Disclosures

• Onyx Pharmaceuticals--Consultant
Objectives

• Discuss recent molecular analyses that have help expand the utility of sub-classification of non-Hodgkin lymphoma.

• Discuss strategies for radiographic assessment of non-Hodgkin lymphoma before and after therapy.

• Discuss novel therapies in the up front and relapsed/refractory setting in non-Hodgkin lymphoma.
Cause of Death

Source: US Mortality Files, National Center for Health Statistics, Centers for Disease Control and Prevention.
Cancer Deaths

Incidence of Lymphoma

Males only; Source: SEER 9 areas. Rates are age-adjusted as appropriate to the 2000 US
## 2013 Estimates (USA)

<table>
<thead>
<tr>
<th></th>
<th>New Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin Lymphoma</td>
<td>69,740</td>
<td>19,020</td>
</tr>
<tr>
<td>Hodgkin Lymphoma</td>
<td>9,290</td>
<td>1,180</td>
</tr>
<tr>
<td>– Nebraska</td>
<td>430</td>
<td>130</td>
</tr>
<tr>
<td>– Alabama</td>
<td>990</td>
<td>320</td>
</tr>
</tbody>
</table>

Thoughts

• We are seeing more of it...but why?
  – If you look for it....you might find it
    • CT scan availability
    • Random biopsy on procedures
    • Abnormalities on routine labs

• If you live long enough...
  – Better technologies in treatment of acute MI and CVA.
REVISITING PRINCIPLES: DIAGNOSIS
### WHO Classification of Lymphoid Neoplasms (2008)

#### Precursor
- B lymphoblastic leukaemia/lymphoma
- B lymphoblastic leukaemia/lymphoma, NOS
- B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL
- B lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged
- B lymphoblastic leukaemia/lymphoma with hyperdiploidy
- B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); IL3-IGH
- B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); TEL-AML1
- B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1
- T lymphoblastic leukaemia/lymphoma

#### Indolent B
- Chronic lymphocytic leukaemia/ small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- Splenic lymphoma/leukaemia, unclassifiable
- Splenic diffuse red pulp small B-cell lymphoma
- Hairy cell leukaemia-variant
- Lymphoplasmacytic lymphoma
- Waldenström’s macroglobulinemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
- Plasma cell myeloma
- Solitary plasmacytoma of bone
- Extramedullary plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone lymphoma
- Paediatric nodal marginal zone lymphoma
- Follicular lymphoma
- Paediatric follicular lymphoma
- Primary cutaneous follicle centre lymphoma

#### Aggressive B
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma (DLBCL), NOS
- T-cell/histiocyte rich large B-cell lymphoma
- Primary DLBCL of the CNS
- Primary cutaneous DLBCL, leg type
- EBV positive DLBCL of the elderly
- DLBCL associated with chronic inflammation
- Lymphomatoid granulomatosis
- Primary mediastinal (thymic) large B-cell lymphoma
- Intravascular large B-cell lymphoma
- ALK positive large B-cell lymphoma
- Plasmablastic lymphoma
- Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease
- Primary effusion lymphoma
- Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma
- B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

#### Mature T/NK
- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorder of NK-cells
- Aggressive NK cell leukaemia
- Systemic EBV positive T-cell lymphoproliferative disease of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukaemia/lymphoma
- Extranodal NK/T cell lymphoma, nasal type
- Enteropathy-associated T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Mycosis fungoides
- Sézary syndrome
- Primary cutaneous CD30 positive T-cell lymphoproliferative disorders
- Lymphomatoid papulosis
- Primary cutaneous anaplastic large cell lymphoma
- Primary cutaneous gamma-delta T-cell lymphoma
- Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
- Primary cutaneous CD4 positive small/medium T-cell lymphoma
- Peripheral T-cell lymphoma, NOS
- Angioimmunoblastic T-cell lymphoma
- Anaplastic large cell lymphoma, ALK positive
- Anaplastic large cell lymphoma, ALK negative

#### HL and PTLD
- HODGKIN LYMPHOMA
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Lymphocyte depleted classical Hodgkin lymphoma
- POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)
  - Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
  - Polymorphic PTLD
  - Monomorphic PTLD (B- and T/NK-cell types) #
  - Classical Hodgkin lymphoma type PTLD
Diagnosis

• How are you going figure out what they have?

