TREATMENT STRATEGY in
INDOLENT LYMPHOMA

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### WHO Classification of the mature B-cell, T-cell, and NK-cell Neoplasms-2008

#### Mature B-Cell Neoplasms
- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Splenic lymphoma/leukemia, unclassifiable*
  - Splenic diffuse red pulp small B-cell lymphoma*
  - Hairy cell leukemia-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
- Extraskeletal plasmacytoma
- Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT type)
- Nodal marginal zone lymphoma
  - Pediatric nodal marginal zone lymphoma*
- Follicular lymphoma
  - Pediatric follicular lymphoma*
- Primary cutaneous follicle center lymphoma
- Mantle cell lymphoma

#### Mature T-Cell and NK-Cell Neoplasms
- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leukemia
  - Chronic lymphoproliferative disorder of NK-cells*
- Aggressive NK cell leukemia
- Systemic EBV positive T-cell lymphoproliferative disorder of childhood
- Hydroa vacciniforme-like lymphoma
- Adult T-cell leukemia/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*
Presentation Flow Chart

- Initial treatment of limited stage (I/II) follicular lymphoma
- Initial treatment of advanced stage (III/IV) follicular lymphoma
- Treatment of relapsed or refractory follicular lymphoma
- Treatment of marginal zone (MALT) lymphoma
- Treatment of Waldenström macroglobulinemia
- Strategy in treating indolent B-cell neoplasia in the future
- Treatment of advanced stage (IIB to IV) mycosis fungoides and Sézary syndrome
- Strategy in treating indolent T-cell neoplasia in the future
Incidence and Survival in Indolent NHL

Adapted from Horning SJ. Semin Oncol. 1993;20(suppl 5):75-88.
Initial treatment in follicular lymphoma
Staging (Ann-Arbor) and Prognosis (FLIPI)

• Ann-Arbor

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RR (Death)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 yrs of age or older</td>
<td>2.38</td>
</tr>
<tr>
<td>Stage III-IV</td>
<td>2.00</td>
</tr>
<tr>
<td>Hemoglobin &lt; 12 g/dL</td>
<td>1.55</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>1.50</td>
</tr>
<tr>
<td>Nodal sites &gt; 4</td>
<td>1.39</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Risk Factors, n</th>
<th>5-Yr OS, %</th>
<th>10-Yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>0-1</td>
<td>91</td>
<td>71</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>78</td>
<td>51</td>
</tr>
<tr>
<td>High</td>
<td>≥ 3</td>
<td>53</td>
<td>36</td>
</tr>
</tbody>
</table>
**Pts with Stg I or Non-bulky Stg II FL**

<table>
<thead>
<tr>
<th>Center</th>
<th>N</th>
<th>Histology</th>
<th>Median Age, Yrs</th>
<th>Treatment</th>
<th>10-Yr Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advani 2004</td>
<td>43</td>
<td>FSC and FM</td>
<td>58</td>
<td>No initial therapy</td>
<td>86</td>
</tr>
<tr>
<td>Stanford</td>
<td>177</td>
<td>FSC and FM</td>
<td>53</td>
<td>35-50 Gy</td>
<td>64</td>
</tr>
<tr>
<td>Princess Margaret</td>
<td>596</td>
<td>Follicular</td>
<td>56</td>
<td>20-35 Gy</td>
<td>58</td>
</tr>
<tr>
<td>BNLI</td>
<td>82</td>
<td>FSC, FM, FL, DSL</td>
<td>59</td>
<td>35 Gy</td>
<td>64</td>
</tr>
<tr>
<td>Royal Marsden</td>
<td>58</td>
<td>FSC, FM, and DSL</td>
<td>55</td>
<td>30-54 Gy</td>
<td>79%</td>
</tr>
<tr>
<td>M.D. Anderson</td>
<td>85</td>
<td>FSC and FM</td>
<td>56</td>
<td>Combined-modality COP-Bleo/CHOP-Bleo +30-40 Gy</td>
<td>80</td>
</tr>
</tbody>
</table>

- **Initial treatment with RT rather than ChT or observation** *(Grade 2B).*
- **Involved lymphoid region, dose 24 Gy**
- **If significant morbidity / Pt against RT**
  - Management similar to advanced disease
Which Pts require specific attention?

