

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

Kahl BS et al.

Cancer 2010;116(1):106-14.

Introduction

- > 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:
 - Assess the safety and efficacy of single-agent bendamustine in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma (NHL).

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

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

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

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

Patient Subgroup	ORR*
Total (n = 100)	75%
Chemosensitive (n = 51)	88%
Chemorefractory (n = 36)	64%
Patient Subgroup	DoR (95% CI)
Overall (n = 75)	9.2 mos (7.1-10.8)
Chemosensitive (n = 45)	10.0 mos (8.4-11.7)
Chemorefractory (n = 23)	6.3 mos (4.9-NA)

NA = not available

* ORR was assessed by independent review committee. ORR was defined as proportion of patients with best response \geq partial response.

Adverse Events* (N = 100)

Hematologic Adverse Events	Grade 3	Grade 4
Anemia	7%	3%
Thrombocytopenia	19%	6%
Neutropenia	38%	23%
Febrile neutropenia	5%	1%
Nonhematologic Adverse Events		
Infection	15%	6%
Fatigue	12%	2%
Diarrhea	5%	0%

* 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.

Faculty Comments

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.

StiL NHL 1-2003: Bendamustine Plus Rituximab versus CHOP Plus Rituximab in the First-Line Treatment of Patients with Indolent and Mantle Cell Lymphoma

Rummel MJ et al.

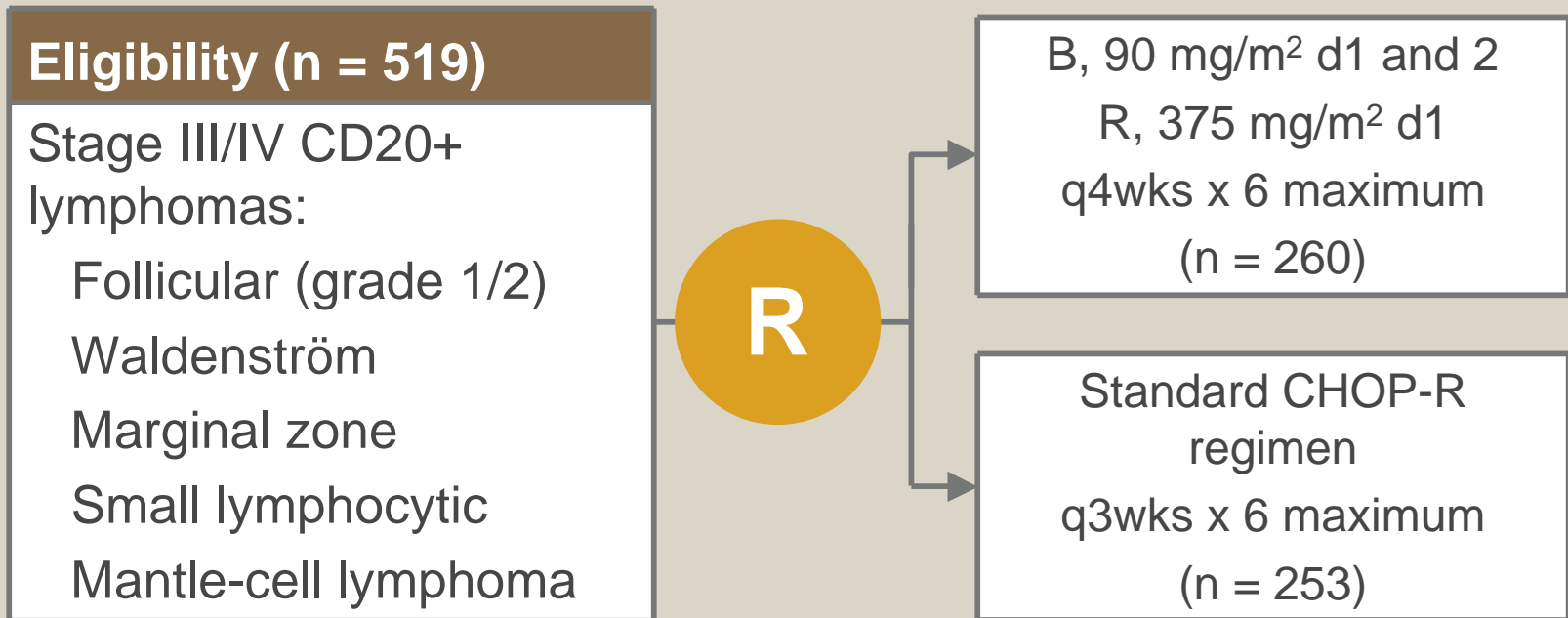
Proc ASH 2009;Abstract 405.