• Tools
  • Biopsy
  • Histology/Morphology
  • Immunohistochemistry (IHC)
  • Cytogenetics/FISH
  • Molecular
Type of Biopsies Matter

FNA
Smallest sample
Bedside or hard to reach
No Architecture

Core
Hollow needle
Less invasive
CT guided
Small Sample

Surgical
Best sample
Most information
Most tissue
Requires an incision
Immunohistochemistry

- Stain
  - Enzyme-color
  - Fluorescence
- Patterns can lead to the subtype of NHL
  - CLL/SLL
  - MCL
  - FL
  - PTCL
Immunohistochemistry

- B-cell vs T-cell vs other
- Patterns...patterns...patterns

CD3  CD4  CD30

CD20  CD10  CD5
Patterns....but in context of architecture
Karyotype/FISH

- **Burkitt Lymphoma**
  - $t(8;14)$ leads to MYC expression

- **Mantle cell lymphoma**
  - $t(11;14)$ leads to cyclin D1 (BCL1) expression

- **Follicular lymphoma**
  - $t(14;18)$ leads to BCL2 expression
FISH....ING

What you don’t FISH for you don’t find......

• Double Hits
  – MYC and BCL2/BCL6
• Triple Hits
  – MYC and BCL2 and BCL6
• Copy number alterations
  – MYC
  – BCL2
Clonality: T-cell Receptor (TCR) and IgH

Molecular studies alone should not be used make a diagnosis: Adjunct
How confident are we?

- **Tiered approach**
  - Morphology
  - IHC
    - Initial tier (CD20; CD3)
    - Secondary tier (CD10; CD5; CD4; CD8)
    - Third (PAX-5; BOB-1; CXCL-13; TIA-1, EBER)
    - Fourth (research)

- May have trouble getting paid for by insurance.
Slicing the NHL Pie

- Diffuse Large B-cell, 31%
- Follicular, 22%
- Marginal zone, extranodal, 8%
- Peripheral T-cell, 7%
- Small Lymphocytic/CLL, 7%
- Mantle Cell, 6%
- Mediastinal Large B-cell, 2%
- Anaplastic Large Cell, 2%
- Burkitt, 2%
- Marginal zone, nodal, 2%
- T-Lymphoblastic, 2%
- Other, 9%

Armitage JO et al. JCO 1998
## Expert Agreement: Consensus Diagnosis

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<thead>
<tr>
<th>Diagnosis</th>
<th>Agreement</th>
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<tbody>
<tr>
<td>ALCL, ALK+</td>
<td>91%</td>
</tr>
<tr>
<td>PTCL, unspecified</td>
<td>74%</td>
</tr>
<tr>
<td>ATLL</td>
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</tr>
<tr>
<td>Panniculitis-like</td>
<td>75%</td>
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<td>84%</td>
</tr>
<tr>
<td>ALCL, ALK-</td>
<td>74%</td>
</tr>
<tr>
<td>Angioimmunoblastic</td>
<td>81%</td>
</tr>
<tr>
<td>Hepatosplenic</td>
<td>72%</td>
</tr>
<tr>
<td>Enteropathy-type</td>
<td>79%</td>
</tr>
<tr>
<td>Cutaneous ALCL</td>
<td>66%</td>
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Source: Vose JM et al, International T-cell Classification Project
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<th>Diagnosis</th>
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Source: Vose JM et al, International T-cell Classification Project
Thoughts

• We continue to split up the pie into smaller and smaller pieces...but often meaningful.

• Pathology is doing its best with the current resources.

