Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

SPECIAL ISSUE
Proceedings from a Clinical Investigator Roundtable Discussion

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Hematologic Oncology Update
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OVERVIEW OF ACTIVITY

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of lymphoproliferative disorders and is one of the most rapidly evolving fields in hematology and oncology. Published results from ongoing clinical trials lead to the continual emergence of new therapeutic agents and changes in the use of existing treatments. To offer optimal patient care — including the option of clinical trial participation — practicing medical oncologists, hematologists and hematology-oncology fellows must be well informed of these advances. This program uses a roundtable discussion with leading clinical investigators to assist practicing clinicians in formulating up-to-date clinical management strategies for NHL and chronic lymphocytic leukemia (CLL).

LEARNING OBJECTIVES

- Develop an algorithm for the evaluation and treatment of newly diagnosed and relapsed/refractory CLL.
- Communicate the existing and emerging roles of proteasome inhibitors and IMiDs® for patients with mantle-cell lymphoma (MCL).
- Integrate the recent trial results of novel agents and regimens into the initial management of follicular lymphoma (FL).
- Counsel patients with responding FL about the risks and benefits associated with consolidation and/or maintenance therapy.
- Incorporate the results of recent research on the use of PET scans into the management of diffuse large B-cell lymphoma (DLBCL).
- Apply emerging research results to develop evidence-based clinical management strategies for newly diagnosed or recurrent T-cell lymphomas.
- Counsel appropriately selected patients with lymphoid tumors about the availability of ongoing clinical trials in which they may be eligible to participate.

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INITIAL TREATMENT OF CLL

DR LOVE: What clinical research issues are currently being addressed in CLL?

DR RAI: Most investigators agree that fludarabine/cyclophosphamide/rituximab (FCR) has excellent activity in front-line CLL. Recently, bendamustine has shown considerable activity both as monotherapy and in combination for most lymphoid tumors. Data from the German CLL Study Group (GCLLSG) with bendamustine/rituximab (BR) were presented at ASH and showed that BR is both safe and effective in the initial treatment of CLL (Fischer 2009; [1.1]).

High response rates around 90 percent occurred in all the genetic subgroups except the 17p-minus group, which had a lesser proportion of 43 percent

1.1

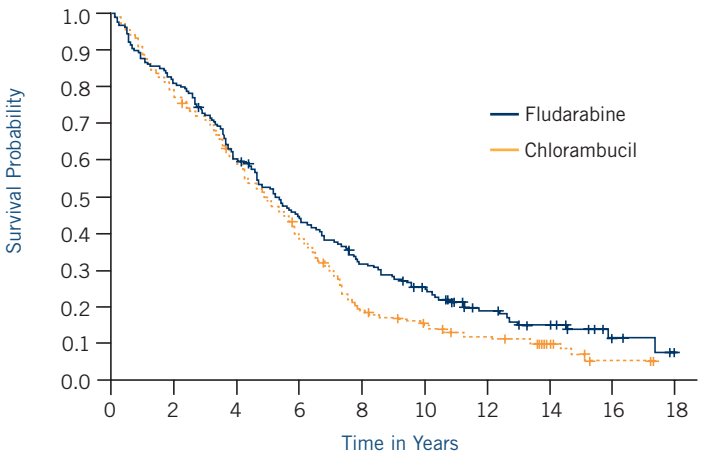
Phase II German CLL Study Group Trial of Initial Treatment with Bendamustine/Rituximab in Chronic Lymphocytic Leukemia

Overall response	Complete response	Partial response (PR)	Nodular PR
90.9%	32.7%	55.5%	2.7%

Fischer K et al. *Proc ASH* 2009;**Abstract 205**.

1.2

CALGB 9011: Long-Term Analysis Showing Survival Advantage with Fludarabine versus Chlorambucil in Previously Untreated CLL



With permission from Rai K et al. *Proc ASH* 2009;**Abstract 536**.

1.3

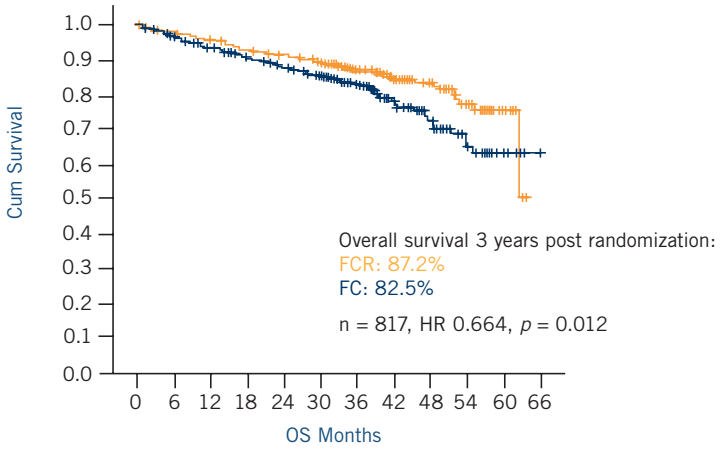
CLL8: A Randomized Phase III Trial Comparing Fludarabine/Cyclophosphamide (FC) to Fludarabine/Cyclophosphamide/Rituximab (FCR)

	Overall response	Complete response	Progression-free survival	Overall survival at 37.7 months
FC	88.4%	21.8%	32.8 months	79.0%
FCR	95.1%	44.1%	51.8 months	84.1%

Hallek M et al. *Proc ASH* 2009;**Abstract 535**.

