INTERVIEW

John P Leonard, MD

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Tracks 1-17

Track 1 **Case discussion:** A 58-year-old woman has low-risk follicular lymphoma (FL) initially managed with "watch and wait" for two years, followed by bendamustine/rituximab (BR) at disease progression

Track 2 German Phase III randomized trial comparing BR to R-CHOP in FL

Track 3 Bendamustine: A unique chemotherapeutic drug with evolving dosing recommendations

Track 4 Current and future role of R-CHOP versus BR in FL

Track 5 Stem cell mobilization in patients with FL who are receiving BR

Track 6 Rationale for the use of bendamustine/rituximab for older patients with mantle-cell lymphoma (MCL)

Track 7 Rituximab maintenance in FL

Track 8 PRIMA trial: Maintenance rituximab after rituximab-containing induction chemotherapy in FL

Track 9 **Case discussion:** A 47-year-old woman with recurrent FL after R-CHOP on a clinical trial of induction R-CVP followed by bortezomib with radioimmuno-therapy (RIT) consolidation

Track 10 FIT trial: Improved complete response (CR) rate and progression-free survival with consolidation ibritumomab after initial induction in FL

Track 11 Rationale and dosing of bortezomib as a radiosensitizer

Track 12 Novel bortezomib combinations in FL and MCL

Track 13 Molecular subtypes of diffuse large B-cell lymphoma (DLBCL): Implications for personalized therapy

Track 14 NF-kappa-B as a therapeutic target in DLBCL

Track 15 Potential neurotoxicity of bortezomib with R-CHOP

Track 16 Lenalidomide in MCL, FL and DLBCL

Track 17 Optimal use of PET scans in the management of DLBCL

Select Excerpts from the Interview

Tracks 2, 4

DR LOVE: Would you discuss the data presented at ASH on the efficacy and safety of bendamustine/rituximab (BR) compared to R-CHOP for follicular lymphoma (FL)?

DR LEONARD: The Study Group Indolent Lymphomas (StiL) from Germany randomly assigned more than 500 patients to either BR or R-CHOP.

Not only were complete remissions increased but progression-free survival (PFS) was also improved with BR (Rummel 2009; [1.1]). BR is at least comparable in efficacy and is much better in terms of safety, with significantly less toxicity (Rummel 2009; [1.2]).

DR LOVE: In what situations would you use R-CHOP, and when would you use BR?

DR LEONARD: The data show improved safety and efficacy with BR. Despite this information, I continue to use R-CHOP when I am concerned about transformation because the role of bendamustine in the more aggressive subtype is not as clear.

1.1

Efficacy Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Indolent Lymphomas

	Overall response	Complete response	Progression-free survival	Time to next treatment
BR (n = 260)	93.8%	40.1%	54.8 months	Not reached
R-CHOP (n = 253)	93.5%	30.8%	34.8 months	40.7 months
p-value	—	0.0323	0.0002	0.0002

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

1.2

Safety Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Indolent Lymphomas

	Grade III/IV neutropenia	Infectious complications	Peripheral neuropathy	Stomatitis	Rash	Alopecia
BR (n = 260)	10.7%	36.5%	6.9%	6.2%	16.2%	15.0%
R-CHOP (n = 253)	46.5%	47.8%	28.8%	18.6%	9.1%	62.0%
p-value	<0.0001	0.0403	<0.0001	<0.0001	0.0122	Not reported

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

In contrast, for an older patient or someone who is worried about side effects, administering BR makes complete clinical sense.

Tracks 8, 10

DR LOVE: What do we know about the PRIMA trial of postinduction therapy after front-line rituximab-containing regimens in FL?

DR LEONARD: PRIMA, the Primary RItuximab and MAintenance study, is the randomized Phase III trial examining rituximab maintenance therapy after rituximab-containing regimens for FL in the front-line setting. This study is being conducted primarily in Europe and has enrolled more than 1,000 patients. All patients received rituximab-containing initial induction and were then randomly assigned to observation or two years of maintenance rituximab.

A press release stated that the study reached the primary endpoint of improving PFS with maintenance rituximab in this setting. Most of these patients received R-CHOP as initial treatment. So when R-CHOP is used as up-front treatment for FL, maintenance rituximab can yield a PFS benefit. I anticipate that these data will be presented at ASCO 2010. So far, all of the maintenance studies have investigated rituximab. Because active oral agents such as lenalidomide are also being investigated in lymphoma, I believe that more data will emerge in the context of maintenance therapy for FL.

DR LOVE: What about consolidation therapy for patients with FL responding to initial induction therapy?

DR LEONARD: The only study that has been published in this setting is FIT, the First-line Indolent Trial. The study was a multinational, randomized Phase III trial that compared radioimmunotherapy with ibritumomab as first-line consolidation therapy to observation for advanced FL that had responded to initial induction therapy. The study showed a significant improvement in complete response rate and PFS on the ibritumomab arm, with acceptable safety (Morschhauser 2008; [1.3]). However, fewer than 20 percent of the patients received rituximab as part of initial induction therapy.

Tracks 12, 15

DR LOVE: What's new in the treatment of mantle-cell lymphoma (MCL)?

DR LEONARD: Bortezomib is clearly an active agent in MCL. It has been approved in the relapsed setting because of response rates of 30 percent and a PFS of nine months. Combination therapies with bortezomib are now being investigated in both front-line and relapsed MCL.

