-III (N=202)

Rituximab 375 mg/m² qw × 4

CR, PR, SD

RANDOMIZE

Rituximab maintenance
375 mg/m² q8w × 4
(n=73)

Observation
(n=78)

RITUXIMAB MAINTENANCE THERAPY IN FL
(SAKK TRIAL): EVENT FREE SURVIVAL

Prolonged: median 23.2 months

Standard: median 11.8 months

P=0.024
UPDATE EFS IN SAKK 35/98:
RITUXIMAB MAINTENANCE VS. OBSERVATION

Median follow-up: 9.4 years

25% still in remission at 8 years

P = 0.0007

Time (years since start of treatment)

Rituximab maintenance therapy vs. Observation

Rituximab 375 mg/m² weekly × 4
Re-treatment at time of progression (n=46)
Rituximab 375 mg/m² weekly × 4

Rituximab-naive patients with previously treated indolent NHL

RAN DOMIZE

114 patients (70%)
CR/PR/SD

Rituximab 375 mg/m² weekly × 4
Rituximab maintenance therapy (n=44)
Rituximab 375 mg/m² weekly × 4
every 6 months for 4 courses


4/16/2015 49

25
LYM-5 - MAINTENANCE VS RETREATMENT AFTER RITUXIMAB: HAINSWORTH REGIMEN

FL, SL rel/refr; R weekly x 4 + (repeat every 6 months x 4 max) or (treat at progression)

Progression Free Survival

% Surviving w/o progression

0 20 40 60 80 100
0 12 24 36 48 60

P=0.007


PRIMA STUDY DESIGN: HIGH TUMOR BURDEN

High tumor burden untreated follicular lymphoma

Immunochemotherapy

- 8 x rituximab
- 8 x CVP or 6 x CHOP or 6 x FCM

CR/CRu PR

Rituximab maintenance

375 mg/m² every 8 weeks for 2 years

Random 1:1

PD/SD off study

Observation

5 YEARS FOLLOW-UP

### PRIMARY ENDPOINT (PFS) MET AT THE PLANNED INTERIM ANALYSIS

Rituximab maintenance significantly reduced the risk of lymphoma progression by 50% (stratified by response and induction regimen, HR=0.50, 95% CI 0.39; 0.64)

**Graph:**
- **Rituximab maintenance** (N=505)
- **Observation** (N=513)

**Patients at risk**:
- 505
- 472
- 443
- 336
- 230
- 103
- 18
- 0
- 513
- 469
- 411
- 289
- 195
- 82
- 15
- 0

**Time (months):**
- 0
- 6
- 12
- 18
- 24
- 30
- 36
- 42

**Progression-free rate**:
- 0.8
- 0.6
- 0.4
- 0.2
- 0
- 1.0

### SUBGROUP ANALYSES RESULTS

<table>
<thead>
<tr>
<th>Category</th>
<th>Subgroup</th>
<th>Hazard ratio</th>
<th>N</th>
<th>Hazard ratio *</th>
<th>95% CIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td></td>
<td>1018</td>
<td>0.49</td>
<td>0.38 0.64</td>
</tr>
<tr>
<td>Age</td>
<td>&lt; 60</td>
<td></td>
<td>624</td>
<td>0.45</td>
<td>0.33 0.62</td>
</tr>
<tr>
<td></td>
<td>≥ 60</td>
<td></td>
<td>394</td>
<td>0.59</td>
<td>0.39 0.90</td>
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<td>Sex</td>
<td>Female</td>
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<td>485</td>
<td>0.58</td>
<td>0.40 0.85</td>
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<td>Male</td>
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<td>533</td>
<td>0.43</td>
<td>0.31 0.61</td>
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<td>FLIPI Index (CRF)</td>
<td>FLIPI ≤ 1</td>
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<td>216</td>
<td>0.38</td>
<td>0.19 0.77</td>
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<td>FLIPI = 2</td>
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<td>370</td>
<td>0.39</td>
<td>0.25 0.61</td>
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<td></td>
<td>FLIPI ≥ 3</td>
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<td>431</td>
<td>0.61</td>
<td>0.43 0.87</td>
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<tr>
<td>Induction</td>
<td>R-CHOP</td>
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<td>768</td>
<td>0.43</td>
<td>0.31 0.59</td>
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<td>Chemotherapy</td>
<td>R-CVP</td>
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<td>222</td>
<td>0.69</td>
<td>0.44 1.08</td>
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<td>R-FCM</td>
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<td>28</td>
<td>0.51</td>
<td>0.13 2.07</td>
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<td>Response to</td>
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<td>290</td>
<td>0.45</td>
<td>0.29 0.72</td>
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*Non-stratified analysis*