- Grade IIIb / grade IIIa, treat as aggressive lymphomas
- Bulky stage II, manage as advanced FL?
- Intrafollicular neoplasia
  - a high content of BCL-2-positive B cells within a LN,
  - after removal of LN, follow clinically for evidence of progression
- Primary intestinal FL / primary cutaneous follicle center lymphoma,
  - manage separately

<table>
<thead>
<tr>
<th>Grade</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>0-5 centroblasts/hpf</td>
</tr>
<tr>
<td>Grade 2</td>
<td>6-15 centroblasts/hpf</td>
</tr>
<tr>
<td>Grade 3</td>
<td>&gt; 15 centroblasts/hpf</td>
</tr>
<tr>
<td>3a</td>
<td>Centrocytes present</td>
</tr>
<tr>
<td>3b</td>
<td>Solid sheets of centroblasts</td>
</tr>
</tbody>
</table>
Initial treatment of advanced Stg (III/IV) FL

- Not curable with conventional treatment
- Major indication for treatment:
  - alleviation of symptoms
  - Pts defer therapy
- Treat with an immunotherapy-based regimen (Grade 1A)
  - rather than chemotherapy alone or hematopoietic cell transplantation.
- A choice among the various regimens depends upon patient characteristics and physician comfort
# First-line Combined Immunochemotherapy in Untreated FL

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>PFS, %</th>
<th>OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>R-Chemo</td>
<td>Chemo</td>
</tr>
<tr>
<td>CHOP[1]</td>
<td>428</td>
<td>82*</td>
<td>64</td>
</tr>
<tr>
<td>CHVP-IFN[2]</td>
<td>358</td>
<td>52*</td>
<td>37</td>
</tr>
<tr>
<td>CVP[3]</td>
<td>321</td>
<td>54*</td>
<td>17</td>
</tr>
<tr>
<td>MCP[4]</td>
<td>201</td>
<td>71*</td>
<td>40</td>
</tr>
</tbody>
</table>

FOLL05: Study Design

- Randomized phase III trial
  - Median follow-up: 34 mos (range: 1-70)

Patients with previously untreated, active stage II-IV FL (N = 504)

3 x 21-day cycles

- CVP-R (n = 168)
- CHOP-R (n = 165)
- FM-R (n = 171)

≥ PR

CVP-R for additional 5 cycles

CHOP-R for additional 3 cycles*

FM-R for additional 3 cycles*

Stratified by FLIPI score (0-2 vs 3-5)

CVP-R: cyclophosphamide 750 mg/m² on Day 1; vincristine 1.4 mg/m² on Day 1; prednisone 40 mg/m² on Days 1-5; rituximab 375 mg/m² on Day 1

CHOP-R: cyclophosphamide 750 mg/m² on Day 1; doxorubicin 50 mg/m² on Day 1; vincristine 1.4 mg/m² on Day 1; prednisone 100 mg/m² on Days 1-5; rituximab 375 mg/m² on Day 1

FM-R: fludarabine 25 mg/m² on Days 1-3; mitoxantrone 10 mg/m² on Day 1; rituximab 375 mg/m² on Day 1

- Primary endpoint: TTF from registration date

*Followed by 2 cycles of rituximab.
FOLL05: TTF and PFS

- Improved 3-yr TTF and PFS with CHOP-R and FM-R vs CVP-R

<table>
<thead>
<tr>
<th>Efficacy Outcome, %</th>
<th>CVP-R (n = 168)</th>
<th>CHOP-R (n = 165)</th>
<th>FM-R (n = 171)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr TTF</td>
<td>45</td>
<td>63</td>
<td>59</td>
</tr>
<tr>
<td>3-yr PFS</td>
<td>52</td>
<td>68</td>
<td>63</td>
</tr>
</tbody>
</table>