1.4

CLL8: Survival Advantage with the Incorporation of Rituximab in a Phase III Randomized Trial



With permission from Hallek M et al. *Proc ASH* 2009;**Abstract 535**.

responding. On the basis of these encouraging Phase II data, the GCLLSG is presently investigating the efficacy of BR versus FCR in the first-line treatment of CLL in a Phase III trial (1.1).

DR GREGORY: FCR is clearly the standard for patients who are younger and physically fit. However, FCR is not the standard for the majority of patients with CLL who are elderly and may not be physically fit. The CLL10 protocol comparing BR to FCR is interesting — I believe BR will be less toxic. I already use it in the front line for my older patients with CLL.

DR SMITH: Another interesting trial is the Intergroup study, which is comparing FCR to FR in the front-line setting. I believe FCR will be more active and potentially more toxic than FR. The study should provide the answer to whether the addition of cyclophosphamide adds benefit.

DR GREGORY: Recently a survival advantage was demonstrated with CLL in aggressive up-front treatment. Two separate randomized trials were reported at ASH 2009 showing an effect on overall survival (OS) in CLL.

The long-term follow-up of Intergroup C9011, which randomly assigned patients with previously untreated CLL to chlorambucil versus fludarabine, was reported at ASH 2009 (Rai 2009; [1.2]). The late emergence of an overall survival benefit in the fludarabine arm of this study is striking and may suggest that receiving the most effective chemotherapy first is optimal.

The second randomized trial (Hallek 2009; [1.3, 1.4]) to show an overall survival benefit was the GCLLSG CLL8 trial. This study randomly assigned patients with CLL who were physically fit to six cycles of fludarabine/cyclophosphamide (FC) or six cycles of FCR. An overall survival benefit has emerged for the rituximab-containing arm at three years of follow-up.

TREATMENT OF RELAPSED/REFRACTORY CLL

DR LOVE: Any important new developments in the management of relapsed/refractory CLL?

DR FRIEDBERG: Approved agents include alemtuzumab and ofatumumab. Novel combinations that include bendamustine and lenalidomide can also be considered.

DR CHESON: Patients respond well to bendamustine-based therapy after disease progression on R-CHOP, hyper-CVAD or fludarabine-based regimens. Active agents such as lenalidomide have shown responses in the range of 35 to 45 percent in relapsed/refractory CLL. Stem cell transplant could also be considered for younger patients.

DR RAI: Ofatumumab is active as a single agent and now is being combined with bendamustine in the protocol setting. Lenalidomide combinations are also active. A Phase II study of lenalidomide and rituximab (Ferrajoli 2009) in 37 patients reported an overall response rate of 68 percent in relapsed/refractory CLL, which was better than the historical controls with lenalidomide alone. All patients had previously received rituximab, and the median number of prior regimens was two.

No increase in toxicity was reported, but lenalidomide-associated tumor flare reaction was less frequent and less severe with the combination than with single-agent lenalidomide. This is an attractive combination — at least one front-line trial of lenalidomide and rituximab is ongoing.

DR ZELENETZ: The challenge with lenalidomide is that it works "too well," but when combined with rituximab at lower doses, it may work well. How it will fit into the treatment of CLL is difficult to determine at this time. The reported combination with rituximab was a good proof of concept and now needs to be evaluated in a larger multicenter study.

DR RAI: The issue with lenalidomide dosing is valid. Initially, lenalidomide was administered at 15 or 25 mg in CLL, and some patients developed tumor lysis syndrome and a few others experienced tumor flare. So it is important to dose low and then escalate as needed. ■

SELECT PUBLICATIONS

Ferrajoli A et al. **Combination therapy with lenalidomide and rituximab in patients with relapsed chronic lymphocytic leukemia (CLL).** *Proc ASH* 2009;**Abstract 206**.

Fischer K et al. **Bendamustine combined with rituximab (BR) in first-line therapy of advanced CLL: A multicenter Phase II trial of the German CLL Study Group (GCLLSG).** *Proc ASH* 2009;**Abstract 205**.

Hallek M et al. **First-line treatment with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) improves overall survival (OS) in previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL): Results of a randomized Phase III trial on behalf of an international group of investigators and the German CLL Study Group.** *Proc ASH* 2009;**Abstract 535**.

Rai KR et al. **Long-term survival analysis of the North American Intergroup study C9011 comparing fludarabine (F) and chlorambucil (C) in previously untreated patients with chronic lymphocytic leukemia (CLL).** *Proc ASH* 2009;**Abstract 536**.

MANTLE-CELL LYMPHOMA (MCL)

FRONT-LINE TREATMENT OF MCL

DR LOVE: Jonathan, can you review the NCCN registry study of MCL reported at ASH?

DR FRIEDBERG: MCL is an uncommon histology of non-Hodgkin lymphoma with an unfavorable prognosis for which optimal initial therapy has not been clearly defined. Despite a number of single-center studies and uncontrolled trials examining first-line therapy options in MCL, no randomized clinical trials have directly compared initial therapeutic options.

A prospective cohort study (LaCasce 2009) collecting comprehensive clinical, treatment and outcome data for patients seen at seven participating NCCN centers was reported at ASH 2009. It is interesting to note that even at this relatively small number of NCCN institutions, the practice patterns differed widely.

