Targeted Radioimmunotherapy for Lymphoma

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Disclosures

Financial Disclosures

Erik Mittra, MD, PhD (speaker)  Nothing to Disclose
John Pagel, MD, PhD (speaker)  Nothing to Disclose
Hossein Jadvar, MD (Co-Organizer):  Nothing to Disclose
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  Spectrum Pharmaceutical Consultant/Advisor
Saima Hedrick, MPH (Moderator):  Nothing to Disclose

FDA Disclosure

This presentation will not include discussion of any device or drug requiring FDA approval.
Non-Hodgkin Lymphoma

• Indolent
  – No urgency to treat if asymptomatic
  – Multiple chemotherapy regimens with responses/relapses

• Aggressive
  – Curable with chemotherapy
  – Relapses cured with high dose therapy and stem cell transplantation
Indolent NHL: Management

- **Indolent NHL:**
  - Management
  - Diagnosis
  - Initial Treatment
  - Progression

**Good or Intermediate Risk (IPI L or LI):**
- Treatment Indicated?
  - Yes
  - Initial Treatment
  - High Risk (IPI HI or H)

- **Workup (Staging):**
  - Initial Treatment

- **Indications for treatment:**
  - Threatened end-organ function
  - Eligible for trial
  - Massive bulk at presentation
  - Cytopenia(s)
  - Steady progression
  - Recurrent infections
  - Symptoms
  - Patient preference

**Progression:**
- Observe
- No
Options for the Management of FL

**INDUCTION**
- Types of therapy:
  - Combination chemo- or immunotherapy

**CONSOLIDATION**
- Types of therapy:
  - Radiolabeled immunotherapy

**MAINTENANCE**
- Types of therapy:
  - Immunotherapy

Goals of therapy over a patient’s course of treatment:
- Reduce tumor load and induce initial response
- Maximize response by rapidly improving quality of response to induction (increased CR rates, bcl-2 conversion)
- Prevent relapse by maintaining best response

Quality of Remission (CR Rate) vs. Remission Duration

- Treated patients who achieved a CR had a significantly longer OS than those only reaching a PR
Influence of CR Achievement during First Line Therapy

Bachy et al. JCO 2010;28:822-9
Strategies for Antibody Use

- Combination with chemotherapy
  - e.g. CHOP plus Rituximab
- Prolonged therapy
- Combinations of multiple Abs
- Combinations with “boosters” to the immune system
- Combined with toxins and/or radioisotopes
- Detect “minimal residual disease”
- Transplantation
Antibody-Host Interactions in Cancer Immunotherapy

-Adapted from Male, 1996.
Limitations of Naked Antibodies

- All tumor cells need to be targeted by Ab
- Patient’s immune mechanisms may not be functional
- Resistant tumor cells
  - To direct anti-tumor mechanisms
  - To immune mechanisms-mediated by the antibody
- Antigen-negative tumor cells may escape
Additional Cell-Killing Mechanisms of Monoclonal Antibodies

- Radiation/Radionuclide
- Toxin/Drug
- Apoptosis
Radioimmunotherapy
Principles of Radioimmunotherapy

- Targeted delivery of radiation to tumor cells
- Greater exposure of radiation to tumors vs surrounding normal organs
- Continuous exposure of tumor cells
- Retention of anti-tumor mechanisms of the antibody
# Anti-CD20 Radioimmunoconjugates for NHL

<table>
<thead>
<tr>
<th></th>
<th>Zevalin</th>
<th>Bexxar</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parent antibody</strong></td>
<td>Ibritumomab</td>
<td>Tositumomab</td>
</tr>
<tr>
<td><strong>Radionuclide</strong></td>
<td>Yttrium-90</td>
<td>Iodine-131</td>
</tr>
<tr>
<td><strong>Properties</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Emission</td>
<td>Pure $\beta$</td>
<td>$\gamma$ and $\beta$</td>
</tr>
<tr>
<td>Radiation penetration</td>
<td>5-10 mm</td>
<td>1 mm</td>
</tr>
<tr>
<td>Half-life</td>
<td>2.7 days</td>
<td>8.1 days</td>
</tr>
<tr>
<td>Dosimetry required</td>
<td>No (optional)</td>
<td>Yes</td>
</tr>
</tbody>
</table>
RIT: Where Does It Fit in a Treatment Plan?

