Bendamustine is Effective Therapy in Patients with Rituximab-Refractory, Indolent B-Cell Non-Hodgkin Lymphoma

Kahl BS et al. 
Bendamustine is a novel alkylating agent with a benzimidazole ring that inhibits tumor cell growth by inducing mitotic failure and apoptosis.

In March 2008, bendamustine was approved for the treatment of chronic lymphocytic leukemia in the United States.

A previously published Phase II study demonstrated that single-agent bendamustine produced durable objective responses in patients with recurrent, rituximab-refractory, indolent B-cell lymphoma (JCO 2008;26:204).

Current study objective:

Phase II Trial of Bendamustine for Rituximab-Refractory Indolent B-Cell NHL

Eligibility (N = 100)

- Rituximab-refractory indolent NHL
- Bidimensional measurable disease
- At least one lesion ≥ 2 cm
- Between 1 and 3 prior treatments allowed
- Prior ASCT allowed

Bendamustine

IV 120 mg/m² d1 and d2 q3wks x 6-8 cycles*

* Dose reductions allowed if Grade IV hematologic or Grade III/IV nonhematologic adverse events developed.

Primary endpoints included overall response rate and duration of response.

### Patient Characteristics — Previous Therapies

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median number of previous chemotherapy regimens [range]</strong></td>
<td>2 [0-6]</td>
</tr>
<tr>
<td><strong>Type of previous therapy</strong></td>
<td></td>
</tr>
<tr>
<td>Single-agent rituximab</td>
<td>1 (1%)*</td>
</tr>
<tr>
<td>CHOP-like chemo rituximab</td>
<td>37 (37%)</td>
</tr>
<tr>
<td>CVP ± rituximab</td>
<td>38 (38%)</td>
</tr>
<tr>
<td>Purine analog-based ± rituximab</td>
<td>44 (44%)</td>
</tr>
<tr>
<td>Radioimmunotherapy</td>
<td>24 (24%)</td>
</tr>
<tr>
<td>External beam radiation therapy</td>
<td>20 (20%)</td>
</tr>
</tbody>
</table>

* Patient in protocol violation but included in primary analysis according to prespecified analysis conditions

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Overall Response Rate (ORR) and Median Duration of Response (DoR)

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>ORR*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 100)</td>
<td>75%</td>
</tr>
<tr>
<td>Chemosensitive (n = 51)</td>
<td>88%</td>
</tr>
<tr>
<td>Chemorefractory (n = 36)</td>
<td>64%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>DoR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n = 75)</td>
<td>9.2 mos (7.1-10.8)</td>
</tr>
<tr>
<td>Chemosensitive (n = 45)</td>
<td>10.0 mos (8.4-11.7)</td>
</tr>
<tr>
<td>Chemorefractory (n = 23)</td>
<td>6.3 mos (4.9-NA)</td>
</tr>
</tbody>
</table>

NA = not available
* ORR was assessed by independent review committee. ORR was defined as proportion of patients with best response ≥ partial response.

### Adverse Events* (N = 100)

<table>
<thead>
<tr>
<th>Hematologic Adverse Events</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19%</td>
<td>6%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>38%</td>
<td>23%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>5%</td>
<td>1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonhematologic Adverse Events</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>15%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>12%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
</tr>
</tbody>
</table>

* Six possible treatment-related deaths occurred on study.
Conclusions

> Single-agent bendamustine produced a high rate of response in patients with recurrent, indolent NHL.
  - ORR: 75% for overall patient group
  - DoR: 9.2 mos for overall patient group
  - Median progression-free survival: 9.3 mos for overall patient group (data not shown)

> The toxicity profile of bendamustine was acceptable.
  - Major toxicities associated with treatment were reversible myelosuppression, gastrointestinal toxicity and infection.

> These data support the clinical benefit of bendamustine in patients with indolent B-cell NHL that is refractory to rituximab.