Mostly, three different approaches were evaluated — a group of 28 patients initially received R-CHOP alone and were observed, a group of 99 patients received R-hyper-CVAD and a group of 29 patients received R-CHOP therapy followed by autologous transplant. Because these were prospectively evaluated patients at various institutions, a major selection bias should not be an issue for any category.

No significant differences were observed between therapy groups with regard to baseline comorbidity, ECOG performance status, B symptoms, bulky disease, IPI risk group or bone marrow involvement.

In terms of the efficacy data, R-CHOP alone yielded significantly poorer progression-free survival (PFS) than either of the two aggressive regimens. In addition, a strong trend of survival benefit favored the aggressive regimens compared to R-CHOP alone.

The most interesting results here are the lack of a difference in efficacy in the two aggressive regimens and that the toxicities were far greater in the R-hyper-CVAD group than with

R-CHOP followed by transplant. Future trials should focus on incorporating novel agents in the front-line regimens rather than comparing the efficacy of different front-line regimens.

DR LEONARD: What struck me is that hyper-CVAD did not perform as well as has been reported in previous trials.

DR ZELENETZ: The hyper-CVAD data are overwhelmingly dominated by MD Anderson. The data reflect what has been reported to the database, and it is interesting that a discrepancy exists between what has been published and what has been reported to the database.

The published data are only from clinical trial participants, and the outcomes data are from trial participants in addition to patients off trial. This suggests that the real world application of hyper-CVAD is not easy.

DR LOVE: What are some of the specific clinical research strategies in the front-line setting?

DR SMITH: Bortezomib is clearly being brought to the front-line setting. Issues of neurotoxicity may emerge if bortezomib is combined with vinca alkaloids.

However, dose adjustments can be made. A Phase II study with 76 patients incorporated bortezomib with modified R-hyper-CVAD (Kahl 2009; [2.1]) using a reduced 1-mg dose of vincristine. Bortezomib was administered on days one and four of a 21-day cycle in this regimen, and the study showed impressive responses. No patients developed Grade III/IV neuropathy, and the overall toxicity profile was acceptable.

Longer follow-up is needed to determine if the high complete response (CR) rate observed in this trial will translate into improved PFS and OS.

DR SMITH: Radioimmunotherapy (RIT) is also being evaluated as part of the initial consolidation. ECOG-E1499 investigators administered ibritumomab tiuxetan after four cycles of R-CHOP as front-line therapy for MCL.

Though the manuscript is in preparation, the responses were increased after RIT consolidation and the duration of response almost doubled to approximately 30 months. It was well tolerated, though a plateau has not been observed, suggesting that the approach is not curative.

Lenalidomide is also active, and a maintenance or consolidation strategy with lenalidomide is also being developed.

DR CZUCZMAN: Studies in MCL with up to five years of rituximab maintenance are being conducted. The issue in MCL is the resistant clones left behind — even with

2.1 **ECOG-E1405: A Phase II Trial of Bortezomib with Modified R-Hyper-CVAD**

Overall response	Complete response	Partial response
96%	75%	21%

Kahl BS et al. *Proc ASH* 2009;**Abstract 1661**.

transplant, resistant clones are not eradicated. Novel drugs such as bortezomib or lenalidomide may have potential. A CALGB trial is evaluating maintenance bortezomib in combination with rituximab. We may see potential synergy with these drugs, which may be able to eradicate the resistant clones.

DR LOVE: Where do you see things heading in up-front treatment of MCL?

DR CZUCZMAN: For younger patients it will be novel agents such as bortezomib in combination with aggressive regimens such as R-hyper-CVAD or transplant.

For older patients the novel agents will likely be combined with BR. In the postinduction setting, some sort of maintenance therapy with rituximab, lenalidomide or the combination might emerge in the future.

TREATMENT OF RELAPSED/REFRACTORY MCL

DR LOVE: What are some of the current important options in relapsed MCL?

DR LEONARD: Bortezomib is an approved agent in this setting and is active and commonly used. Lenalidomide and bendamustine have also demonstrated significant activity. The trial reported at ASH comparing BR to R-CHOP for indolent lymphomas had some patients with MCL.

DR CHESON: Single-agent lenalidomide has been reported to have good activity in relapsed MCL (Habermann 2009; [2.2]). I have a patient who received single-agent lenalidomide and has been in remission for more than two and a half years.

DR SMITH: Subsequent to single-agent lenalidomide, an Italian group published data on relapsed MCL treated with lenalidomide and dexamethasone (Zaja 2009; [2.3]). Patients had received a median of three previous lines of therapy, and approximately one third of the patients had previously undergone transplant.

Clearly it confirms the activity of lenalidomide, but the addition of dexamethasone does not appear to improve the activity.

DR LOVE: What do we know about the schedule of administration of bortezomib in MCL and efficacy and neuropathy?

DR CHESON: Bortezomib is associated with painful neuropathy, and sensory or motor neuropathy could also develop. It is usually reversible, but not always. Less neuropathy occurs with a weekly schedule, yet weekly bortezomib is slightly less

2.2

Efficacy in a Phase II Trial of Single-Agent Lenalidomide for Relapsed Mantle-Cell Lymphoma

Overall response	Complete response	Median response duration	Median prior regimens
53%	20%	13.7 months	4

Habermann TM et al. *Br J Haematol* 2009;145(3):344-9.

active than the standard twice-a-week regimen in MCL.