• In less common subtypes a second hematopathologists opinion is often of utility.
REVISITING PRINCIPLES: STAGING
Factors That Influence Treatment

**Stage I**
- Localized disease
- Single lymph node region
- Single organ outside of the lymph nodes

**Stage II**
- Two or more lymph node regions near to each other

**Stage III**
- Two or more lymph node regions in different parts of the body

**Stage IV**
- Widespread disease
- Multiple organs
- With or without lymph node involvement
Tools: CT Scan

Oral contrast—bowel wall from other structures
IV contrast—Better define size of lymph nodes
Tools: PET/CT

Oral contrast and IV contrast—If your lucky
FDG metabolic activity PET shows areas with:

1. Infection
2. Inflammation
3. Malignancy
PET/CT with Fusion Images
Better Visualization of Extranodal Disease
Additional sites: Outside of C/A/P

PET/CT with Fusion
Before and After Treatment

T-cell lymphoma patient with PET avid lymph nodes under arms and in chest

Complete remission after chemotherapy. PET activity in bones from GCSF administration.
Thoughts

• PET/CT has the ability to stage patients with NHL.
  – Often upstage, but rarely down stage
• Almost all NHL subtypes are PET avid.
• Allows for selection of biopsy if concerned for transformation of disease.
• Be careful of mimics
  – Sarcoidosis
  – GCSF effect
PUSHING PARADIGMS: PROGNOSIS
What is the purpose of prognostic indices?

• Tell the patient how many people with a disease, X treatment, and Y risk factors are:
  – Progression free (PFS)
  – Alive (Overall survival)
  – Death due to treatment (Toxicity)

• **Guide therapy!!!**
  – Risk Adapted Approaches
Best of the BEST?

• **International Prognostic Index (IPI)**
  - Age > 60
  - Performance status > 1
  - LDH > Upper limit of normal
  - Extranodal site > 1
  - Stage > 2

Risk stratification
• Low risk = 0,1
• Low-intermediate = 2
• High-intermediate = 3
• High = 4,5

Shipp et al. NEJM 1993
IPI in R-CHOP era

Original IPI

Revised IPI

Sehn et al. Blood 2007
<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio</th>
<th>Score</th>
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<tbody>
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<td><strong>Age</strong></td>
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<tr>
<td>&gt; 40 to ≤ 60</td>
<td>1.0</td>
<td>1</td>
</tr>
<tr>
<td>&gt;60 to ≤ 75</td>
<td>2.4</td>
<td>2</td>
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<tr>
<td>&gt;75</td>
<td>3.2</td>
<td>3</td>
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<tr>
<td><strong>Performance Status ≥ 2</strong></td>
<td>1.9</td>
<td>1</td>
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<tr>
<td><strong>LDH (ratio)</strong></td>
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<td></td>
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<tr>
<td>&gt;1 to ≤ 3</td>
<td>2.1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3.3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Extranodal disease</strong></td>
<td>1.5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Stage (Ann Arbor) III/IV</strong></td>
<td>1.5</td>
<td>1</td>
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</table>

Zhou et al. Blood 2013

X/8
### Overall Outcome

<table>
<thead>
<tr>
<th>Score</th>
<th>5-y OS</th>
<th>5-y PFS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>NCCN-IPI</td>
<td>IPI</td>
</tr>
<tr>
<td>NCCN cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 1650)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 0-1 (19%)*</td>
<td>0-1 (38%)</td>
<td>96%</td>
</tr>
<tr>
<td>L-I 2-3 (42%)</td>
<td>2 (26%)</td>
<td>82%</td>
</tr>
<tr>
<td>H-I 4-5 (31%)</td>
<td>3 (22%)</td>
<td>64%</td>
</tr>
<tr>
<td>High Ω6 (8%)</td>
<td>4-5 (14%)</td>
<td>33%</td>
</tr>
<tr>
<td>BCCA cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n = 1138)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low 0-1 (12%)</td>
<td>0-1 (33%)</td>
<td>96%</td>
</tr>
<tr>
<td>L-I 2-3 (37%)</td>
<td>2 (24%)</td>
<td>77%</td>
</tr>
<tr>
<td>H-I 4-5 (37%)</td>
<td>3 (22%)</td>
<td>56%</td>
</tr>
<tr>
<td>High Ω6 (14%)</td>
<td>4-5 (21%)</td>
<td>38%</td>
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</table>
Thoughts

• IPI remains well entrenched in DLBCL and other aggressive NHL in clinical trials.