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.

StiL NHL 1-2003 Phase III Trial Design

Accrual: 549



Efficacy Results

Clinical Parameter	BR (n = 260)	CHOP-R (n = 253)	p-value
ORR	92.7%	91.3%	—
Complete response (CR)	39.6%	30.0%	0.0262
Progression-free survival (PFS) Follicular lymphoma patients (n = 277)	54.9 mos Not reached	34.8 mos 46.7 mos	0.00012 0.0281

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

Grade 3/4 Adverse Events - Hematologic

Adverse Event	BR (n = 1,450) % of cycles	CHOP-R (n = 1,408) % of cycles	p-value
Leukocytopenia	12.1	38.2	< 0.0001
Neutropenia	10.7	46.5	< 0.0001
G-CSF administered	4.0	20.0	< 0.0001
Thrombocytopenia	0.7	1.2	—
Anemia	1.4	1.9	—

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

Adverse Events - All CTC Grades

Adverse Event	BR (n = 260) # of patients	CHOP-R (n = 253) # of patients	p-value
Alopecia	—	+++	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Erythema	42	23	0.0122
Allergic reaction (skin)	40	15	0.0003
Infectious complications	96	127	0.0025

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

Summary and Conclusions

- > 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.

Faculty Comments

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.

Introduction

- > 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 alone¹ or R alone² (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.

PRIMA: Phase III Study Design

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

R maintenance

n = 505
R 375 mg/m²
q8wk x 2y

Observation

n = 513

* Followed by two additional R infusions

Primary Endpoint: Progression-Free Survival

Progression-Free Survival	Observation (n = 513)	R Maintenance (n = 505)
2-year progression-free survival (PFS)	66%	82%
Hazard ratio (95% CI)	0.50 (0.39-0.64)	
p-value	<0.0001	

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

Response Status at the End of Maintenance or Observation

Clinical Response After Maintenance	Observation (n = 398)	R (n = 389)
Complete response (CR/CRu)	190 (47.7%)	260 (66.8%)
Partial response (PR)	29 (7.3%)	28 (7.2%)
Progressive disease (PD)	162 (40.7%)	79 (20.3%)

Safety: Rituximab Maintenance

	Observation (n = 508)	Rituximab (n = 501)
Any adverse event	35%	52%
Grade ≥ 2 infections	22%	37%
Grade 3/4 adverse events	16%	22%
Grade 3/4 neutropenia	<1%	4%
Grade 3/4 infections	<1%	4%

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.