This decreased activity may be ameliorated if weekly bortezomib is combined with other agents such as rituximab. We have not seen much in the way of neurotoxicity when bortezomib is combined with lenalidomide, but more data are needed. ■

2.3

Efficacy in a Phase II Trial of Lenalidomide and Dexamethasone in Relapsed Mantle-Cell Lymphoma

Overall response	Complete response	Median response duration
52%	14%	Not reached

Zaja F et al. *Proc ASH* 2009;**Abstract 1713**.

SELECT PUBLICATIONS

Habermann TM et al. **Lenalidomide oral monotherapy produces a high response rate in patients with relapsed or refractory mantle cell lymphoma.** *Br J Haematol* 2009;145(3):344-9.

Kahl BS et al. **The VcR-CVAD regimen produces a high complete response rate in untreated mantle cell lymphoma (MCL): First analysis of E1405 — A phase II study of VcR-CVAD with maintenance rituximab for MCL.** *Proc ASH* 2009;**Abstract 1661**.

LaCasce A et al. **R-CHOP, followed by high dose therapy and autologous stem cell rescue (HDT/ASCR), and R-HyperCVAD have equivalent progression-free survival and are superior to R-CHOP alone in younger patients with mantle cell lymphoma: A comparative effectiveness analysis from the National Comprehensive Cancer Network (NCCN) non-Hodgkin's lymphoma outcomes database project.** *Proc ASH* 2009;**Abstract 403**.

Zaja F et al. **Salvage treatment with lenalidomide and dexamethasone in patients with relapsed refractory MCL.** *Proc ASH* 2009;**Abstract 1713**.

FOLLICULAR LYMPHOMA (FL)

CHANGING LANDSCAPE OF INITIAL TREATMENT FOR FL

DR LOVE: What are your thoughts on the German Phase III trial comparing BR to R-CHOP in the front-line setting of indolent lymphomas?

DR GREGORY: This was one of the highlights of ASH 2009. BR was much better tolerated and showed a statistically significant superiority in efficacy compared to R-CHOP, which is the current standard (Rummel 2009; [3.1, 3.2]).

More than 500 patients in need of treatment were randomly assigned to receive BR every 28 days versus R-CHOP every 21 days for a maximum of six cycles.

BR improved PFS and CR rates when compared to R-CHOP and showed a better tolerability profile. The serious adverse events were less frequent with BR — approximately 19 percent with BR versus 29 percent with R-CHOP.

These promising results suggest that the BR combination has the potential

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

	Overall response	Complete response	Progression-free survival	Time to next treatment
BR	93.8%	40.1%	54.8 months	Not reached
R-CHOP	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**.

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

	Grade III/IV neutropenia	Infectious complications	Peripheral neuropathy	Stomatitis	Drug-related rash	Alopecia
BR	10.7%	36.5%	6.9%	6.2%	16.2%	15%
R-CHOP	46.5%	47.8%	28.8%	18.6%	9.1%	62%
p-value	<0.0001	0.0403	<0.0001	<0.0001	0.0122	—

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

to become a new standard first-line treatment option for FL and other indolent lymphomas.

DR LOVE: Should BR be used as up-front therapy?

DR CZUCZMAN: I would like to see the final analysis before adopting this strategy because of a couple of caveats. The study only included patients with Grade I and II FL. No patients with Grade III disease were included. If someone is older and frail, I believe BR may be a much better regimen.

DR ZELENETZ: My belief is that this will be the number one regimen in the next five years. Currently, it might mostly be older patients who meet the criteria to initiate treatment. However, I will also present this as an option to younger patients.

One of the important questions is, "Is there life after bendamustine?" When patients receive chlorambucil or fludarabine-based regimens, it becomes impossible to mobilize their stem cells. I would want to know if bendamustine may have a similar adverse effect on bone marrow reserve. This was slightly examined in the pivotal trial as a secondary objective and was presented as a poster (Burchardt 2009).

Stem cell mobilization was performed in consenting patients on both arms. On each arm, 23 patients underwent stem cell mobilization. The results surprised me because it was quite easy to mobilize stem cells after BR. Although the study was underpowered, it appeared that stem cell yield after BR was equivalent or even superior to the yield after R-CHOP.

DR LEONARD: Although long-term marrow toxicity may be a concern, it is difficult to argue when a study

has shown both superior efficacy and safety. I recently started a patient in her sixties on BR — she did not want to lose her hair — and I did not think that she needed an anthracycline because I was not worried about a transformation.

DR CHESON: The results in this study held true both for the lower- and the higher-risk FLIPI subsets.

I have been working with bendamustine for a decade now and have had opportunities to review the data and administer the agent to a large number of patients. I present patients with untreated FL the pros and cons of BR and R-CHOP. I even have younger patients on BR if they are concerned about the potential cardiac toxicity down the line or don't want to lose their hair and want the improved toxicity profile.

I am liberal in recommending BR as the initial treatment, and most of my patients now receive BR as the initial treatment for their FL. Only if I have a concern about transformation will I start with R-CHOP.

DR LOVE: What do we know about optimal bendamustine dosing?

DR CHESON: We had a consensus meeting last year at which we reviewed all available data at various doses and schedules.

The bottom line is that we still need to optimize the dose and schedule. In the front-line setting with rituximab, 90 mg/m^2 on days one and two every four weeks should be acceptable because rituximab appears to increase the myelosuppression related to a number of agents.

