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Recent Developments in Clinical and Translational Research in NHL and CLL

Proceedings from a Clinical Investigator Think Tank

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Recent Developments in Clinical and Translational Research in NHL and CLL

A Continuing Medical Education Activity

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.
- Integrate recent trial results with 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 CNS prophylaxis into the management of diffuse large B-cell lymphoma.
- 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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FRONT-LINE AND MAINTENANCE TREATMENT

DR LOVE: Bruce, what are your thoughts on the watch and wait versus rituximab study in FL?

DR CHESON: Years ago, Ardeshna and colleagues presented a study of watch and wait versus chlorambucil that reported no benefit with early intervention (Ardeshna 2003). Now they have conducted a similar trial with rituximab for patients with asymptomatic advanced-stage disease and low tumor burden.

Four hundred sixty-two patients were randomly assigned, and some of the findings were as expected. Patients experienced a higher response rate if they received rituximab than if they didn't.

In addition, time to next treatment was significantly longer on the rituximab arms than on the watchful waiting arm. Both time to new therapy and time to progression were longer on the rituximab arms, but no survival difference was evident (Ardeshna 2010; [1.1]).

DR LEONARD: I'm not sure this changes practice. The data are interesting, but it's early. Overall survival and quality of life are most important. The difference between this study and the chlorambucil study is that rituximab is a more attractive agent.

DR LOVE: How do patients respond to the watch-and-wait approach?

DR KAHL: For those with a low tumor burden, there are three types of patients. Some are comfortable with the idea of observation and will wait until the last possible moment to start treatment. Others are uncomfortable with observation, and I will typically opt to administer a chemotherapy-rituximab combination with the objective of providing the most effective therapy that will yield the most durable remission without too much toxicity. The third group of

1.1

Rituximab (R) versus Watch and Wait (W + W) Strategy for Patients with Advanced, Asymptomatic, Nonbulky Follicular Lymphoma

Response at 25 months	W + W (n = 186)	R induction (RI) (n = 84)	RI → R maintenance (n = 192)
Overall response rate	8%	53%	79%
CR/CRu	4%	40%	70%
Initiated new treatment	44%	23%	10%
No new treatment at three years	48%	80%	91%
Three-year progression-free survival	33%	60%	81% ($p < 0.001$ vs W + W)

CR = complete response; CRu = unconfirmed complete response

Ardeshna KA et al. *Proc ASH* 2010;**Abstract 6**.

patients are also uncomfortable with observation but are deathly afraid of chemotherapy. Those are the patients for whom single-agent rituximab fills a niche.

DR LOVE: Jonathan, how would you approach initial treatment of FL in a patient who is not comfortable with observation?

DR FRIEDBERG: I would probably favor a chemoimmunotherapy combination rather than single-agent rituximab. For a younger patient in otherwise good health, once treatment is initiated a reasonable goal is to attain a complete remission and maximize the progression-free survival interval. I believe the best way to accomplish that goal would be with a regimen like bendamustine/rituximab (BR).

DR KAHL: I agree. Until a year or two ago, I probably would have recommended R-CHOP, but in the current era I would recommend BR based on the STiL study (Rummel 2010; [1.2]).

DR LOVE: Brad, would you summarize what was observed in the PRIMA maintenance study (Salles 2011; [1.3]) and describe how you incorporate this into your practice?

DR KAHL: A profound progression-free survival benefit was reported with maintenance rituximab. At three years, approximately 60 percent of the patients not receiving maintenance are still in remission, but that

1.2

StiL NHL 1-2003 Study: Bendamustine/Rituximab (BR) versus R-CHOP as First-Line Therapy for Advanced Follicular, Indolent and Mantle-Cell Lymphomas: Final Results of a Phase III Study