**DR FOSS:** This is an important paper as it demonstrated a high overall response rate and a median response duration and progression-free survival of approximately nine months for patients with disease that was refractory to other therapies, including rituximab. The toxicity was relatively mild, and patients tolerated the therapy well. It gives us another option for patients with low-grade lymphomas who will receive multiple lines of therapy during the course of their disease.

**DR VOSE:** The study used a bendamustine dose of 120 mg/m² on days 1 and 2 every three weeks. I would say that most people nowadays use the 90-mg/m² days 1 and 2 dose to start with, and that is better tolerated.

Rummel MJ et al.  
Proc ASH 2009;Abstract 405.
Introduction

> Bendamustine is approved as a single-agent treatment for relapsed/refractory indolent non-Hodgkin’s lymphoma (NHL).
> A Phase II trial of bendamustine and rituximab (BR) showed high activity in relapsed indolent lymphomas that was accompanied by low toxicity (*JCO* 2005;23:3383).
  - Overall response rate (ORR): 90%
  - Complete remission rate: 60%
> Current study objective:
  - Compare BR to CHOP-R as a first-line treatment for indolent and mantle-cell lymphomas.

Eligibility (n = 519)

Stage III/IV CD20+ lymphomas:
- Follicular (grade 1/2)
- Waldenström
- Marginal zone
- Small lymphocytic
- Mantle-cell lymphoma

Accrual: 549

R

B, 90 mg/m² d1 and 2
R, 375 mg/m² d1
q4wks x 6 maximum
(n = 260)

Standard CHOP-R regimen
q3wks x 6 maximum
(n = 253)

# Efficacy Results

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>BR (n = 260)</th>
<th>CHOP-R (n = 253)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>92.7%</td>
<td>91.3%</td>
<td>—</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>39.6%</td>
<td>30.0%</td>
<td>0.0262</td>
</tr>
<tr>
<td>Progression-free survival (PFS) Follicular lymphoma patients (n = 277)</td>
<td>54.9 mos Not reached</td>
<td>34.8 mos 46.7 mos</td>
<td>0.00012 0.0281</td>
</tr>
</tbody>
</table>
### Grade 3/4 Adverse Events - Hematologic

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>BR (n = 1,450) % of cycles</th>
<th>CHOP-R (n = 1,408) % of cycles</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytopenia</td>
<td>12.1</td>
<td>38.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>10.7</td>
<td>46.5</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>G-CSF administered</td>
<td>4.0</td>
<td>20.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0.7</td>
<td>1.2</td>
<td>—</td>
</tr>
<tr>
<td>Anemia</td>
<td>1.4</td>
<td>1.9</td>
<td>—</td>
</tr>
</tbody>
</table>

## Adverse Events - All CTC Grades

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>BR (n = 260) # of patients</th>
<th>CHOP-R (n = 253) # of patients</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia</td>
<td>—</td>
<td>+++</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Paresthesias</td>
<td>18</td>
<td>73</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>16</td>
<td>47</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Erythema</td>
<td>42</td>
<td>23</td>
<td>0.0122</td>
</tr>
<tr>
<td>Allergic reaction (skin)</td>
<td>40</td>
<td>15</td>
<td>0.0003</td>
</tr>
<tr>
<td>Infectious complications</td>
<td>96</td>
<td>127</td>
<td>0.0025</td>
</tr>
</tbody>
</table>

BR significantly improved CR and PFS compared to CHOP-R in patients with indolent and mantle-cell lymphoma.

- **CR**: 39.6% vs 30.0%
- **PFS**: 54.9 mos vs 34.8 mos

Overall survival did not differ between the two study arms (data not shown).

The tolerability profile with BR was better compared to CHOP-R.

- No alopecia
- Less hematotoxicity, less G-CSF used and fewer infections and neuropathy

BR has the potential to become a standard treatment option for select patients with indolent and mantle-cell lymphoma.

**DR FISHER:** This paper was impressive in its results, and it evaluated BR compared to R-CHOP in all kinds of indolent lymphomas, particularly follicular lymphoma (FL) and mantle-cell lymphoma (MCL). Though we have not seen publication yet, BR produced a better PFS and CR rate with less toxicity. BR also appears to work better preferentially in FL and MCL. When the toxicity of CHOP is prohibitive, BR is a reasonable option, and with additional analysis it may emerge as a treatment with value to all patients.