Favors maintenance Favors observation

Efficacy Across Secondary Endpoints
Substantial Improvement with R-Maintenance

**Time to next anti-lymphoma treatment**
- HR = 0.61
- p = 0.0003

**Time to next chemotherapy treatment**
- HR = 0.60
- p = 0.0011


Prima 6-Year Follow-Up: PFS from Randomization

**PFS according to maintenance (ITT patients)**
- HR = 0.57
- P < .0001
- 6 years = 59.2%
- 6 years = 42.7%


**Median follow-up since randomization:** 73 months
**PRIMA 6-YEARS FOLLOW-UP: OVERALL SURVIVAL**

**OS according to maintenance (ITT patients)**
With number of subjects at risk and 95% confidence intervals

<table>
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<th>Observation</th>
<th>Rituximab</th>
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<tr>
<td>No of Subjects</td>
<td>513</td>
<td>505</td>
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<tr>
<td>Event</td>
<td>503</td>
<td>492</td>
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<tr>
<td>Censored</td>
<td>491</td>
<td>482</td>
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<tr>
<td>Median Survival (95% CI)</td>
<td>NA (NA - NA)</td>
<td>NA (NA - NA)</td>
</tr>
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</table>

6 years = 88.7%
6 years = 87.4%

**HR = 1.027**
P = .885

Median follow-up since randomization: 73 months


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**ECOG 4402 (RESORT)**

Accruing 389 patients with low-tumor-burden stage III/IV indolent NHL

- **Rituximab maintenance**
  - 375 mg/m² q12w
- **Rituximab re-treatment at progression**
  - 375 mg/m² qw x 4

Primary End-point - Time to treatment failure
Secondary endpoint - Time to first cytotoxic therapy

MAINTENANCE RITUXIMAB IN FOLLICULAR LYMPHOMA
WHERE DO WE STAND?

- The data do consistently demonstrate an improved PFS in most circumstances
- The data do not demonstrate any improvement in OS; no study ever statistically powered to find OS benefit
- There may be a benefit to increasing time between treatments for maintenance rituximab....
- There are significant side effects of protracted rituximab:
  - Hypogammaglobulinemia (low IgG, get checked!)
  - Sinusitis
  - Bronchopulmonary infections

Rapidly emerging novel biological approaches
HIGHLY PROMISING NEW APPROACHES
THE ULTIMATE PRECISION THERAPY?

Surface and cytoplasmic proteins targeted by antibodies are:

- Differentially expressed on different types of lymphoma
- Can serve as targets for new biological drugs
- Could lead to new biological agents in rare sub-types of hematological malignancies

TARGETING CELL SURFACE PROTEINS

- Often lineage specific expression offers opportunity for cell type specific targeting
- Expression on normal cellular counterparts can be associated with toxicity (Ex: hypogamma-globulinemia with Rituximab).
- Engineered features of the Anti-CD targeted drug:
  - Patterns of glycosylation
  - ADCC
  - CDC
  - Apoptosis
  - Conjugation to cytotoxic
CLUSTERS OF DIFFERENTIATION DEFINE DISCRETE HEMATOPOIETIC CELL LINES: THE ULTIMATE PRECISION THERAPY?

<table>
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<tr>
<th>Cell Type</th>
<th>CD Markers</th>
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<tbody>
<tr>
<td>Stem Cells</td>
<td>CD34+; CD31-, CD117+; CD123?</td>
</tr>
<tr>
<td>All White Blood Cells</td>
<td>CD45+</td>
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<tr>
<td>Granulocyte</td>
<td>CD45+; CD11b; CD15+; CD24+ CD114+; CD182+</td>
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<tr>
<td>Monocyte</td>
<td>CD45+; CD14+; CD114+; CD11a; CD11b; CD91+; CD16+</td>
</tr>
<tr>
<td>T-Lymphocyte</td>
<td>CD45+; CD3+; CD30+ activated</td>
</tr>
<tr>
<td>T-Helper Cell</td>
<td>CD45+; CD3+; CD4+</td>
</tr>
<tr>
<td>T-Regulatory Cell</td>
<td>CD45+; CD25+; Foxp3+</td>
</tr>
<tr>
<td>Cytotoxic T-Cell</td>
<td>CD45+; CD3+; CD8+</td>
</tr>
<tr>
<td>B-Lymphocyte</td>
<td>CD45+; CD19+; CD20+; CD24+; CD79a; CD38+; CD22+; CD37+</td>
</tr>
<tr>
<td>Natural Killer Cell</td>
<td>CD16+; CD56+; CD3-; CD31; CD30; CD38+</td>
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</table>