In the relapse setting as a single agent, 120 mg/m^2 on days one and two every four weeks is recommended rather than the package insert's suggested schedule of every three weeks at the same dose. If it is combined with rituximab in the relapse setting, then the dose should be reduced to 90 mg/m^2 on days one and two every four weeks. When combined with other agents, the optimal way to administer it may even be every five weeks.

DR LOVE: Do we know how bendamustine works?

DR CHESON: Bendamustine has both alkylator and antimetabolite activity. It has three active moieties: an alkylating group, a benzimidazole ring — which may act as a purine analog — and a butyric acid side chain. Although its exact mechanism of action is unknown, this agent appears to act primarily as an alkylator.

Bendamustine may differ from other alkylators in that it may be more potent in activating p53-dependent stress pathways and inducing apoptosis and thus may induce mitotic catastrophe. Accordingly, it may be more efficacious and less susceptible to drug resistance than other alkylators.

POSTINDUCTION STRATEGIES IN FL

DR LOVE: Where are we today with consolidation therapy in FL?

DR FRIEDBERG: The First-line Indolent Trial (FIT) was a multinational, randomized Phase III trial that compared RIT with ibritumomab as first-line consolidation therapy to observation after initial induction for advanced FL. The study showed a significant improvement in PFS

with acceptable safety (Morschhausser 2008; [3.3]). The issue is that fewer than 20 percent of patients on either arm received rituximab as part of initial induction.

SWOG has completed a large randomized trial with more than 500 patients comparing CHOP followed by consolidation tositumomab to R-CHOP. No rituximab is administered as part of induction on the RIT consolidation arm. The results are expected in late 2010.

DR LEONARD: A related issue is rituximab maintenance, and the randomized Phase II study presented at ASCO is also worth mentioning. Approximately one third of the patients had disease that was chemotherapy naïve, and two thirds had previously received treatment.

Responding patients, or at least those who had stable disease, were randomly assigned to either observation or four doses of consolidation rituximab delivered at two-month intervals. The event-free survival emerged to be better on the consolidation arm (Ghielmini 2009; [3.4]).

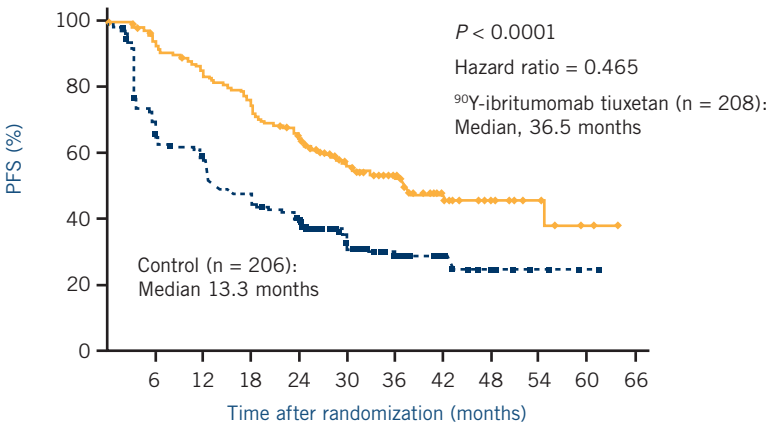
It is striking that four additional rituximab doses would have this profound effect on event-free survival, suggesting that some sort of prolonged rituximab administration may add benefit. Furthermore, weekly times four may not be the optimal way to deliver rituximab if administered as a single agent.

DR LOVE: So where are we in terms of rituximab maintenance in FL?

DR FRIEDBERG: PRIMA is the pivotal study evaluating this in patients receiving rituximab-containing front-line regimens. Patients were randomly assigned to a maintenance course of rituximab administered every two months for two years versus observation.

3.3

FIT: Progression-Free Survival (PFS) with Ibritumomab Tiuxetan Rituximab Consolidation in Advanced FL



With permission from Morschhausser F et al. *J Clin Oncol* 2008;26(32):5156-64. Originally published by the American Society of Clinical Oncology.

A press release in September 2009 reported that the study met its primary endpoint of improving PFS by 45 percent. The presentation from the study is expected at ASCO 2010.

DR LOVE: How about extended duration of rituximab maintenance?

DR GREGORY: The RESORT trial is examining that issue in asymptomatic FL without massive adenopathy or organomegaly. Patients received four weeks of rituximab up front, and responding patients were randomly assigned to maintenance rituximab every three months until disease progression versus observation. The study is closed for enrollment, and patients have received as many as six years of maintenance rituximab so far.

DR LOVE: What are the translational implications of longer-term exposure to rituximab?

DR CZUCZMAN: The interesting issue would be when these patients' disease relapses or progresses — then clinically this will be a pure population of rituximab resistance. A rebiopsy should be performed and compared to the pretreatment biopsy. We don't know what we will see, though CD20 density may change.

3.4

Long-Term Event-Free Survival (EFS) with Consolidation Rituximab in a Randomized Phase II Trial

	Median EFS	Five-year EFS	Eight-year EFS
Observation	13 months	10%	4%
Consolidation rituximab	24 months	26%	18%

Ghielmini ME et al. *Proc ASCO* 2009;**Abstract 8512**.

NOVEL COMBINATIONS IN RELAPSED/REFRACTORY FL

DR LOVE: What novel combinations are being evaluated in relapsed/refractory FL?