**DR FOSS:** This is a key study for the initial management of low-grade lymphomas, and based on the efficacy and tolerability data, BR is an option for first-line therapy for patients with low-grade lymphomas who require cytotoxic chemotherapy.
Rituximab Maintenance for 2 Years in Patients with Untreated High Tumor Burden Follicular Lymphoma After Response to Immunochemotherapy

Salles GA et al.  
*Proc ASCO* 2010;Abstract 8004.
Rituximab (R) maintenance has shown clinical benefit for patients with follicular lymphoma (FL):
- In the relapsed setting after induction with chemotherapy plus R (JCO 2010;28:2853).
- In the first-line setting after induction chemotherapy alone\(^1\) or R alone\(^2\) (\(^1\)JCO 2009;27:1607, \(^2\)Blood 2004;103:4416).

The role of R maintenance in FL after first-line R-chemotherapy induction has not been defined.

Current study objective:
- Assess the benefit of two years of R maintenance for patients (pts) with FL responding to first-line R-chemotherapy induction.

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.
Eligibility (n = 1,217)
- Untreated FL
- Grade I, II or IIIa
- ≥3 nodal sites

Induction
- R-CVP (x8) OR
- R-CHOP (x6)* OR
- R-FCM (x6)*

≥PR (n = 1,018)

R maintenance
- n = 505
- R 375 mg/m²
- q8wk x 2y

Observation
- n = 513

* Followed by two additional R infusions

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.
Primary Endpoint: Progression-Free Survival

<table>
<thead>
<tr>
<th>Progression-Free Survival</th>
<th>Observation (n = 513)</th>
<th>R Maintenance (n = 505)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-year progression-free survival (PFS)</td>
<td>66%</td>
<td>82%</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.50 (0.39-0.64)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.
### Response Status at the End of Maintenance or Observation

<table>
<thead>
<tr>
<th>Clinical Response After Maintenance</th>
<th>Observation (n = 398)</th>
<th>R (n = 389)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR/CRu)</td>
<td>190 (47.7%)</td>
<td>260 (66.8%)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>29 (7.3%)</td>
<td>28 (7.2%)</td>
</tr>
<tr>
<td>Progressive disease (PD)</td>
<td>162 (40.7%)</td>
<td>79 (20.3%)</td>
</tr>
</tbody>
</table>
## Safety: Rituximab Maintenance

<table>
<thead>
<tr>
<th></th>
<th>Observation (n = 508)</th>
<th>Rituximab (n = 501)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>35%</td>
<td>52%</td>
</tr>
<tr>
<td>Grade ≥2 infections</td>
<td>22%</td>
<td>37%</td>
</tr>
<tr>
<td>Grade 3/4 adverse events</td>
<td>16%</td>
<td>22%</td>
</tr>
<tr>
<td>Grade 3/4 neutropenia</td>
<td>&lt;1%</td>
<td>4%</td>
</tr>
<tr>
<td>Grade 3/4 infections</td>
<td>&lt;1%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Salles GA et al. *Proc ASCO* 2010;Abstract 8004.
Conclusions

> R maintenance therapy for two years significantly improved PFS for pts with previously untreated FL who responded to induction with R-chemotherapy.
> Benefits of R maintenance were seen in all major subgroups (data not shown).
> These data provide evidence of an incremental benefit with R maintenance following initial R-chemotherapy for patients with FL.
> Data from the ongoing ECOG-E4402 (RESORT) trial will address how R maintenance compares to re-treatment with R at disease progression.

**DR FISHER:** This is a landmark study and confirms the role of maintenance rituximab in patients with FL treated with rituximab/chemotherapy as initial therapy. The study shows convincingly that two years of rituximab maintenance adds to failure-free-survival, progression-free-survival and time to treatment failure. The benefit was in all patient subgroups, and in my view it is indicated for all of these patients and should be used in a uniform fashion. Most people agree with me, though some believe that we should wait for a survival benefit.