• NCCN-IPI may see more utility await next lymphoma guidelines

• Role of IPI in a risk adapted approach is lacking to date.
PUSHING PARADIGMS: PET/CT AS PREDICTIVE
“Negative” PET/CT

A negative scan at the end of therapy is the best predictor of a durable remission!
End of treatment PET/CT

patients
n=93

PET –
n=67

CDM –
n=53

CR
n=43*

R (DFS 321)
n=10

CR
n=13°

PET +
n=26

CDM –
n=14

PR (DFS=933)
n=1*

CDM +
n=12

PR/R (DFS=73)
n=26

Spaepen et al. JCO 2001

CDM= CONVENTIAL DIAGNOSTIC MODALITIES
<table>
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<tr>
<th>Score</th>
<th>Criteria</th>
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<tr>
<td>1</td>
<td>No uptake</td>
</tr>
<tr>
<td>2</td>
<td>Uptake $\leq$ mediastinum</td>
</tr>
<tr>
<td>3</td>
<td>Uptake $&gt;$ mediastinum but $\leq$ liver</td>
</tr>
<tr>
<td>4</td>
<td>Uptake $&gt;$ liver</td>
</tr>
<tr>
<td>5</td>
<td>Uptake $&gt;&gt;$ liver $\pm$ new sites</td>
</tr>
</tbody>
</table>
Interim PET-2 in aggressive NHL

Haioun et al. Blood 2005
Interim PET/CT Concerns

Moskowitz CH et al. JCO 2010
Interim PET/CT Concerns

- PET Negative (n = 59; censored = 51)
- PET Positive/Biopsy Negative (n = 33; censored = 26)
- PET Positive/Biopsy Positive (n = 5; censored = 3)

**P = 0.275 PET Negative v PET Positive/Biopsy Negative**
Thoughts

• Deauville score is a visual assessment, not a quantitative assessment
  – Liver and mediastinum are averages
  – Delta SUV is also being investigated.

• In order to be helpful to nuclear medicine/radiology list as: Pre-treatment, Interim (PET-2; PET-4) or post treatment

• Interim PET/CT in aggressive NHL remains a research question.
PUSHING PARADIGMS: AFTER THE SCOPE
Fact

- Not all lymphomas are the same even though they look the same under the microscope.
Subtyping DLBCL

GCB

ABC (non-GCB)
Figure 1. Decision tree for immunoperoxidase TMA classification of DLBCL.

DLBCL Subtyping (1%)—Nanostring

20 genes

Able to perform on formalin-fixed paraffin embedded samples

David et al. Blood 2014
Outcomes by subtype

Graph showing survival outcomes by subtype with the following details:

- **P = 0.04**
- **RR = 2.3 (0.8-6.3)**

Legend:
- Orange: Germinal-Center B-cell-like DLBCL
- Green: Unclassified DLBCL
- Blue: Activated B-cell-like DLBCL
<table>
<thead>
<tr>
<th>Morphology</th>
<th>Genetic Double Hit</th>
<th>Only MYC+</th>
<th>Double Expressers of BCL-2 and MYC protein by IHC</th>
<th>Ki-67 ≥ 90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkitt Lymphoma</td>
<td>&lt;1%</td>
<td>~100%</td>
<td>&lt;20%</td>
<td>~100%</td>
</tr>
<tr>
<td>High grade B-cell lymphoma with features intermediate between DLBCL and Burkitt lymphoma</td>
<td>29%</td>
<td>36%</td>
<td>N/A</td>
<td>61%</td>
</tr>
<tr>
<td>DLBCL</td>
<td>0-12%</td>
<td>3-8%</td>
<td>29-44%</td>
<td>7-8%</td>
</tr>
</tbody>
</table>