- Consistent across all patient subgroups tested

<table>
<thead>
<tr>
<th>Comparison</th>
<th>TTF HR (95% CI)</th>
<th>P Value*</th>
<th>PFS HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHOP-R vs CVP-R</td>
<td>0.60 (0.43-0.83)</td>
<td>.007</td>
<td>0.61 (0.43-0.87)</td>
<td>.006</td>
</tr>
<tr>
<td>FM-R vs CVP-R</td>
<td>0.64 (0.46-0.88)</td>
<td>.020</td>
<td>0.67 (0.47-0.94)</td>
<td>.022</td>
</tr>
<tr>
<td>CHOP-R vs FM-R</td>
<td>0.94 (0.66-1.33)</td>
<td>.971</td>
<td>0.91 (0.63-1.33)</td>
<td>.628</td>
</tr>
</tbody>
</table>


*Adjusted.

October, 2013
Euasia, Hematology, Antalya
Bendamustine + Rituximab vs R-CHOP in Advanced FL, MCL, and Indolent NHL

- Regimen: bendamustine 90 mg/m² on Days 1 and 2 + rituximab Day 1 every 28 days

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Bendamustine + Rituximab</th>
<th>R-CHOP</th>
<th>( P ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, %</td>
<td>40.1</td>
<td>30.8</td>
<td>.0323</td>
</tr>
<tr>
<td>PFS, mos</td>
<td>54.8</td>
<td>34.8</td>
<td>.0002</td>
</tr>
<tr>
<td>PFS (FL), mos</td>
<td>NR</td>
<td>47.0</td>
<td>.02</td>
</tr>
<tr>
<td>TTNT, mos</td>
<td>NR</td>
<td>40.7</td>
<td>.0002</td>
</tr>
<tr>
<td>Deaths, n</td>
<td>34</td>
<td>33</td>
<td>--</td>
</tr>
</tbody>
</table>

First-line CHOP + Rituximab vs CHOP vs $^{131}$I-Tositumomab for FL: SWOG S0016

Patients with untreated advanced FL (bulky stage II, III, or IV) 
(N = 554)

• Primary endpoints: OS, PFS

CHOP x 6 cycles 
Rituximab x 6 doses 
(n = 279)

CHOP x 6 cycles 
(n = 275)

2 wks 
Tositumomab/ $^{131}$I-tositumomab

PFS

Median FU: 4.9 yrs

At Risk

Event

2-Yr Estimate

% Patients

Yrs From Registration

CHOP-R

CHOP-RIT

80%

76%

80%

100

60

40

20

0

0 2 4 6 8 10

CHOP-R

CHOP-RIT

At Risk

Event

2-Yr Estimate

% Patients

Yrs From Registration

OS

Median FU: 4.9 yrs

At Risk

Event

2-Year Estimate

% Patients

Yrs From Registration

CHOP-R

CHOP-RIT

93%

97%

80%

100

60

40

20

0

0 2 4 6 8 10

2-sided, multivariate $P = .11$

2-sided, multivariate $P = .08$
Lenalidomide + Rituximab as Initial Therapy in Indolent NHL: Response Rate

<table>
<thead>
<tr>
<th>Response, %</th>
<th>SLL (n = 30)</th>
<th>Marginal Zone Lymphoma (n = 27)</th>
<th>Follicular Lymphoma (n = 46)</th>
<th>All Patients Evaluable (n = 103)</th>
<th>ITT (n = 110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>80</td>
<td>89</td>
<td>98</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>• CR/CRu</td>
<td>27</td>
<td>67</td>
<td>87</td>
<td>64</td>
<td>60</td>
</tr>
<tr>
<td>• PR</td>
<td>53</td>
<td>22</td>
<td>11</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>SD</td>
<td>13</td>
<td>11</td>
<td>2</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>PD</td>
<td>7</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

- Responses in follicular lymphoma independent of GELF criteria or disease bulk
- Molecular responses in follicular lymphoma increased with treatment duration

<table>
<thead>
<tr>
<th>Molecular Response, %</th>
<th>Polymerase Chain Reaction* Positive</th>
<th>Polymerase Chain Reaction* Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>41</td>
<td>59</td>
</tr>
<tr>
<td>After cycle 3</td>
<td>11</td>
<td>89</td>
</tr>
<tr>
<td>After cycle 6</td>
<td>5</td>
<td>95</td>
</tr>
</tbody>
</table>

*Major or minor breakpoints from bone marrow, peripheral blood samples.