**DR FOSS:** This is a long-awaited paper and is quite important as it demonstrates the benefit of rituximab maintenance even after receiving a rituximab-based induction regimen.
Rituximab Maintenance Treatment of Relapsed/Resistant Follicular Non-Hodgkin’s Lymphoma: Long-Term Outcome of the EORTC-20981 Phase III Study

van Oers MH et al.

> In previously untreated and relapsed/refractory (rel/ref) FL, R maintenance has a clinical benefit after induction with R-chemotherapy, chemotherapy alone or R alone (Haematologica 2007;92:826; Proc ASCO 2010;Abstract 8004).

> Initial reports of R-CHOP induction for patients with rel/ref FL resulted in increased complete and overall response rates, and R maintenance (at median 33 months follow-up) strongly improved median progression-free survival (PFS) — both after induction with CHOP and R-CHOP — and overall survival (OS) when compared to observation (Blood 2006;108:3295).

> Current study objective:
  – To evaluate the long-term outcome of R maintenance treatment, with a median follow-up of 6 years.

EORTC-20981: Phase III Study Design

Eligibility (n = 465)
CD20-positive, Grade I-III, relapsed/refractory FL

Induction
R-CHOP (x6) OR CHOP (x6)

≥Partial remission

R maintenance
n = 167
R 375 mg/m² once every 3 months

Observation
n = 513

## Overall Efficacy and Safety

<table>
<thead>
<tr>
<th></th>
<th>Maintenance rituximab (n = 167)</th>
<th>Observation (n = 167)</th>
<th>Hazard ratio (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>3.7 years</td>
<td>1.3 years</td>
<td>0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5-year OS</td>
<td>74%</td>
<td>64%</td>
<td>0.70</td>
<td>0.07</td>
</tr>
<tr>
<td>Grade 3/4 infection</td>
<td>9.7%</td>
<td>2.4%</td>
<td>–</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Median follow-up = 6 years

## Effect of R Maintenance on PFS After CHOP or R-CHOP Induction

<table>
<thead>
<tr>
<th>Maintenance rituximab</th>
<th>Observation</th>
<th>Hazard ratio (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS after R-CHOP induction (n = 98, 91)</td>
<td>4.4 years</td>
<td>1.9 years</td>
<td>0.69</td>
</tr>
<tr>
<td>Median PFS after CHOP induction (n = 69, 76)</td>
<td>3.1 years</td>
<td>1.0 year</td>
<td>0.37</td>
</tr>
</tbody>
</table>

Median follow-up = 6 years

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Conclusions

> Rituximab maintenance significantly improved PFS compared with observation.
  – Median - 3.7 years vs 1.3 years (HR 0.55; \( p < 0.001 \))
  – After CHOP induction (HR 0.37; \( p < 0.001 \))
  – After R-CHOP induction (HR 0.69; \( p = 0.043 \))

> The 5-year OS was 74% in the rituximab maintenance arm and 64% in the observation arm (\( p = 0.07 \)).

> Rituximab maintenance was associated with a significant increase in Grade 3/4 infections: 9.7% vs 2.4% (\( p = 0.01 \)).

> With long-term follow-up, the superior PFS with rituximab maintenance in rel/ref FL is confirmed.

**DR FOSS:** R maintenance in the setting of relapsed/refractory FL was shown to have improved clinical outcome compared to observation. These long-term data reconfirm the benefit on PFS with R maintenance in this setting. The study is important in providing insight on how to care for patients with low-grade lymphoma who achieve remission in the relapsed setting.