Efficacy	BR (n = 260)	R-CHOP (n = 253)	*p*-value
Overall response	92.7%	91.3%	—
Complete response	39.6%	30.0%	0.0262
Median progression-free survival (all)	54.9 mo	34.8 mo	0.00012
Median progression-free survival (FL only)	Not reached	46.7 mo	0.0281
≥Grade III adverse events	(n = 1,450) (% of cycles)	(n = 1,408) (% of cycles)	*p*-value
Neutropenia	10.7%	46.5%	<0.0001
G-CSF administered	4.0%	20.0%	<0.0001
All CTC-grade adverse events	(n = 260)	(n = 253)	*p*-value
Alopecia	—	+++	<0.0001
Paresthesias	6.9%	28.9%	<0.0001
Stomatitis	6.2%	18.6%	<0.0001
Skin (erythema)	16.2%	9.1%	0.0122
Allergic reaction (skin)	15.4%	5.9%	0.0003
Infectious complications	36.9%	50.2%	0.0025

Rummel MJ et al. 2010 ASCO/ASH Joint Session;**Abstract 405**.

number is closer to 80 percent for those who did receive maintenance. That's quite a striking absolute difference. No overall survival difference was observed between the two groups. From a toxicity standpoint, immunoglobulin levels did not drop in the patients receiving maintenance rituximab. The infection rates were slightly higher, but the infections were generally not serious.

The question is, is extending remission a worthwhile goal, or is an overall survival benefit necessary? I believe that if you can achieve a longer remission without adding too much toxicity and adversely affecting quality of life, then it's worthwhile. So in my own practice I offer rituximab maintenance to patients and explain what we hope to achieve. I also explain that it's reasonable to decline it, but in my experience most patients will opt for maintenance therapy.

DR LOVE: John, what's your approach?

DR LEONARD: I offer maintenance rituximab and we discuss it, but I don't necessarily advocate for it.

DR MCLAUGHLIN: I offer maintenance therapy to patients, but I believe it's also important to discuss radioimmunotherapy consolidation as an alternative.

DR ZELENETZ: We discuss three options: radioimmunotherapy, maintenance rituximab and observation. I assist in decision-making, but I don't advocate maintenance as essential.

DR LOVE: Bruce, how do you approach this issue?

DR CHESON: I do not offer maintenance therapy because I am not yet convinced that it's appropriate for all patients.

1.3

Phase III PRIMA Study: Efficacy Results with Maintenance Rituximab for Previously Untreated Follicular Lymphoma

	Observation (n = 513)	Maintenance rituximab (n = 505)	Hazard ratio	*p*-value
Two-year PFS	57.6%	74.9%	0.55	<0.0001

PFS = progression-free survival

Salles G et al. *Lancet* 2011;377(9759):42-51.

NOVEL INVESTIGATIONAL AGENTS AND COMBINATIONS

DR LOVE: What are the major cooperative studies and other trials currently ongoing in FL?

DR CHESON: At present, we have a CALGB study of rituximab and lenalidomide for patients with low and intermediate FLIPI scores, and the cooperative groups are developing trials for patients with higher-risk FLIPI scores, also with rituximab and lenalidomide.

Patients with high-risk FLIPI scores and with higher tumor burden are receiving chemotherapy-based regimens along with the novel agents, while in the CALGB trial the patients

1.4

Bortezomib (V) and Rituximab (R) versus R Alone for Patients with Relapsed, R-Naïve or R-Sensitive Follicular Lymphoma

	V/R (n = 315)	R only (n = 324)	Odds ratio	*p*-value
Overall response	63%	49%	0.57	0.0004
Durable response (≥6 months)	50%	38%	0.61	0.002
Complete response	18%	14%	NS	NS
	V/R (n = 336)	R only (n = 340)	Hazard ratio	*p*-value
Progression-free survival	12.8 mo	11.0 mo	0.82	0.039
Time to next treatment	23.0 mo	17.7 mo	0.80	0.024

NS = not significant

Coiffier B et al. *Lancet Oncol* 2011;12(8):773-84.

with low/intermediate FLIPI scores are receiving only the biologic doublet.

For patients with high-risk FLIPI scores, we are planning to activate a randomized Phase II trial of up-front bendamustine/ofatumumab versus bendamustine/bortezomib/ofatumumab. Bortezomib/rituximab maintenance will also be built in.

DR KAHL: At ECOG we have a trial of BR followed by a rituximab maintenance backbone, and one of the arms is evaluating bortezomib built into the induction therapy. The third arm is evaluating lenalidomide built into the rituximab maintenance therapy.