October, 2013
Euasia, Hematology, Antalya
Which Regimen to Prefer?

- R-CHOP is a standard treatment, but
- Bendamustin+rituximab (BR) regimen, in a heterogeneous group
  - improved PFS rates and
  - less toxicity when compared with R-CHOP.
- R-CVP would be an acceptable alternative
  - in pts, not candidates for anthracyclines (cardiac!)
FIT (Consolidation with RIT)

**INDUCTION**
First-line therapy with CVP, CHOP-like, fludarabine combinations, chlorambucil, or rituximab combination

6-12 wks

**RANDOMIZATION**

**CONSOLIDATION**

90Y-Ibritumomab tiuxetan consolidation (n = 207)
Rituximab 250 mg/m\(^2\) IV on Days 0 and 7 + 90Y 14.8 MBq/kg

Primary endpoint: PFS*

**CONTROL**
No further treatment (n = 202)

*Calculation of PFS starts at enrollment, not from induction.

FIT (Consolidation with RIT)

PFS for All Patients

HR: 0.465 (95% CI: 0.357-0.605; 2-sided log rank $P < 0.0001$)

$^{90}$Y-ibritumomab tiuxetan (n = 208):
median 36.5 mos

Control (n = 206):
median 13.3 mos

Rituximab Maintenance: PRIMA- PFS

Patients with previously untreated grade I-III FL (N = 1200)

- CHOP x 6 + Rituximab x 8
- CVP x 8 + Rituximab x 8
- FCM x 6 + Rituximab x 8

Maintenance Rituximab 375 mg/m² q2m x 2 yrs

Observation

Event-Free Rate

HR 0.55 (95% CI: 0.44-0.68; P < .0001)

Summary: Consolidation and Maintenance

- The efficacy of rituximab maintenance (versus no maintenance) may be dependent upon the choice of initial therapy
- at least a PR to initial therapy: maintenance rituximab rather than observation (Grade 2B).
- Use one of the established regimens, such as that used in the PRIMA study (rituximab every two months for a total of two years)
- No published data regarding the safety or efficacy of therapy extending beyond this; as such rituximab maintenance should not exceed two years.
Treatment of relapsed or refractory FL

- Almost all pts will ultimately develop progression requiring subsequent treatment
  - most commonly presents as asymptomatic PD
    - not necessarily require immediate treatment, but should be followed closely for symptoms
  - No standart therapy for symptomatic pts

- Histologic transformation to a more aggressive variant
  - rapid progression of LAP, infiltration of uncommon extranodal sites, development of systemic symptoms, or laboratory abnormalities.
  - Such patients should undergo LN biopsy
Treatments in Relapsed Pts

- Single agent Rituximab
- Rituximab+ChT
- RIT
- Low dose RT
- HCT
- Rituximab maintenance
- Rituximab+other biologic agents
Symptomatic Relapsed/Refractory Disease

- **RIT**: excellent alternative, but not a common practice due to the complexity.

- **Single agent rituximab**: Pts with a poor PS and/or a indolent clinic, suggested for low toxicity (Grade 2C).

- **Rituximab+ChT**: Pts with a good PS and aggressive clinic
  - **R-CVP / R-CHOP /BR**: based upon the pt’s history of prior therapy
    - superior response rates despite greater toxicity and no proven improvement in survival rates
Symptomatic Relapsed/Refractory Disease

• **Low dose RT:** palliation of local symptoms

• **HCT:**
  – relapse after a short initial response (<1 year) to chemoimmunoT and a chemo-sensitive disease; AuHCT rather than treatment with chemoimmunoT alone (**Grade 2B**).
  – relapse after AuHCT; consider for NMA-alloHCT.