**DR FISHER:** This study asked the question of clinical benefit with R maintenance for relapsed/refractory FL. The benefit is clear in terms of PFS, for which — even in the relapsed/refractory setting — R maintenance is valuable and works effectively, and the difference in five-year survival is reported as 74 percent with R maintenance and 64 percent with observation, although it is not statistically superior with a p-value of 0.07.
Bortezomib, Bendamustine, and Rituximab in Patients with Relapsed or Refractory Follicular Lymphoma: Encouraging Activity in the Phase 2 VERTICAL Study

Fowler N et al.  
*Proc ASH 2009;Abstract 933.*
Introduction

> The introduction of rituximab (R) has led to improved survival for patients with follicular lymphoma (FL).
> Despite improved survival with R, relapse is inevitable and new treatment algorithms are needed.
> The addition of R to bortezomib (V) or to bendamustine (B) has demonstrated activity in relapsed or refractory (rel/ref) FL.
  – Overall response rate (ORR) V + R: 49% (*JCO* 2009;27:5023)
  – ORR B + R: 92% (*JCO* 2008;26:4473)
> Current study objective:
  – Determine the safety and efficacy of bortezomib and rituximab plus bendamustine (VBR) in patients with rel/ref FL.

VERTICAL: Phase II Study Design

Eligibility (N = 63)
- Rel/Ref FL
- ≥4 prior doses of R
- No prior tx with V or B
- ≥1 measurable tumor mass
- No active CNS lymphoma
- No Grade ≥2 peripheral neuropathy (PN)

- V 1.6 mg/m² (d1, 8, 15, 22)
- B 90 mg/m² (d1, 2)
- R 375 mg/m² (cycle 1: d1, 8, 15, 22; cycles 2-5: d1)
- q35 days x 5

When given on the same day, the order of administration was V, B, R.

**Best Response Status**

<table>
<thead>
<tr>
<th>Status</th>
<th>Last Prior Regimen n = 62*</th>
<th>VBR n = 59</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>37 (59%)</td>
<td>51 (86%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>20 (32%)</td>
<td>31 (53%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>17 (27%)</td>
<td>20 (34%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>18 (29%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>7 (11%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

* Data are missing for one patient
- Time since last regimen (range): 9 mos (0-76)
- Median follow-up was 177 days (11 patients remained on treatment)
- Improved VBR response rates compared to last prior regimen

Percent Change in Tumor Burden with VBR

With permission from Fowler N et al. *Proc ASH* 2009;Abstract 933.
### Adverse Events (N = 63)

<table>
<thead>
<tr>
<th>Adverse Event (AE)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event</td>
<td>100</td>
</tr>
<tr>
<td>Grade 3/4 AEs</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>27</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral neuropathy (PN)</td>
<td>10*</td>
</tr>
</tbody>
</table>

* Of the 6 patients with PN, 3 (50%) had neuropathy symptoms at baseline.

Conclusions

> VBR was generally well tolerated in this patient population, which included patients with heavily pretreated (46% ≥3 prior lines of therapy) and high-risk FL (data not shown).
> The response rates were improved in patients treated with VBR when compared to their last prior regimens.
> Additional follow-up is required to assess long-term outcomes, including progression-free survival and overall survival.
DR VOSE: This is a single-arm, Phase II study, which combined weekly bortezomib with standard doses of bendamustine and rituximab. The patient characteristics were fairly typical of relapsed/refractory follicular lymphoma.

The waterfall plot shows that the majority of patients had an excellent response, with most having a more than 50 percent reduction in the tumors. Among the safety endpoints, the major adverse events were hematologic, and neuropathy was also reported in some patients. Overall, the regimen was fairly well tolerated by most patients.

I believe this is an active combination that will have to be evaluated with a randomized trial to determine whether it is better than the current standard regimens.
Tositumomab and Iodine I-131 Tositumomab for Previously Untreated, Advanced-Stage, Follicular Lymphoma: Median 10-Year Follow-Up Results

Kaminski MS et al. 
Proc ASH 2009;Abstract 3759.

- ORR = 47-68%; CR = 20-38%

Phase II trial of this regimen for previously untreated, advanced-stage FL also demonstrated clinical activity (NEJM 2005;352:441).