- Treatment plans differ with:
  - Patient’s clinical status
  - Patient’s medical history
  - Histologic type
  - Presence of bulky disease
### Suggested Treatment Regimens

#### (in alphabetical order)

#### First-line Therapy
- Bendamustine + rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab (category 1)
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab (category 1)
- Fludarabine + rituximab
- FND (fludarabine, mitoxantrone, dexamethasone) + rituximab
- Radioimmunotherapy (category 2B)
- Rituximab

#### First-line Consolidation or Extended Dosing
- Chemotherapy followed by radioimmunotherapy (category 1)
- Rituximab maintenance (category 2B) [It is strongly recommended this treatment be on a prospective clinical study.]

#### Second-line and Subsequent Therapy
- Chemoimmunotherapy (as in first-line therapy)
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- High dose therapy with autologous stem cell rescue
- High dose therapy with allogeneic stem cell rescue, for highly selected patients
- Radioimmunotherapy (category 1)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)

#### Second-line Extended Dosing
- Rituximab maintenance (category 1)

For patients with locally bulky or symptomatic disease, consider IFRT 4-30 Gy ± additional systemic therapy.
Randomized Phase III Study in Relapsed or Refractory Low Grade or Follicular NHL

N=130

STUDY ELIGIBILITY

- Relapsed or refractory low-grade or follicular B-cell NHL
- No prior rituximab therapy
- Histologically confirmed NHL requiring therapy
- WHO PS ≤2
- Less than 25% bone marrow involvement by NHL
- No prior BMT
- Acceptable hematologic function

ZEVALIN (n=64)

Day 1: Rituximab 250mg/m²
In-111 ZEVALIN 5mCi

Day 8: Rituximab 250mg/m²
Y-90 ZEVALIN 0.4 mCi/kg

Rituximab (n=66)

Weeks 1-4: Rituximab 375 mg/m²

## Significantly Higher ORR and CR/CRu Rate in Zevalin Arm

<table>
<thead>
<tr>
<th></th>
<th>ZEVALIN (n=64)</th>
<th>Rituximab (n=66)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall RR</td>
<td>83%</td>
<td>55%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CR/CRu rate</td>
<td>38%</td>
<td>18%</td>
<td>N/A</td>
</tr>
</tbody>
</table>


Earlier Treatment with Zevalin Produces Higher CR/CRu Rates

Response Rate by Treatment Encounter
BEXXAR and Chemotherapy

Percent with Response
2nd 3rd 4th 5th 6th 7 or more
Treatment Encounter Number

Bexxar
Chemotherapy
FIT Trial: Study Schema

FIRST-LINE CHEMOTHERAPY
- CHOP/CHOP-like
- CVP/COP
- Rituximab combinations
- Chlorambucil
- Fludarabine/fludarabine combinations

Enrollment in Study

CR/CRu or PR

RANDOMIZATION

ZEVALIN (n=208)
- Day 1, 7 rituximab 250 mg/m² IV
- Day 7 Y-90 ZEVALIN 0.4mCi/kg IV

CONTROL (n=206)
- No Further Treatment

Median 7 months interval from start of initial treatment until entry into the study

PFS was calculated from time of randomization

Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Control (n = 202)</th>
<th>⁹⁰Y-Ibritumomab (n = 207)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>101 (50)</td>
<td>99 (48)</td>
</tr>
<tr>
<td>Age at randomization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, y (range)</td>
<td>53 (27-74)</td>
<td>55 (29-78)</td>
</tr>
<tr>
<td>Aged &gt; 60 y, n (%)</td>
<td>48 (24)</td>
<td>58 (28)</td>
</tr>
<tr>
<td>Ann Arbor classification, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>62 (31)</td>
<td>73 (35)</td>
</tr>
<tr>
<td>Stage IV</td>
<td>134 (66)</td>
<td>132 (64)</td>
</tr>
<tr>
<td>Response to first-line treatment, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR/CRu</td>
<td>108 (53)</td>
<td>107 (52)</td>
</tr>
<tr>
<td>PR</td>
<td>88 (44)</td>
<td>100 (48)</td>
</tr>
</tbody>
</table>