THE ANATOMY OF ANTIBODY DRUG CONJUGATES THE POSSIBILITIES ARE ENDLESS

Target Rich! Any cell surface protein
Perhaps the most important: need ‘clean break’

The mechanism for tumor cell killing: too toxic to be injected directly into body
BRENTUXIMAB VEDOTIN PHARMACOLOGY

Brentuximab vedotin (SGN-35) ADC

- monomethyl auristatin E (MMAE), potent antimicrotubule agent
- protease-cleavable linker
- anti-CD30 monoclonal antibody

ADC binds to CD30
MMAE disrupts microtubule network
ADC-CD30 complex traffics to lysosome
MMAE is released

Apoptosis
G2/M cell cycle arrest

CD37 IS STRONGLY EXPRESSED IN NHL, CLL & NOT HL

- CD37 is frequently & highly expressed in B- (n=201) & T- (n=17) cell lymphomas: >80% of B/T cell lymphomas exhibit an H-score > 100.

- CD37 is expressed in rituxan resistant NHL & CLL.
- CD37 is not expressed in Hodgkin’s lymphoma (n=58).
- CD37 is expressed in 100% of patient-derived CLL (58/58) with an average flow cytometry MFIR of 83.
- CD37 is expressed in 100% of patient-derived AML stem cells & blasts (26/26) with an average flow cytometry MFIR of 126 & 85 respectively.

Courtesy L. Reyno
MECHANISM OF ACTION SGN-CD19A

Microtubule-disrupting agent, monomethyl auristatin F (MMAF)
Maleimidoacaproyl (mc) linker
Humanized anti-CD19 monoclonal antibody

Endocytosis
ADC traffics to lysosome
cys-mcMMAF binds tubulin
cys-mcMMAF release from ADC
G2/M cell cycle arrest and apoptosis
© 2014 Seattle Genetics, Inc.

Best % Change Per Patient in Index Lesions

Note: includes only patients with both baseline and postbaseline measurements; 3 patients had a >100% increase over baseline, indicated by arrows

Moskowitz et al. ASH 2014
**PINATUZUMAB VEDOTIN (CD22-ADC)**

**POLATUZUMAB VEDOTIN (CD79b-ADC)**

- Antibody drug conjugates (ADC) consisting of the potent microtubule inhibitor monomethyl auristatin E (MMAE) conjugated to anti-CD22 and CD79b monoclonal antibodies via a protease-cleavable peptide linker
- CD22 and CD79b are expressed by most B-cell hematologic malignancies
- Both ADCs have shown clinical activity in Phase I studies

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**ROMULUS STUDY DESIGN**

**Archival Tumor Biopsy**

**Biopsy at Progression**

**Randomize 1:1**

- **R + CD22 ADC**
- **R + CD79b ADC**

**R + CD22 ADC**

**R + CD79b ADC**

- **r/r FL = 41**
- **r/r DLBCL = 81**

**Rituximab (R) (375 mg/m²) + ADC (2.4 mg/kg) administered in every-21-day cycles up to one year**

**Clinical Evaluations**
- Treatment-emergent adverse events graded per NCI CTCAE v4.0
- Anti-tumor activity was evaluated per revised IWG criteria (Cheson et al. 2007) every three months; PET scans were performed at the discretion of the investigator

**Pharmacokinetic and Pharmacodynamic Evaluations**
- Total antibody, conjugate (antibody-conjugated cytotoxic agent MMAE [acMMAE]), unconjugated MMAE

**Data as of 21 February 2014; median time of follow up was 9.9 months (Range 0.23-14.9 months)**
- Data from crossover patients not included in this presentation

*Courtesy F. Morschhauser*
# Investigator-Assessed Best Responses in Treated Patients

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<thead>
<tr>
<th></th>
<th>DLBCL</th>
<th>FL</th>
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<tbody>
<tr>
<td></td>
<td>R+CD22 ADC (N=42)</td>
<td>R+CD79b ADC (N=39)</td>
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<tr>
<td><strong>Objective response, n (%)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Complete Response</td>
<td>24 (57%)</td>
<td>22 (55%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[12%-39%]</td>
<td>[6%-31%]</td>
</tr>
<tr>
<td>Partial Response</td>
<td>14 (33%)</td>
<td>16 (41%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>[20%-50%]</td>
<td>[26%-58%]</td>
</tr>
<tr>
<td>Stable disease, n (%)</td>
<td>3 (7%)</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Progressive disease, n (%)</td>
<td>7 (21%)</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>Unable to evaluate, n (%)</td>
<td>8 (19%)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td><strong>Median Duration of Response, mo. (95% CI)</strong></td>
<td>6.0 (2.9-12.2)</td>
<td>NR (2.6-NR)</td>
</tr>
</tbody>
</table>

*Patients who received ≥ 1 dose of study treatment; patients unable to evaluate did not have a post-baseline tumor assessment.