Source: Courtesy of Jim Armitage M.D.
## Double HIT DLBCL: Down Right Bad

<table>
<thead>
<tr>
<th>Author</th>
<th>Cases</th>
<th>OS (months)</th>
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<tbody>
<tr>
<td>Tomita et al.</td>
<td>27</td>
<td>6</td>
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<tr>
<td>Macpherson et al.</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Kanungo et al.</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>LeGouill et al.</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>Niitsu et al.</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Johnson et al.</td>
<td>54</td>
<td>4</td>
</tr>
<tr>
<td>Snuderl et al.</td>
<td>20</td>
<td>4</td>
</tr>
</tbody>
</table>
Does MYC IHC expression = Double Hit?


5-year OS = 70% (other) and 30% (MYC+/BCL2+), p = .020
5-year PFS = 63% (other) and 21% (MYC+/BCL2+), p = .018
Thoughts

- Technology to assess GCB versus ABC in an IHC based system is not mainstream.
- IHC for DLBCL subtype determination remains appropriate outside and inside of clinical trials.
- Novel regimens and/or adjunctive strategies against true double/triple hit DLBCL are necessary.
- MYC/BCL2 expression does not equal double hit by cytogenetics/FISH.
PUSHING PARADIGMS: HOW WE TREAT
US 5-Year Survival NHL (Whites)
Thought Experiment on Therapy

All patients with the same diagnosis

No Benefit No Toxicity

No Benefit + Toxicity

+ Benefit + Toxicity

+ Benefit No Toxicity
How Do We Cure or How Do We Control

Aggressive NHL

Indolent NHL
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- B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1
- T lymphoblastic leukaemia/lymphoma with t(1;16)(p13.1;q22); TCF3-PBX1

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Is There A Best Regimen in DLBCL