Patient baseline characteristics and distribution of first-line induction treatments were well balanced between treatment arms.
<table>
<thead>
<tr>
<th>FLIPI scores, n (%)</th>
<th>Control</th>
<th>(^{90}\text{Y-Ib} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 146* (%)</td>
<td>n = 150* (%)</td>
</tr>
<tr>
<td>Low risk (0-1 factors)</td>
<td>62 (42.5)</td>
<td>56 (37.3)</td>
</tr>
<tr>
<td>Intermediate risk (2 factors)</td>
<td>54 (37.0)</td>
<td>58 (38.7)</td>
</tr>
<tr>
<td>High risk (3-5 factors)</td>
<td>30 (20.5)</td>
<td>36 (24.0)</td>
</tr>
</tbody>
</table>

* FLIPI data could be collected retrospectively in 71% of intent-to-treat population.

Overall CR Rates After Randomization

<table>
<thead>
<tr>
<th>CR/CRu</th>
<th>Control, %</th>
<th>$^{90}$Y-Ibritumomab, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 202</td>
<td>n = 207</td>
</tr>
<tr>
<td>After induction therapy</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>After randomization</td>
<td>53</td>
<td>87</td>
</tr>
</tbody>
</table>
## Conversion to *bcl*-2 PCR-Negative Status in the Blood

<table>
<thead>
<tr>
<th></th>
<th>Control, n/N* (%)</th>
<th>^{90}Y-ibritumomab, n/N* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>21/59 (36)</td>
<td>61/68 (90)</td>
</tr>
</tbody>
</table>

*Patients with PCR-positive status at randomization who had at least 1 post-randomization PCR assessment; all other patients were either PCR negative at randomization or lacked a second assessment.

90% of patients converted from *bcl*-2 PCR-positive to PCR-negative status after ^{90}Y-ibritumomab consolidation
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patient Population</th>
<th>CR/CRu Rate After 90Y-ibritumomab Consolidation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FIT 90Y-ibritumomab arm:</strong> Chemo induction + 90Y-ibritumomab consolidation</td>
<td>Stage III-IV FL 64% stage IV 24% high FLIPI</td>
<td>87%</td>
<td>Morschhauser et al(^1)</td>
</tr>
<tr>
<td>R (4 weeks) + R-CHOP (3 cycles) + 90Y-ibritumomab consolidation</td>
<td>Stage II-IV FL 66% stage IV</td>
<td>72%</td>
<td>Hainsworth et al(^2)</td>
</tr>
<tr>
<td>R-CHOP (3 cycles) + 90Y-ibritumomab consolidation + R maintenance</td>
<td>FL 90% stage III-IV 42% high FLIPI</td>
<td>89%*</td>
<td>Jacobs et al(^3)</td>
</tr>
</tbody>
</table>

*Assessed by PET imaging

The 7-year overall PFS was 23% in the control arm compared with 47% in the $^{90}$Y-ibritumomab arm. HR = 2.09 (95% CI: 1.63 – 2.67); $P < 0.001$
The 5-year PFS among patients with a PR after induction was 14% in the control arm compared with 38% in the $^{90}$Y-ibritumomab arm.

HR = 2.62 (95% CI: 1.88 – 3.66); $P < 0.001$
Patients in the $^{90}$Y-ibritumomab arm had a greater than 5-year advantage in TTNT compared with patients in the control arm

HR = 2.03 (95% CI: 1.53 – 2.69); $P < 0.0001$

$^{90}$Y-ibritumomab: n = 207
Median TTNT: > 99 mo

Control: n = 202
Median TTNT: 35 mo
Hematologic Toxicities: Timeline

* Based on median time to nadir and recovery for ZEVALIN-treated patients
*Grade 3 or 4 AEs reported in ≥ 5 patients in either treatment arm.