Faculty Comments

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

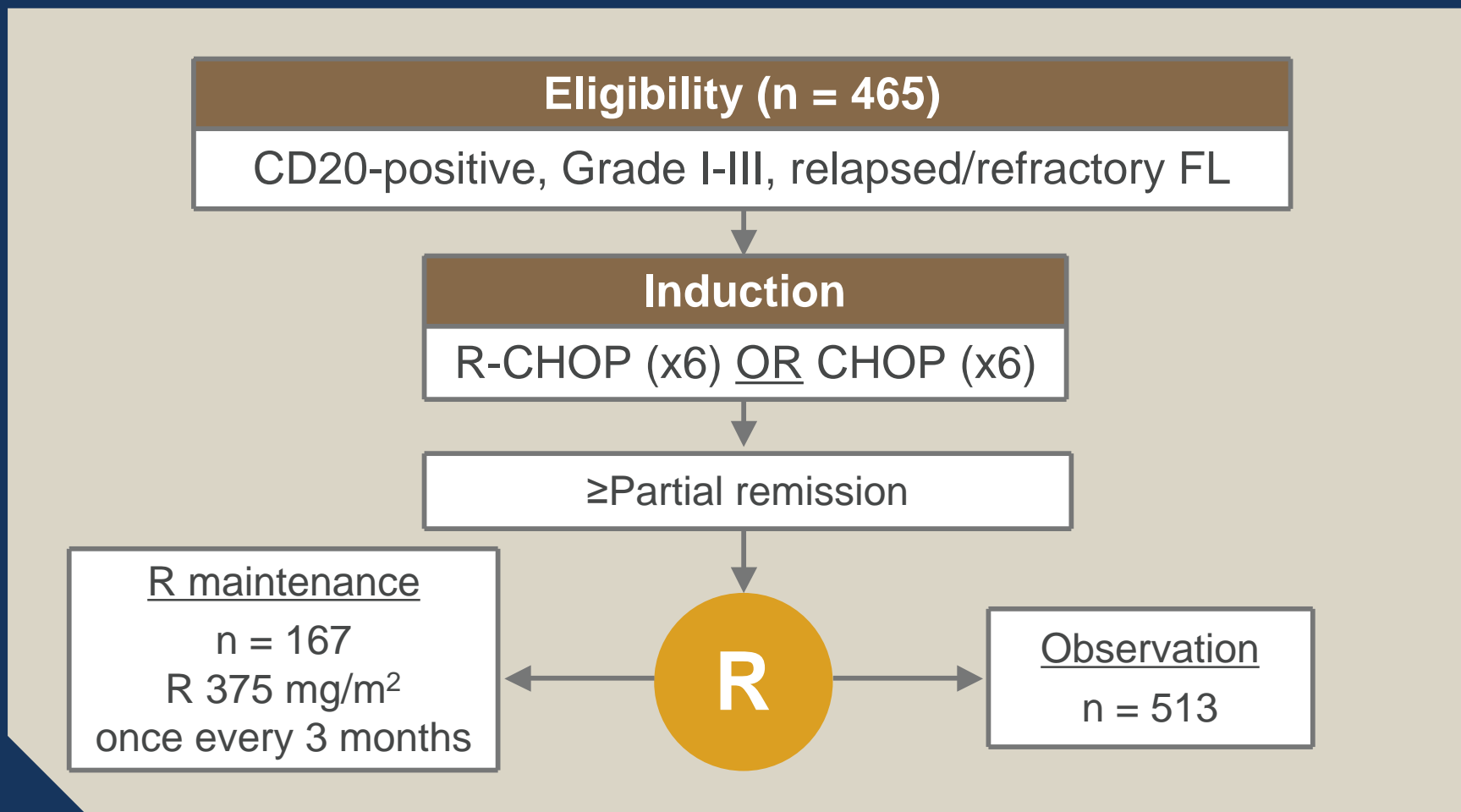
van Oers MH et al.

J Clin Oncol 2010;28(17):2853-8.

Introduction

- > 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



Overall Efficacy and Safety

	Maintenance rituximab (n = 167)	Observation (n = 167)	Hazard ratio (HR)	p-value
Median PFS	3.7 years	1.3 years	0.55	<0.0001
5-year OS	74%	64%	0.70	0.07
Grade 3/4 infection	9.7%	2.4%	—	0.01

Median follow-up = 6 years

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

	Maintenance rituximab	Observation	Hazard ratio (HR)	p-value
Median PFS after R-CHOP induction (n = 98, 91)	4.4 years	1.9 years	0.69	0.043
Median PFS after CHOP induction (n = 69, 76)	3.1 years	1.0 year	0.37	<0.001

Median follow-up = 6 years

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 ($p = 0.07$).
 - Lack of statistical significance possibly due to unbalanced use of rituximab in post-protocol salvage treatment.
- > 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.

Faculty Comments

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.