1. R-CHOP
2. Dose Adjusted EPOCH-R
3. R-ACVBP
R-CHOP-14 versus R-CHOP-21

Cunningham et al. Lancet 2013
Dose Adjusted-EPOCH-R

Wilson et al. Haematologica 2012
Thoughts

• DLBCL remains curable at any age.
• R-CHOP remains the standard chemotherapy.
  – Awaiting result of CALGB 50303 (R-CHOP vs DA-EPOCH-R)
• Autologous transplantation is potentially curative at relapse
  – Remissions to second-line (ICE/DHAP/Gem+?) in rituximab pre-treated patient is more difficult.
• Strategies to build on R-CHOP and DA-EPOCH-R are necessary:
  – Proteasome inhibitors (bortezomib)
  – BTK inhibitors (Ibrutinib)
  – IMiDS (lenalidomide)
  – HDACs (romidepsin, vorinostat, panobinostat, belinostat)
  – PD1 inhibitors
PUSHING PARADIGMS: NOVEL THERAPIES
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<td>B lymphoblastic leukaemia/lymphoma NOS</td>
<td>Chronic lymphocytic leukaemia/ small lymphocytic lymphoma</td>
<td>Mantle cell lymphoma</td>
<td>T-cell prolymphocytic leukaemia</td>
<td>HODGKIN LYMPHOMA</td>
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<td>B-cell prolymphocytic leukaemia</td>
<td>Diffuse large B-cell lymphoma (DLBCL), NOS</td>
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<td>— Nodular lymphocyte predominant Hodgkin lymphoma</td>
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<td>B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1</td>
<td>Splenic marginal zone lymphoma</td>
<td>T-cell/histiocyte rich large B-cell lymphoma</td>
<td>Chronic lymphoproliferative disorder of NK-cells</td>
<td>— Classical Hodgkin lymphoma</td>
</tr>
<tr>
<td>B lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged</td>
<td>Hairy cell leukaemia</td>
<td>Primary DLBCL of the CNS</td>
<td>Aggressive NK cell leukaemia</td>
<td>— Nodular sclerosis classical Hodgkin lymphoma</td>
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<tr>
<td>B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)</td>
<td>Splenic lymphoma/leukaemia, unclassifiable*</td>
<td>Primary cutaneous DLBCL, leg type</td>
<td>Systemic EBV positive T-cell lymphoproliferative disease of childhood</td>
<td>— Lymphocyte-rich classical Hodgkin lymphoma</td>
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<td>B lymphoblastic leukaemia/lymphoma with hyperdiploidy</td>
<td>Splenic diffuse red pulp small B-cell lymphoma</td>
<td>EBV positive DLBCL of the elderly</td>
<td>Hydroa vacciniforme-like lymphoma</td>
<td>— Mixed cellularity classical Hodgkin lymphoma</td>
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<tr>
<td>B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)</td>
<td>Hairy cell leukaemia-variant lymphoplasmacytic lymphoma</td>
<td>DLBCL associated with chronic inflammation</td>
<td>Adult T-cell leukaemia/lymphoma</td>
<td>— Lymphocyte depleted classical Hodgkin lymphoma</td>
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<td>B lymphoblastic leukaemia/lymphoma with t(5;14)(q31;q32); IL3-IGH</td>
<td>Waldenström’s macroglobulinemia</td>
<td>Lymphomatoid granulomatosis</td>
<td>Extramedial NK/T cell lymphoma, nasal type</td>
<td>POST-TRANSPLANT LYMHOPOPLORIFERATIVE DISORDERS (PTLD)</td>
</tr>
<tr>
<td>B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1; (TCF3-PBX1)</td>
<td>Heavy chain diseases</td>
<td>Primary mediastinal (thymic) large B-cell lymphoma</td>
<td>Enteropathy-associated T-cell lymphoma</td>
<td>— Early lesions</td>
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<tr>
<td>T lymphoblastic leukaemia/lymphoma</td>
<td>Hodgkin lymphoma</td>
<td>Intravascular large B-cell lymphoma</td>
<td>Hepatosplenic T-cell lymphoma</td>
<td>— Plasmaclastic hyperplasia</td>
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<td>Lymphoma of-associated multisystemic Castleman disease</td>
<td>ALK positive large B-cell lymphoma</td>
<td>Subcutaneous panniculitis-like T-cell lymphoma</td>
<td>— Infectious mononucleosis-like PTLD</td>
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<td>Plasmablastic lymphoma</td>
<td>Mycosis fungoides</td>
<td>— Polymorphic PTLD</td>
</tr>
<tr>
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<td>Splenic marginal zone lymphoma</td>
<td>Large B-cell lymphoma arising in HHV8-associated multicentric Castleman disease</td>
<td>Sézary syndrome</td>
<td>— Monomorphic PTLD (B- and T/NK- cell types) #</td>
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<td>Follicular lymphoma</td>
<td>Primary cutaneous CD30 positive T-cell lymphoproliferative disorders</td>
<td>Primary cutaneous CD30 positive T-cell lymphoma</td>
<td>Classical Hodgkin lymphoma type PTLD #</td>
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<tr>
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<td>Paediatric follicular lymphoma</td>
<td>Lymphomatoid papulosis</td>
<td>Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma</td>
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</tr>
<tr>
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<td>Primary cutaneous CD30 positive T-cell lymphoma</td>
<td>Primary cutaneous gamma-delta T-cell lymphoma</td>
<td>Primary cutaneous CD4 positive small/medium T-cell lymphoma</td>
<td></td>
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<tr>
<td></td>
<td>Primary cutaneous follicle centre lymphoma</td>
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<td>Peripheral T-cell lymphoma, NOS</td>
<td></td>
</tr>
<tr>
<td></td>
<td>B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and Burkitt lymphoma</td>
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<td></td>
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<td></td>
<td>B-cell lymphoma, unclassifiable, with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma</td>
<td>Primary cutaneous CD4 positive small/medium T-cell lymphoma</td>
<td>Anaplastic large cell lymphoma, ALK positive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anaplastic large cell lymphoma, ALK negative</td>
<td></td>
</tr>
</tbody>
</table>
Follicular Lymphoma