Secondary Malignancies That Have Emerged During Extended Follow-up

<table>
<thead>
<tr>
<th>Secondary Malignancy</th>
<th>Control, n (%)</th>
<th>⁹⁰⁸-Y-ibritumomab, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 202</td>
<td>n = 207</td>
</tr>
<tr>
<td>Basocellular carcinoma of the skin</td>
<td>1 (0.5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Basocellular epithelioma</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1 (0.5)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Endometrial carcinoma</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>MDS/AML</td>
<td>1 (0.5)</td>
<td>6 (2.9)</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Papillary thyroid carcinoma</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary adenocarcinoma</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma of the lung</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Squamous cell carcinoma of the skin</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Vesical transitional cell carcinoma TgGA-2</td>
<td>0</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9 (4.5)</strong></td>
<td><strong>16 (7.7)</strong></td>
</tr>
</tbody>
</table>
MDS/AML: Annualized Rates in $^{90}$Y-Ibritumomab Studies Compared With FL Patients Generally (SEER Data)

<table>
<thead>
<tr>
<th></th>
<th>FIT Study,$^1$</th>
<th>Witzig Studies$^2$</th>
<th>SEER data$^3$ (R)-Chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annualized rate</td>
<td>0.55%</td>
<td>1.0%</td>
<td>1.03%</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.25% - 1.23%</td>
<td>0.4% - 1.7%</td>
<td>0.96% - 1.11%</td>
</tr>
</tbody>
</table>

The annualized rate of secondary MDS/AML in patients treated with $^{90}$Y-Ibritumomab does not appear higher than the annualized rate of MDS/AML observed in patients treated for FL generally.

Overall Survival

All patients
40 deaths

- Control
  22 deaths

- 90Y-ibritumomab
  18 deaths

• At current follow-up, there is no significant difference in OS between treatment arms ($P = 0.465$)
  - 5-year OS was 93% in the 90Y-ibritumomab arm compared with 89% in the control arm
The 5-year OS was 89% in the control arm compared with 93% in the $^{90}$Y-ibritumomab arm. HR = 1.26 (95% CI: 0.68 – 2.35); $P = 0.465$

$^{90}$Y-ibritumomab: n = 207
Median OS: > 98 mo

Control: n = 202
Median OS: > 101 mo
# Subsequent Management After PD

<table>
<thead>
<tr>
<th>Treatment After PD</th>
<th>Control, n (%)</th>
<th>⁹⁰Y-Ibritumomab, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 141*</td>
<td>n = 104*</td>
</tr>
<tr>
<td>Rituximab</td>
<td>102 (72)</td>
<td>63 (61)</td>
</tr>
<tr>
<td>⁹⁰Y-Ibritumomab tiuxetan</td>
<td>12 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Autologous transplantation</td>
<td>31 (22)</td>
<td>13 (13)</td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>3 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fludarabine, FC (M), FM</td>
<td>15 (11)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>ICE</td>
<td>2 (1)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>DHA (P) / DHA (Oxa) / ESHA (P)</td>
<td>13 (9)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Bendamustine</td>
<td>0 (0)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (9)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>No treatment given</td>
<td>19 (13)</td>
<td>22 (21)</td>
</tr>
</tbody>
</table>

*Patients may have received ≥ 1 treatment.
Patients in Control and $^{90}$Y-Ibritumomab Arms Achieved Comparable Responses to Second-Line Therapy

<table>
<thead>
<tr>
<th>Response to Second-Line Therapy After Progressive Disease, %</th>
<th>Control (n = 122*)</th>
<th>$^{90}$Y-Ibritumomab (n = 82*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>78%</td>
<td>79%</td>
</tr>
<tr>
<td>CR/CRu</td>
<td>59%</td>
<td>57%</td>
</tr>
<tr>
<td>PR</td>
<td>19%</td>
<td>22%</td>
</tr>
<tr>
<td>SD</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

*Number of patients who received treatment after progressive disease.