DR GREGORY: The single-arm, multicenter, Phase II VERTICAL study was conducted to determine the efficacy and safety of bortezomib/bendamustine/rituximab (VBR) for relapsed or refractory FL.

Patients received weekly bortezomib in the regimen, and bendamustine was administered at 90 mg/m^2 on days one and two of each five-week cycle.

VBR was well tolerated and showed promising activity in this population that was heavily pretreated and at high risk (Fowler 2009; [3.5]).

DR CHESON: The VBR data from the VERTICAL study are interesting. We need to separate out the contribution of bortezomib to this regimen, and cooperative groups are evaluating BR versus VBR in the front-line setting in a number of lymphoid cancer types.

DR LOVE: Are there other Phase II studies with bortezomib in the relapsed/refractory setting?

DR CHESON: A multicenter randomized Phase II study of weekly or twice-weekly bortezomib and ritux-

imab was reported in patients with relapsed/refractory FL (de Vos 2009; [3.6]). Bortezomib was administered at 1.3 mg/m^2 in the twice-weekly regimen and at 1.6 mg/m^2 in the weekly regimen. The response rates were similar in the two regimens, though the weekly regimen was better tolerated with less thrombocytopenia and less neuropathy.

The weekly combination is now being compared to single-agent rituximab in an ongoing Phase III study in relapsed FL. ■

3.5

VERTICAL: Efficacy Results from a Phase II Study of Bortezomib/Bendamustine/Rituximab in FL

Overall response	Complete response	Partial response
84%	47%	37%

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

3.6

Efficacy and Safety Data from a Randomized Phase II Study Evaluating Rituximab in Combination with Twice-Weekly versus Weekly Bortezomib

	Overall response	Time to disease progression	Grade III/IV thrombocytopenia	Grade III/IV neuropathy	Grade III/IV adverse event
Twice-weekly bortezomib	49%	7 months	10%	10%	54%
Weekly bortezomib	43%	10 months	0%	5%	35%

De Vos S et al. *J Clin Oncol* 2009;27(30):5023-30.

SELECT PUBLICATIONS

Burchardt CA et al. **Peripheral blood stem cell mobilization after bendamustine containing chemotherapy in indolent lymphomas is possible. Results from the phase III study of B-R vs CHOP-R (NHL 1-2003 trial) of the StIL (Study group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 2679**.

De Vos S et al. **Multicenter randomized phase II study of weekly or twice-weekly bortezomib plus rituximab in patients with relapsed or refractory follicular or marginal-zone B-cell lymphoma.** *J Clin Oncol* 2009;27(30):5023-30.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory FL: Encouraging activity in the Phase 2 VERTICAL study.** *Proc ASH* 2009;**Abstract 933**.

Ghielmini ME et al. **Long-term follow-up of patients with follicular lymphoma (FL) receiving single agent rituximab at two different schedules in study SAKK 35/98.** *Proc ASCO* 2009;**Abstract 8512**.

Morschhausser 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.

Rummel MJ et al. **B-R is superior in respect of PFS and CR rate when compared to R-CHOP 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**.

T-CELL LYMPHOMAS

DR LOVE: What's new in T-cell lymphoma?

DR LEONARD: Two new drugs recently received approval for T-cell lymphomas — pralatrexate and romidepsin.

Pralatrexate is a novel targeted antifolate designed to accumulate preferentially in cancer cells. The pivotal Phase II PROPEL study showed a good overall response rate for patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) (O'Conner 2009; [4.1]). The main side effect is mucositis, which can be ameliorated by vitamin B12 and folate supplementation. It is clearly an active drug.

A multicenter dose-finding trial of pralatrexate in cutaneous T-cell lymphoma (CTCL) showed activity with an overall objective response rate of 35 percent (Horwitz 2009).

DR LOVE: How about the other new agent, romidepsin?

DR ROSEN: Romidepsin is a histone deacetylase (HDAC) inhibitor approved for CTCL (Demierre 2009; [4.2]). Another HDAC inhibitor, vorinostat, has been previously approved for CTCL. Both are active drugs, and approximately one third of patients respond, with a small proportion, five percent, experiencing complete remissions.

The main side effects are nausea, fatigue and transient cytopenias. Some of the earlier cardiac concerns with QT prolongation have not amounted to anything that would inhibit our use.

DR LOVE: What about immunoconjugates in T-cell lymphomas?

DR ROSEN: Denileukin diftitox is a genetically engineered protein combining interleukin-2 (IL-2) with diphtheria toxin. It targets lymphoma cells expressing IL-2 receptor. It is approved for CD25-positive CTCL, although it is now known that the drug could be internalized in both CD25-positive and CD25-negative cells and thus is active in both CD25-positive and CD25-negative CTCL.

The complete remission rate in the refractory/relapsed CTCL setting was recently reported as 10 percent, and the responses were independent of the dose used, the stage of the disease or if the CTCL was CD25-positive or CD25-negative (Foss 2009). The compound is clearly active, but it is not used as much as it should be.

DR CHESON: A fair number of adverse events occurred in the initial

4.1

PROPEL: Efficacy Data from the Phase II Study of Pralatrexate in Relapsed/Refractory Peripheral T-Cell Lymphoma

Overall response	Duration of response	Progression-free survival	Overall survival
28%	9.4 months	108 days	14.7 months

O'Conner OA et al. *Proc ASCO* 2009;**Abstract 8561**.