• Not all need treatment at diagnosis (GELF criteria)

• Recognize concern for histologic transformation
  – PET/CT SUVs > 10-12; biopsy necessary
BR versus R-CHOP: PFS

Median follow-up 45 months

- Follicular lymphoma
- Mantle cell Lymphoma
- Marginal zone lymphoma
- Lymphoplasmacytic Lymphoma

Rummel et al. Lancet 2013
Erythematous rash was greater in the Bendamustine cohort
B-cell pathway
Idelalisib

- 1\textsuperscript{st} in class PI3-K inhibitor
- Inhibitor the delta isoform (alpha, beta, gamma, delta)
- Oral and taken and taken continuously
  - 3 weeks on 1 weeks off
  - No MTD—dosed 350 mg PO BID
- Phase I fairly well tolerated in heavily pre-treated
  - Grade 3:
    - LFT elevation—25%
    - Anemia—25%
  - No tumor lysis
Idelalisib: Waterfall Plot

Phase I previously treated iNHL

97% had seen Rituximab
ORR: 47% (1.3% CR)
DOR: 18.4 months

Flinn et al. Blood 2014

Rituximab and Akylator Refractory iNHL

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

Gopal et al. ASH 2013 abs #85
WHO Classification of Lymphoid Neoplasms (2008)

Precursor
- B lymphoblastic leukaemia/lymphoma NOS
- B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
- B lymphoblastic leukaemia/lymphoma with t(9;22)(q34;q11.2); BCR-ABL1
- B lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged
- B lymphoblastic leukaemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)
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- B lymphoblastic leukaemia/lymphoma with hypodiploidy (hypodiploid ALL)
- B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3); E2A-PBX1
- (TCF3-PBX1)
- T lymphoblastic leukaemia/lymphoma

Indolent B
- Chronic lymphocytic leukaemia/ small lymphocytic lymphoma
- B-cell prolymphocytic leukaemia
- Splenic marginal zone lymphoma
- Hairy cell leukaemia
- Splenic lymphoma unclassifiable
- B-cell lymphoma (Hairy cell, T-cell, T/NK)
- Waldenström's macrogammaglobulinaemia
- Heavy chain diseases
  - Alpha heavy chain disease
  - Gamma heavy chain disease
  - Mu heavy chain disease
  - Plasma cell myeloma
  - Solitary plasmacytoma of bone
  - Extrasosseous plasmacytoma
  - Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
  - Nodal marginal zone lymphoma
  - Paediatric nodal marginal zone lymphoma
  - Follicular lymphoma
  - Paediatric follicular lymphoma
  - Primary cutaneous follicle centre lymphoma

Mature T/NK
- T-cell prolymphocytic leukaemia
- T-cell large granular lymphocytic leukaemia
- Chronic lymphoproliferative disorder of NK-cells
- T-cell/histiocyte-rich large B-cell lymphoma
- Primary effusion lymphoma of the CNS
- Primary cutaneous DLBCL, leg type
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- Post-transplant lymphoproliferative disorders (PTLD)
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
  - Primary cutaneous gamma-delta T-cell lymphoma
  - Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
  - Primary cutaneous CD4 positive small/medium T-cell lymphoma
  - Peripheral T-cell lymphoma, NOS
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma, ALK positive
  - Anaplastic large cell lymphoma, ALK negative

Hodgkin lymphoma (HL) and PTLD
- Hodgkin lymphoma
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
- Lymphocyte depleted classical Hodgkin lymphoma
- Post-transplant lymphoproliferative disorders (PTLD)
  - Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
  - Polymorphic PTLD
  - Monomorphic PTLD (B- and T/NK-cell types) #
  - Classical Hodgkin lymphoma type PTLD #