• **Rituximab Maintenance:**
  – Yes: no initially rituximab
  – Reasonable: relapse following induction
  – No: relapse while rituximab maintenance
Rituximab ± Bortezomib in Relapsed, Rituximab-Naive or -Sensitive FL: Phase III

- **Rituximab 375 mg/m²**
  - Cycle 1: Days 1, 8, 15, 22
  - Cycles 2-5: Day 1 only

- **Rituximab + Bortezomib**
  - Rituximab 375 mg/m²
  - Cycle 1: Days 1, 8, 15, 22
  - Cycles 2-5: Day 1 only + Bortezomib 1.6 mg/m²

**Patients with relapsed, rituximab-naive or -sensitive FL** (N = 670)

- Median PFS, Mos (95% CI)
  - Rituximab: 11.0 (9.1-12.0)
  - Bortezomib/rituximab: 12.8 (11.5-15.0)
  - HR: 0.822 (95% CI: 0.681-0.991; P = .039)

- Median follow-up: 33.9 mos
- Estimated 2-yr PFS: 31.2% vs 23.5% for bortezomib + rituximab vs rituximab, respectively

October, 2013
Euasia, Hematology, Antalya
CALGB 50401: Randomized phase II trial

Patients with FL who relapsed following ≥ 1 rituximab-based regimen (N = 89)

Rituximab + Lenalidomide (n = 44)

Lenalidomide (n = 45)


<table>
<thead>
<tr>
<th>Efficacy Outcome</th>
<th>Lenalidomide + Rituximab (n = 44)</th>
<th>Lenalidomide (n = 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, %</td>
<td>72.7</td>
<td>51.1</td>
</tr>
<tr>
<td>• CR</td>
<td>36.4</td>
<td>13.3</td>
</tr>
<tr>
<td>• PR</td>
<td>36.4</td>
<td>37.8</td>
</tr>
</tbody>
</table>

EFS

- Median EFS, yrs: 2.0* vs 1.2
- 2-yr EFS, %: 44 vs 27
  - Unadjusted HR
  - Adjusted HR†: 2.1 (P = .010) vs 1.9 (P = .061)

- Primary endpoint: ORR (≥ 35% ORR considered of statistical interest)
- Secondary endpoints: CR rate; EFS; toxicity; immunologic correlates; identify benchmarks for future studies

Lenalidomide active both as monotherapy and combined with rituximab

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Histologically Transformed Disease

- Confirm by biopsy showing the presence of a more aggressive NHL variant
- Treat with ChT regimens similar to those used for the treatment of the aggressive NHL (rarely curative in HT)

- Limited stage + limited prior therapy: ChT alone (R-CHOP)
- Resistant / relapsed disease: salvage regimen similar to that used in relapsed/resistant aggressive NHL (Grade 2C)
- Selected younger pts with chemosensitive disease: ASCT (Grade 2C).
Treatment of marginal zone (MZL) lymphoma

- Three distinct diseases
  - arise from post-germinal center marginal zone B cells
  - share a similar immunophenotype

- Extranodal MZL (MALT lymphoma)
  - Developing in stomach (gastric MALT)
  - non-gastric extranodal locations (non-gastric MALT)
  - Any MALT in any stage, coexistent large cell lymphoma, treat as DLBCL

Splenic MZL: indolent, >10y OS
Nodal MZL: no consensus on Tx
Gastric

- H. pylori eradication
  - advanced / progressive disease after this initial treatment: IFRT
- H. pylori negative gastric MALT
  - treat with IFRT without antibiotics

non-Gastric MALT

- Limited stage (stage I/II)
  - Treatment with locoregional RT (Grade 2B)
  - Observe for PD
- Advanced stage
  - Chemoimmunotherapy (similar to FL treatment)

Splenic MZL

Involves the spleen, splenic hilar LNs, BM, and PB
Indolent course, >mOS (10 years)

• Asymptomatic:
  – observation rather than initial treatment (Grade 2C).