4.2

Pooled Analyses of Two International, Multicenter Studies of Romidepsin in CTCL (Evaluable Patients; N = 135)

Overall response	Duration of response	Time to disease progression
41%	14.9 months (median)	8.3 months (median)

Demierre M et al. *Proc ASCO* 2009;**Abstract 8546**.

studies, and physicians remember that. Adverse events included fluid overload and capillary leak syndrome.

DR LEONARD: Premedication with steroids is effective in preventing capillary leak syndrome.

DR GREGORY: Patients should be screened before physicians administer this compound. Patients who are not hypoalbuminemic and don't have congestive heart failure or pleural effusions tolerate it well. Patient weight should be monitored daily, and gentle diuresis should be implemented if fluid overload occurs. However, diuresis must be carefully monitored because patients should not become intravascularly dry, either. Because community oncologists deal with this drug uncommonly, they may not be comfortable with it. I use denileukin diftitox and have seen good responses.

DR SMITH: A Phase II trial of denileukin diftitox and CHOP was presented in front-line PTCL and showed a high response rate. However, the contribution from denileukin diftitox will not be known until a randomized trial comparing denileukin diftitox/CHOP to CHOP alone is conducted. ■

SELECT PUBLICATIONS

Demierre M et al. **Pooled analyses of two international, multicenter clinical studies of romidepsin in 167 patients with cutaneous T-cell lymphoma (CTCL).** *Proc ASCO* 2009;**Abstract 8546**.

Foss F et al. **Complete responses with denileukin diftitox in cutaneous T-cell lymphoma studies.** *Proc ASH* 2009;**Abstract 3745**.

Horwitz M et al. **Pralatrexate is active in cutaneous T-cell lymphoma (CTCL): Results of a multicenter, dose-finding trial.** *Proc ASH* 2009;**Abstract 919**.

O'Conner OA et al. **PROPEL: Results of the pivotal, multicenter, phase II study of pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma (PTCL).** *Proc ASCO* 2009;**Abstract 8561**.

HEPATITIS B SCREENING IN LYMPHOMA/CLL

DR LOVE: Andy, what's your perspective of hepatitis B screening for patients with lymphoma?

DR ZELENETZ: At the Memorial Sloan-Kettering Cancer Center, all our patients with cancer are tested for hepatitis B before starting rituximab.

We consider it a standard practice and have diagnosed many patients with hepatitis B.

DR LOVE: Do other faculty members agree?

DR FRIEDBERG: Reactivation of hepatitis B could occur in patients who receive rituximab. So we screen all patients who are candidates for rituximab-based regimens.

DR GREGORY: For a carrier of the hepatitis B virus, receiving rituximab could cause the virus to become an active infection again (Stange 2010). This may cause serious liver problems and death.

Therefore, we also screen for hepatitis B in all patients scheduled to receive rituximab.

DR CZUCZMAN: In addition to hepatitis B, we also screen younger patients for HIV.

DR CHESON: I have seen a few patients who underwent liver transplants after they received rituximab without screening.

DR FRIEDBERG: Although we have been screening all patients who are scheduled to receive rituximab, we still have not found a patient who screens positive. I believe it is indicative of the background prevalence of hepatitis B in the population that the patients come from.

Still, it is standard practice to screen for hepatitis B in patients who will receive rituximab. A patient was referred to us from the community who was not screened, was administered rituximab and ended up receiving a liver transplant.

So this is clearly an important issue, and patients who are carriers of hepatitis B should be offered prophylactic antivirals (Ziakas 2009). ■

SELECT PUBLICATIONS

Francisci D et al. **Management of hepatitis B virus reactivation in patients with hematological malignancies treated with chemotherapy.** *Infection* 2010;38(1):58-61.

Hanbali A, Khaled Y. **Incidence of hepatitis B reactivation following rituximab therapy.** *Am J Hematol* 2009;84(3):195.

Koo YX et al. **Hepatitis B virus reactivation and role of antiviral prophylaxis in lymphoma patients with past hepatitis B virus infection who are receiving chemoimmunotherapy.** *Cancer* 2010;116(1):115-21.

Koo YX et al. **Risk of hepatitis B virus reactivation in patients who are hepatitis B surface antigen negative/antibody to hepatitis B core antigen positive and the role of routine antiviral prophylaxis.** *J Clin Oncol* 2009;27(15):2570-1.

Pei SN et al. **Reactivation of hepatitis B virus following rituximab-based regimens: A serious complication in both HBsAg-positive and HBsAg-negative patients.** *Ann Hematol* 2010;89(3):255-62.

Stange MA et al. **Fulminant hepatic failure to chemotherapy-induced hepatitis B reactivation: Role of rituximab.** *Z Gastroenterol* 2010;48(2):258-63.

Yeo W et al. **Hepatitis B virus reactivation in lymphoma patients with prior resolved hepatitis B undergoing anticancer therapy with or without rituximab.** *J Clin Oncol* 2009;27(4):605-11.