CLL/SLL

- Post-transplant lymphoproliferative disorders (PTLD)
  - Lymphomatoid papulosis
  - Primary cutaneous anaplastic large cell lymphoma
  - Primary cutaneous gamma-delta T-cell lymphoma
  - Primary cutaneous CD8 positive aggressive epidermotropic cytotoxic T-cell lymphoma
  - Primary cutaneous CD4 positive small/medium T-cell lymphoma
  - Peripheral T-cell lymphoma, NOS
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma, ALK positive
  - Anaplastic large cell lymphoma, ALK negative

- Classic Hodgkin lymphoma
  - Lymphocyte depleted classical Hodgkin lymphoma
  - Lymphocyte rich classical Hodgkin lymphoma
  - Mixed cellularity classical Hodgkin lymphoma
  - Nodular sclerosis classical Hodgkin lymphoma
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Post-transplant lymphoproliferative disorders (PTLD)
  - Early lesions
  - Plasmacytic hyperplasia
  - Infectious mononucleosis-like PTLD
  - Polymorphic PTLD
  - Monomorphic PTLD (B- and T/NK-cell types) #
  - Classical Hodgkin lymphoma type PTLD #

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  - Peripheral T-cell lymphoma, NOS
  - Angioimmunoblastic T-cell lymphoma
  - Anaplastic large cell lymphoma, ALK positive
  - Anaplastic large cell lymphoma, ALK negative
B-cell pathway
• Immunophenotype
  – CD 20 dim +
  – CD 5 +
  – CD 23 +
  – Cyclin D1 negative (rules out MCL)

• Cytogenetics/FISH: Trisomy 12, 13q, and 17p

• Molecular: IgH mutated or unmutated

• Flow: CD38 +/- and ZAP-70 +/-
Ibrutinib

- Oral drug and once daily
  - CLL 420 (3 tabs)
  - MCL 560 mg (4 tabs)
- High potency (likely-dirty)
- Covalently bind to the cysteine 481 of BTK
- Affects ERK, NF-kB, DNA binding, CpG epigenetics
- No toxic effects on T-cells
  - No BTK in T-cells, weird
- Bleeding?
  - Do not use with Coumadin
Ibrutinib in Relapsed CLL/SLL

Byrd et al. NEJM 2013
Last but not least: What is sexy in DLBCL?

Autologous
<table>
<thead>
<tr>
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<th>Histology</th>
<th>Prior TXT</th>
<th>Response (mo.)</th>
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<tr>
<td>1</td>
<td>SMZL</td>
<td>4</td>
<td>PR 20+</td>
</tr>
<tr>
<td>2</td>
<td>PMBCL</td>
<td>4</td>
<td>CR 19+</td>
</tr>
<tr>
<td>3</td>
<td>CLL</td>
<td>2</td>
<td>CR 16+</td>
</tr>
<tr>
<td>4</td>
<td>PMBCL</td>
<td>3</td>
<td>NE</td>
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</tr>
<tr>
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<td>13</td>
<td>PR 2+</td>
</tr>
<tr>
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<tr>
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<td>CLL</td>
<td>4</td>
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</tr>
<tr>
<td>14</td>
<td>DLBCL</td>
<td>2</td>
<td>PR 1+</td>
</tr>
</tbody>
</table>

Chimeric Antigen Receptor T-Cells (CARs) for Refractory NHL

Kochenderfer et al. ASH 2013 Abs 168
Thoughts

• CARs are on FIRE
  – Center that has done before (toxicities)
  – When to use….relapse single agent or with consolidation

• New agents and combinations iNHL
  – BR versus R-CHOP/R-CVP
    • BR likely to become standard of care for iNHL
  – Lenalidomide (Relevance study)
  – Combination oral trials are coming

• New targets for drug development
  – PI3 kinase inhibitors
    • Idelalisib
    • IPI-145
    • Etc...
  – Ibrutinib
  – BCL2 inhibitors

• Price of these drugs may break the bank!!!
• I could keep going but I don’t think we have enough time.

Thank you!!

(Red is my favorite color)