• Isolated splenic MZL / local symptoms
  – splenectomy rather than rituximab (Grade 2C).

• Cytopenias + no concomitant HCV
  – rituximab rather than splenectomy / observation (Grade 2C).

• Coexisting HCV
  – Anti-viral therapy rather than rituximab, splenectomy, or observation (Grade 2C)

Nodal MZL

• Primary nodal lymphoma features identical to LNs involved by extranodal (MALT) lymphoma, but without evidence of extranodal disease

• No general consensus regarding the treatment

• Treat in a similar fashion to those with the more common indolent lymphoma, FL.

Treatment of WMG

- Many pts, asymptomatic, can be observed
- No clear advantage to early tx
- Indications for treatment
  - presence of systemic symptoms, cytopenia, organomegaly
  - Signs and symptoms due to the presence of hyperviscosity
  - Presence of severe neuropathy
Initial Treatment of WMG

- Asymptomatic and have adequate hemoglobin and platelet levels (hemoglobin $\geq 11\text{ g/dL}$ and platelet count $\geq 120,000/\text{microL}$): observation alone (every 6 mo)

- Symptomatic WM: rituximab (either alone or with other agents)
  - Low tumor burden / minimally symptomatic: rituximab alone
  - High tumor burden / heavy-symptomatic: ChT + rituximab
    - Candidate for HCT?: cylophosphamide + dexamethasone
    - Not candidate: chlorambucil, cladribine
  - Hyperviscosity symptoms: therapeutic plasmapheresis

Strategy in treating indolent B-cell neoplasia in the future

• **Proapoptotic agents**
  - GDC-0617
  - TL 32711

• **Targetting B-cell**
  - CD20, CD22, CD19
    (Ofatumumab, obinutuzumab)
  - BCR
    - Ibrutinib
    - Fostamatinib
    - Idelalisib
Critical Signaling Pathways and New Targeted Agents in B-Cell Malignancies

- B-cell antigen receptor (BCR) signaling is required for tumor expansion and proliferation
- High response rates with Idelalisib in combination with rituximab/ bendamustine
  - ORR 78% overall
  - PFS at 24 months: 62.5%
  - DOR at 24 months 69%

ASCO 2013, Leonard JP
Treatment of advanced stage (IIB to IV) mycosis fungoides (MF) and Sézary (SS) syndrome

- MF: extranodal, indolent, CTCL; primarily develops in the skin, but can ultimately involve the LNs, PB, and visceral organs
- SS: more aggressive leukemic variant of CTCL with circulating malignant (Sézary) cells in PB
- Pts require systemic tx
  - Early stage with folliculotrophic / transformed large cell variants
  - Advanced stage: extracutaneous / advanced skin disease
Treatment of advanced stage MF (IIB to IV)

- **Stg IIB**
  - Limited: RT+skin-directed Tx
  - Generalized: Total skin electron beam RT+ systemic Tx

- **Stg III**
  - IIIA: skin-directed+ a systemic Tx (eg, bexarotene)
  - IIIB: systemic Tx ± skin directed

- **Stg IV (Non SS/Solid organ involved)**
  - Romidepsin, denileukin diftitox, or systemic ChT (Grade 2B)
  - Combination ChT (vs conservative sequential): Faster response but no survival advantage
Sézary syndrome

• Low tumor borden:
  – a systemic therapy with or without skin directed Tx
  – prefer nonimmunosuppressive systemic extracorporeal photochemotherapy (ECP)

• High tumor borden:
  – combination systemic biologic therapies or histone deacetylase (HDAC) inhibitors are usually needed

Conclusion

• Indolent NHLs are distinct group of diseases with indolent course and can be treated with large spectrum of therapeutic approach, from observation to allogeneic SCT

• Generally early or limited staged-pts can be observed or locally treated

• Pts with symptomatic, high tumor burden, relapsed or transformed disease require systemic treatments