Ziakas PD et al. **Effect of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in lymphoma: A meta-analysis of published clinical trials and a decision tree addressing prolonged prophylaxis and maintenance.** *Haematologica* 2009;94(7):998-1005.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Fludarabine/cyclophosphamide/rituximab resulted in improved overall survival in initial treatment of chronic lymphocytic leukemia (CLL) in a randomized Phase III study compared to which regimen?**
   a. Fludarabine/rituximab
   b. Fludarabine/cyclophosphamide
   c. Bendamustine/rituximab (BR)
2. **Which of the following is true regarding the results of the NCCN outcomes prospective cohort study in mantle-cell lymphoma (MCL) presented at ASH 2009 by LaCasce and colleagues?**
   a. R-CHOP alone was as effective as R-hyper-CVAD
   b. R-hyper-CVAD was more effective than R-CHOP followed by transplant
   c. R-hyper-CVAD and R-CHOP followed by transplant are equally effective and better than R-CHOP alone
3. **Which of the following agents is approved for the treatment of relapsed or refractory MCL?**
   a. Lenalidomide
   b. Bortezomib
   c. Ibritumomab tiuxetan
4. **Dexamethasone contributes to the efficacy of lenalidomide in relapsed/refractory MCL.**
   a. True
   b. False
5. **Which of the following is incorrect regarding MCL?**
   a. MCL is incurable with currently available treatment options
   b. A proportion of MCL is indolent
   c. R-hyper-CVAD has demonstrated survival improvement in MCL in randomized Phase III trials compared to R-CHOP
6. **In a Phase III study of front-line treatment for follicular lymphoma, BR demonstrated improved efficacy compared to R-CHOP.**
   a. True
   b. False
7. **Incidences of adverse events were greater with BR than with R-CHOP in a Phase III study of front-line treatment for FL.**
   a. True
   b. False
8. **Which of the following therapies has shown an overall survival advantage in the postinduction setting in FL?**
   a. Consolidation ibritumomab tiuxetan
   b. Consolidation rituximab
   c. Maintenance rituximab
   d. All of the above
   e. None of the above
9. **Denileukin diftitox is active in the following subtype of T-cell lymphomas:**
   a. CD 25-positive T-cell lymphomas
   b. CD 25-negative T-cell lymphomas
   c. Both a and b
10. **Which of the following is correct regarding hepatitis B screening for patients scheduled to receive rituximab?**
    a. Hepatitis B screening is needed only if background prevalence of hepatitis B is high in the population
    b. Hepatitis B screening is needed for all patients regardless of background prevalence of hepatitis B
    c. Hepatitis B screening is unnecessary

Post-test answer key: 1b, 2c, 3b, 4b, 5c, 6a, 7b, 8e, 9c, 10b

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Think Tank Issue 1, 2010

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
German study of BR as initial therapy for advanced CLL	4 3 2 1	4 3 2 1
Phase III trial of BR versus R-CHOP for FL	4 3 2 1	4 3 2 1
FIT: Effect of consolidation radioimmunotherapy after a response to initial induction treatment for FL	4 3 2 1	4 3 2 1
PRIMA trial: Rituximab (R) maintenance therapy for FL after front-line induction therapy with R-containing regimens	4 3 2 1	4 3 2 1
NCCN outcomes database: Comparison of initial treatments for younger patients with MCL	4 3 2 1	4 3 2 1
Lenalidomide in relapsed/refractory aggressive lymphomas	4 3 2 1	4 3 2 1
Clinical research with denileukin diftitox in CTCL	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No

If no, please explain:.....

Will this activity help you improve patient care?

☐ Yes ☐ No ☐ Not applicable

If no, please explain:.....

Did the activity meet your educational needs and expectations?

☐ Yes ☐ No

If no, please explain:.....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Develop an algorithm for the evaluation and treatment of newly diagnosed and relapsed/refractory CLL. . . . . 4 3 2 1 N/M N/A
- Communicate the existing and emerging roles of proteasome inhibitors and IMiDs® for patients with mantle-cell lymphoma (MCL) . . . . . 4 3 2 1 N/M N/A
- Integrate the recent trial results of novel agents and regimens into the initial management of follicular lymphoma (FL).. . . . . 4 3 2 1 N/M N/A
- Counsel patients with responding FL about the risks and benefits associated with consolidation and/or maintenance therapy.. . . . . 4 3 2 1 N/M N/A
- Incorporate the results of recent research on the use of PET scans into the management of diffuse large B-cell lymphoma (DLBCL) . . . . . 4 3 2 1 N/M N/A
- Apply emerging research results to develop evidence-based clinical management strategies for newly diagnosed or recurrent T-cell lymphomas. . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients with lymphoid tumors about the availability of ongoing clinical trials in which they may be eligible to participate . . . . . 4 3 2 1 N/M N/A

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

- ☐ Yes, I am willing to participate in a follow-up survey.
- ☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Bruce D Cheson, MD	4 3 2 1	4 3 2 1
Myron S Czuczman, MD	4 3 2 1	4 3 2 1
Jonathan W Friedberg, MD	4 3 2 1	4 3 2 1
Stephanie A Gregory, MD	4 3 2 1	4 3 2 1
John P Leonard, MD	4 3 2 1	4 3 2 1
Kanti R Rai, MD	4 3 2 1	4 3 2 1
Steven T Rosen, MD	4 3 2 1	4 3 2 1
Mitchell R Smith, MD, PhD	4 3 2 1	4 3 2 1
Andrew D Zelenetz, MD, PhD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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Name: ..... Specialty: .....

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Hematologic Oncology™ UPDATE

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Hematologic Oncology™

UPDATE

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