ORR = overall response rate; CR = complete response; CRu = unconfirmed CR; PR = partial response; SD = stable disease.
Conclusions to FIT Study

• $^{90}$Y-Ibritumomab consolidation resulted in high conversion rates from PR to CR/CRu and high overall CR rate

• $^{90}$Y-Ibritumomab consolidation significantly prolonged median PFS compared with no further treatment in patients responsive to first-line induction treatment

• $^{90}$Y-Ibritumomab consolidation was well tolerated with manageable hematologic adverse events
  – Annualized rate of $2^0$ MDS/AML was 0.55

• $^{90}$Y-Ibritumomab consolidation confers a durable PFS benefit
  – Nearly 3-year PFS advantage for patients in the ITT population
  – At least a 5-year PFS advantage with a CR/CRu after induction
  – 2-year PFS advantage for patients with a PR after induction
  – > 5-year advantage in time to next treatment

• At current follow-up, there is no significant difference in OS between treatment arms ($P = 0.465$)
Responses to CHOP $\rightarrow$ Bexxar (N=84*)

- **After CHOP**
  - CR: 54%
  - PR: 44%
  - SD: 2%

- **After Bexxar**
  - PR: 24%
  - CR: 74%

* evaluable pt.

Press, et al., ASH 2005 (abstract)
Hematologic Toxicities (Grade 3-4)

- **CHOP (N=89)**
- **Bexxar (N=81)**

**SWOG 9911**

Treatment-Related Deaths: 0

Progression-Free and Overall Survival
SWOG-9911

Overall Survival
Progression-Free Survival

Median FU = 5.1 yr

OS
PFS

5-Year Estimate
Overall Survival 87%
Progression-Free Survival 67%

Press, et al., ASH 2005 (abstract)
38 informative patients:
PCR + for t(14;18) at study entry
and serial BM PCR available
32 (84%) PCR neg. after therapy

- **PCR neg. after Bexxar**
  - 24 pt (63%)*

- **PCR neg. after CHOP**
  - 7 pt (18%)

- **PCR + after Rx**
  - 6 pt (16%)

- **PCR neg. but timing unclear**
  - 1 pt (3%)

*1 pt subsequently reconverted to PCR +

Press, et al., ASH 2005 (abstract)
Progression-Free Survival
SWOG-9911 vs. Historical CHOP Studies

CHOP + Bexxar (S9911)

CHOP (S7426,S7713)

5-Year Estimate
CHOP + Bexxar
Historical CHOP

67%
44%

Press, et al., ASH 2005 (abstract)
Overall Survival
SWOG-9911 vs. Historical CHOP Studies

CHOP + Bexxar (S9911)

CHOP (S7426,S7713)

5-Year Estimate

CHOP + I-131 Tx  87%
Historical CHOP    64%

Press, et al., ASH 2005 (abstract)
CHOP vs R-CHOP vs Tositumomab + $^{131}$I-Tositumomab in Untreated FL

- End points: response rates, toxicity, and molecular response rates of t(14;18)/bcl-2 rearrangements in BM
Bexxar: initial FL therapy

- 95% response rate!
- 75% complete response!
- 89% 5 yr overall survival!
Bexxar: initial FL therapy

N=76 patients

Kaminski et al, NEJM, 352:441, 2005
Single Agent Zevalin
Overall survival
Results: Time to next treatment

Median n.r.
# NCCN Treatment Guidelines

## Non-Hodgkin’s Lymphomas

### NCCN Clinical Practice Guidelines in Oncology™ – V.1.2010

### Suggested Treatment Regimens

#### First-line Therapy
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- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- High dose therapy with autologous stem cell rescue
- High dose therapy with allogeneic stem cell rescue, for highly selected patients

#### First-line Therapy for Elderly or Infirm (if none of the above are tolerable)
- Radioimmunotherapy
- Rituximab, preferred
- Single agent alkylators (e.g., chlorambucil or cyclophosphamide)

For patients with locally bulky or symptomatic disease, consider IFRT 4–30 Gy ± additional systemic therapy.
Questions?
Join us for other webinars in the
Targeted Radioisotope Therapy Series
Visit SNMMI.org/webinars for more information
You will receive a link for the post-webinar test in an email.
You must successfully complete the test to receive the credit.