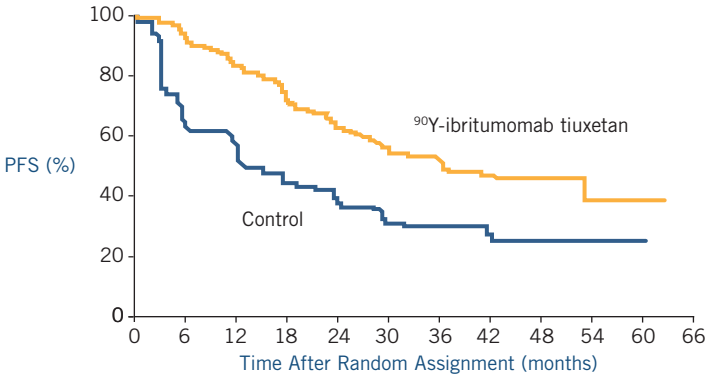
A Phase II study with the combination of bendamustine, bortezomib and rituximab (BVR) was reported at ASH 2009. The study included patients with heavily pretreated relapsed or refractory indolent lymphomas in addition to those with MCL. BVR is definitely active in both MCL and FL (Friedberg

2009; [1.4]). We need randomized trials of BR with or without bortezomib to investigate the benefit of adding bortezomib to the BR regimen.

Our group reported a Phase I/II study of R-CHOP with reduced-dose bortezomib as initial therapy for MCL. Among 32 evaluable patients, the overall response rate is 91 percent, with a complete response rate of 72 percent. The PFS for all 36 patients is 21 months, and the two-year overall survival rate is 86 percent (Ruan 2009).

1.3

Phase III Trial of Consolidation Therapy with Yttrium-90-Ibritumomab Tiuxetan versus No Additional Therapy After First Remission in Advanced Follicular Lymphoma: Progression-Free Survival (PFS)



	Ibritumomab tiuxetan (n = 208)	No additional therapy (n = 206)	Hazard ratio	*p*-value
Median PFS	36.5 months	13.3 months	0.465	<0.0001

Originally published by the American Society of Clinical Oncology. Morschhauser F et al. **Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma.** *J Clin Oncol* 2008;26(32):5156-64.

1.4

Efficacy of Bendamustine/Bortezomib/Rituximab in Relapsed or Refractory Mantle-Cell Lymphomas (MCL) and Indolent Lymphomas

	Overall response
All patients (n = 29*)	79%
Relapsed or refractory FL (n = 16)	85%
Relapsed or refractory MCL (n = 7)	71%

FL = follicular lymphoma
* Remaining patients had marginal-zone non-Hodgkin lymphoma, small lymphocytic lymphoma or lymphoplasmacytic lymphomas

Friedberg JW et al. *Proc ASH* 2009;**Abstract 924**.

So bortezumib is clearly an exciting drug in MCL that warrants combination studies with various chemotherapeutic regimens in both the front-line and relapsed settings. ECOG is studying modified hyper-CVAD with bortezomib, and The University of Texas MD Anderson Cancer Center has examined full-dose hyper-CVAD with bortezomib in MCL.

DR LOVE: How do patients fare in terms of neuropathy when bortezomib is added to vincristine-containing regimens?

DR LEONARD: NCI Canada combined standard R-CVP with weekly bortezomib 1.3 mg/m^2 intravenously on days 1 and 8 every 21 days (Sehn 2009). None of the patients developed Grade IV neuropathy, and the incidence of Grade III neuropathy was 6.3 percent.

In the trial of reduced-dose bortezomib, 1 or 1.3 mg/m^2 intravenously on days 1 and 4 every 21 days with R-CHOP in MCL reported by my group (Ruan 2009), no patient developed Grade IV neuropathy and only one out of 36, or 2.7 percent, developed Grade III neuropathy. Neurotoxicity is primarily low grade, is reversible and does not limit the delivery of bortezomib or vincristine.

So the combination of bortezomib and vincristine can be administered, although dose modification of one or both agents may be needed. Nevertheless, the available data suggest that even with dose modification, the combination may be sufficiently active to affect patient outcomes. ■

SELECT PUBLICATIONS

Friedberg JW et al. **Bendamustine, bortezomib and rituximab in patients (pts) with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma (NHL): A multicenter Phase II clinical trial.** *Proc ASH* 2009;**Abstract 924**.

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Morschhauser F et al. **Phase III trial of consolidation therapy with yttrium-90-ibritumomab tiuxetan compared with no additional therapy after first remission in advanced follicular lymphoma.** *J Clin Oncol* 2008;26(32):5156-64.

O'Connor OA et al. **Patients with chemotherapy-refractory mantle cell lymphoma experience high response rates and identical progression-free survivals compared with patients with relapsed disease following treatment with single agent bortezomib: Results of a multicentre Phase 2 clinical trial.** *Br J Haematol* 2009;145(1):34-9.

Ruan J et al. **CHOP-R + bortezomib as initial therapy for mantle cell lymphoma (MCL).** *Proc ASH* 2009;**Abstract 2682**.

Rummel MJ et al. **B-R is superior in respect of PFS and CR rate when compared to CHOP-R as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized Phase III study of the StIL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

Sekeres MA et al. **A study comparing dosing regimens and efficacy of subcutaneous to intravenous azacitidine (AZA) for the treatment of myelodysplastic syndromes (MDS).** *Proc ASH* 2009;**Abstract 3797**.

Sehn LH et al. **Bortezomib added to CVP-R is safe and effective for previously untreated advanced stage follicular lymphoma: A Phase II study by the NCIC Clinical Trials Group.** *Proc ASH* 2009;**Abstract 407**.