NR = Not reached

F. Morschhauser et al., ASH 2014

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# Anti-Tumor Responses Observed by Lymphoma Subtypes and Refractoriness to Last Prior Therapy

**R-CD22 ADC**

- **Max % Change Tumor Decrease from Baseline**
  - DLBCL
  - FL

**R-CD79b ADC**

- **Max % Change Tumor Decrease from Baseline**
  - DLBCL
  - FL

- **Rituximab-containing regimen**
- **Non-rituximab-containing regimen**
- **Not refractory**

F. Morschhauser et al., ASH 2014

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Data Cut-Off: 21FEB2014
PD-1 BLOCKADE WITH PEMBROLIZUMAB IN PATIENTS WITH CLASSICAL HODGKIN LYMPHOMA AFTER BRENTUXIMAB FAILURE: PHASE 1B

Principles of Treatment – 101
PRINCIPLES OF TREATMENT

Assume a treatment that kills 99% of all tumor cells (highly optimistic), then……

First cycle of therapy

Kill 99%

10,000,000

Second cycle of therapy

Kill 99%

1,000,000

Third cycle of therapy

Kill 99%

100,000

Fourth cycle of therapy

Kill 99%

10,000

EFFECTS OF TREATMENT ON TUMOR BURDEN

Succumb to Disease

Palliative Chemotherapy

1,000,000,000

Frei, 1984

Succumb to Disease

(99%)

1 kg

1 gm

surgery

1 mg

Curative Chemotherapy

Cure

Tumor clinically detectable

1,000,000,000

50% volume reduction

0
THE INDOLENT LYMPHOMA’S SUMMARY

• These disease entities are very heterogenous, each possessing its own unique features
• Treatment is often tailored based upon the degree of tumor burden, vital organ compromise, symptoms and patient co-morbidities
• Chemotherapy plays an important role in patients with advanced tumor burden
• There is an increasing emphasis on immunological treatments and targeted therapies.

Thank You!

Columbia University Medical Center
NewYork-Presbyterian
The University Hospital of Columbia and Cornell
# Center for Lymphoid Malignancies at Columbia University Medical Center

<table>
<thead>
<tr>
<th>Physicians</th>
<th>Research Study Coordinators</th>
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<tbody>
<tr>
<td>Owen A. O’Connor, M.D., Ph.D.</td>
<td>Molly Patterson, LMSW</td>
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<tr>
<td>Jennifer Amengual, M.D.</td>
<td>Celeste Rojas, B.S.</td>
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<td>Changchun Deng, M.D., Ph.D.</td>
<td>Renee Lichtenstein, B.A</td>
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<td>Ahmed Sawas, M.D.</td>
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<td>Donald Colburn, M.D.</td>
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<td>Lauren Geskin, M.D.</td>
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<td>(Dermatology / CTCL)</td>
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<td>Kathleen Maignan, NP</td>
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<td>Michael Smith, RN</td>
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<td>Emily Lichtenstein,</td>
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<td>Joanne Scibilla</td>
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<td>Erica Guerva</td>
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<td>Chermaine Ford, B.S.</td>
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<td>Joanna Duarte.</td>
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## NHL: Update on Slow-Growing Lymphomas

### Question and Answer Session

Dr. O’Connor’s slides are available for download at [www.LLS.org/programs](http://www.LLS.org/programs)
The Leukemia & Lymphoma Society (LLS) offers:

• **Live, Online Chats** that provide a friendly forum to share experiences with others. Living with non-Hodgkin lymphoma chat held on Monday and Wednesday nights, 7:30-10:00 pm ET, & Caregiver Chat held on Monday nights from 8:00-10:00 pm ET.
  ➢ WEBSITE: [www.LLS.org/chat](http://www.LLS.org/chat)

• **What to ask:** For a list of suggested questions to ask about certain topics, download and print any of the following guides.
  ➢ WEBSITE: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)

• **Free education materials:** [www.LLS.org/publications](http://www.LLS.org/publications)

• **Past NHL education programs:** [www.LLS.org/leukemiaeducation](http://www.LLS.org/leukemiaeducation)

• **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  ➢ EMAIL: infocenter@LLS.org  TOLL-FREE PHONE: (800) 955-4572