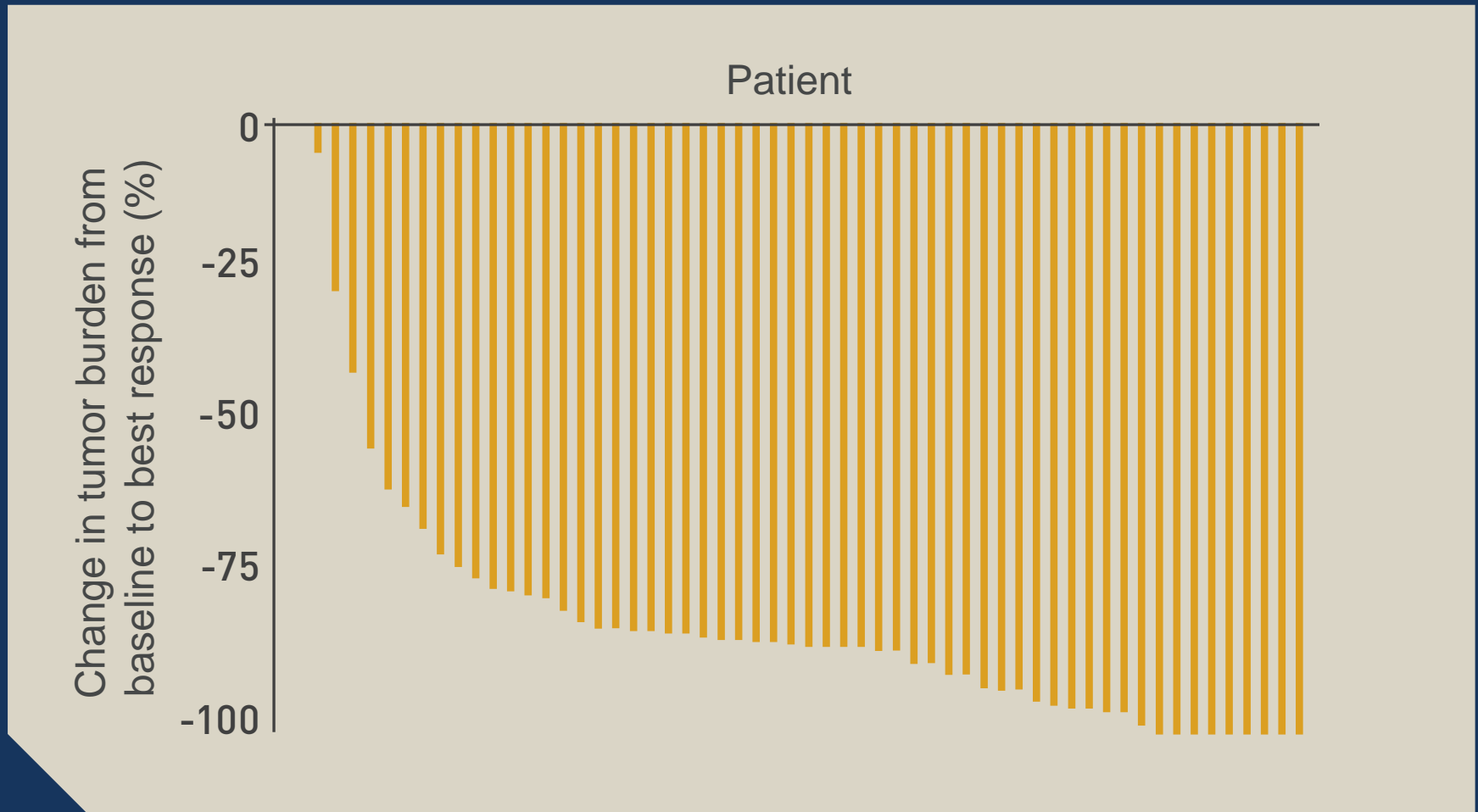
Best Response Status

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

* 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)

Adverse Event (AE)	%
Any adverse event	100
Grade 3/4 AEs	
Anemia	3
Neutropenia	27
Thrombocytopenia	6
Peripheral neuropathy (PN)	10*

* 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.

Faculty Comments

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.

Introduction

- > Patients with relapsed follicular lymphoma (FL) or FL refractory to chemotherapy or to rituximab respond to tositumomab and iodine I-131 tositumomab treatment (*JCO* 2000;18:1316, *Blood* 2000;96:1259, *JCO* 2001;19:3918).
 - 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; $\leq 25\%$ 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

Patient Characteristics (n = 76)

Median age (range), years	49 (23-69)
≤60 years	91%
>60 years	9%
Female	46%
FL stage at study entry	
III	30%
IV	70%
Grade I FL, Grade II FL, mantle-cell lymphoma	70%, 29%, 1%
Bone marrow involvement of 1-25%, none	64%, 36%
FLIPI risk: low, intermediate, high	15%, 50%, 35%

Efficacy: Median 10-Year Follow-Up

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

Adverse Events (n = 76)

Grade 3/4 Acute Toxicity	Incidence
Neutropenia	5% (Grade IV)
Arthralgia and myalgia	13%
Headache	5%
Long-Term Toxicity	Incidence
Elevated TSH or began thyroid medication before therapy	12%
Elevated TSH or began thyroid medication after therapy	25%
Deaths from lymphoma progression	8%

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

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.

Faculty Comments

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.