- ORR = 95%; CR = 75%

Current study objective:

- Provide 10-year median follow-up of the Phase II trial of a single one-week course of tositumomab and iodine I-131 tositumomab in patients with untreated Stage III and IV FL.
Phase II, Open-Label, Single-Center Study of Tositumomab and Iodine I-131 Tositumomab

Eligibility (Accrual = 76, closed)

Grade I or II FL, Ann Arbor Stage III or IV; no prior therapy; ≤25% marrow involvement; stable or progressive disease

Dosimetric dose: 2 infusions (Day 0): 450 mg tositumomab; 35 mg tositumomab labeled with 5 mCi of iodine-131

Therapeutic dose: 2 infusions (Days 7-14): 450 mg tositumomab; 35 mg iodine I-131 tositumomab for 75 cGY whole body radiation

Long-term follow-up for safety and efficacy

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.
### Patient Characteristics (n = 76)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>49 (23-69)</td>
</tr>
<tr>
<td>≤60 years</td>
<td>91%</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>9%</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>46%</td>
</tr>
<tr>
<td><strong>FL stage at study entry</strong></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>30%</td>
</tr>
<tr>
<td>IV</td>
<td>70%</td>
</tr>
<tr>
<td><strong>Grade I FL, Grade II FL, mantle-cell lymphoma</strong></td>
<td>70%, 29%, 1%</td>
</tr>
<tr>
<td><strong>Bone marrow involvement of 1-25%, none</strong></td>
<td>64%, 36%</td>
</tr>
<tr>
<td><strong>FLIPI risk: low, intermediate, high</strong></td>
<td>15%, 50%, 35%</td>
</tr>
</tbody>
</table>

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.
Efficacy: Median 10-Year Follow-Up

<table>
<thead>
<tr>
<th>Patient Subgroup (total n = 76)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective response (CR, CCR, PR), n (%)</td>
<td>74 (97%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>6.2 years</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>6.0 years</td>
</tr>
<tr>
<td>Complete response (CR), n (%)</td>
<td>56 (74%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>10.9 years</td>
</tr>
<tr>
<td>Complete and clinical complete response (CR, CCR), n (%)</td>
<td>59 (78%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>9.2 years</td>
</tr>
<tr>
<td>Partial response, n (%)</td>
<td>15 (20%)</td>
</tr>
<tr>
<td>Median PFS</td>
<td>0.8 years</td>
</tr>
</tbody>
</table>

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.
Adverse Events (n = 76)

Kaminski MS et al. *Proc ASH* 2009;Abstract 3759.

<table>
<thead>
<tr>
<th>Grade 3/4 Acute Toxicity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>5% (Grade IV)</td>
</tr>
<tr>
<td>Arthralgia and myalgia</td>
<td>13%</td>
</tr>
<tr>
<td>Headache</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-Term Toxicity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated TSH or began thyroid medication before therapy</td>
<td>12%</td>
</tr>
<tr>
<td>Elevated TSH or began thyroid medication after therapy</td>
<td>25%</td>
</tr>
<tr>
<td>Deaths from lymphoma progression</td>
<td>8%</td>
</tr>
</tbody>
</table>
Conclusions

> Long-term follow-up of a one-week course of front-line treatment with tositumomab and iodine I-131 tositumomab therapy demonstrated:
  – Median PFS: 6.2 years
  – 10-yr PFS rate: 38% (data not shown)
  – 10-yr OS rate: 83% (data not shown)

> One case of MDS occurred 8 years after initial therapy, but any causal relationship with the tositumomab-based regimen is unclear (data not shown).

> These data suggest clinical benefit of tositumomab and iodine I-131 tositumomab at front-line therapy, and further studies including combination treatments are warranted.

DR VOSE: This is a 10-year follow-up of the previously published study of tositumomab as initial treatment for untreated, advanced FL. With a long follow-up, the good data continue to hold. The median duration of response was six years, and about 40 percent of patients remained progression free at 10 years.

The short-term hematological toxicity is minimal, with Grade 4 only toxicity occurring in only five percent of patients. The long-term toxicities are also few with some cases of hypothyroidism and a small number of cases of secondary cancer, including one case of MDS diagnosed eight years after initial treatment. For a single agent, this is a high response rate with excellent survival data and minimal short- and long-term toxicities.