DR LOVE: What do we know about the activity of bortezomib in FL?

DR CHESON: Phase I and II data from multiple histologies of lymphoma have indicated that bortezomib has activity, probably other than in CLL/small lymphocytic lymphoma. We studied it in the VERTICAL trial in the combination of bendamustine/bortezomib/rituximab (Fowler 2011). Bertrand Coiffier presented data from LYM-3001, a randomized trial of rituximab with or without bortezomib (Coiffier 2011; [1.4]).

The investigators reported a significantly higher response rate and a complete response rate that was not statistically different. Progression-free survival was longer, but the trial did not meet its projected endpoint of a 33 percent improvement. The regimen was also associated with considerably more toxicity — myelosuppression and a high rate of neurotoxicity — although most of that was at least partially reversible. ■

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Ardeshna KM et al. **Long-term effect of a watch and wait policy versus immediate systemic treatment for asymptomatic advanced-stage non-Hodgkin lymphoma: A randomised controlled trial.** *Lancet* 2003;362(9383):516-22.

Coiffier B et al. **Bortezomib plus rituximab versus rituximab alone in patients with relapsed, rituximab-naïve or rituximab-sensitive, follicular lymphoma: A randomised phase 3 trial.** *Lancet Oncol* 2011;12(8):773-84.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: The Phase II VERTICAL study.** *J Clin Oncol* 2011;[Epub ahead of print].

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab 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.** 2010 ASCO/ASH Joint Session;**Abstract 405**.

Salles G et al. **Rituximab maintenance for 2 years in patients with tumour burden follicular lymphoma responding to rituximab plus chemotherapy (PRIMA): A phase 3, randomised controlled trial.** *Lancet* 2011;377(9759):42-51.

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

INITIAL TREATMENT OF CLL

DR LOVE: In general, what initial systemic therapy would you recommend for an older patient with CLL with deletion 11q?

DR FRIEDBERG: Assuming the patient is in good health, I would probably recommend FCR because I believe some benefit comes from adding cyclophosphamide for patients with deletion 11q. Another consideration — depending on performance status — would be BR.

DR CHESON: An older patient may have some renal compromise as a function of age, and I would administer BR based on this factor. Older patients don't tolerate FCR well due to myelosuppression and other symptoms. Based on the available data in the up-front setting, BR and FCR have comparable response rates, more

2.1

CLL-10: A Phase III Trial of Combined Immunochemotherapy with FCR versus BR as Up-Front Treatment for Chronic Lymphocytic Leukemia (CLL)

Protocol IDs: GCLLSG-CLL10, EU-20883

Target Accrual: 550

Eligibility

B-cell CLL with Binet Stage C, or Stage B or A requiring treatment (B symptoms; progressive lymphocytosis; progressive marrow failure; massive, progressive or painful splenomegaly or hypersplenism; massive lymph nodes or lymph node clusters)

R

- Fludarabine + cyclophosphamide + rituximab x 6
- Bendamustine + rituximab x 6

Primary Endpoint: Progression-free survival rate after 24 months

www.clinicaltrials.gov. Identifier NCT00769522.

than 90 percent with both, and the complete response rates are high with both. That's why the CLL-10 study, which is directly evaluating BR versus FCR, is so important (2.1).

DR LOVE: Andy, what is your preferred regimen in this setting, and what are some of the key data sets from your perspective?

DR ZELENETZ: Patients who have the 11q deletion clearly have a different response rate to fludarabine-based regimens with or without an alkylator included. The addition of cyclophosphamide dramatically increases response rates in patients with 11q abnormality (Ding 2010). I believe these patients should receive an alkylator-based regimen for that reason.

That brings us to the data. We've had an evolution of trials from F versus FC to FC versus FCR. The FC versus FCR trial is an important one for which results were recently published (Hallek 2010; [2.2]).

The median age of patients on that study was 61. That's at least 10 years younger than the median age of patients with CLL. So it raises an issue as to what the right treatment is for an older patient.

Of course, another big question now is, FCR or BR (2.1)? I believe that's an essential trial. The long-term follow-up of the bendamustine versus chlorambucil trial, which was presented at ASH, continues to confirm the benefit of bendamustine over chlorambucil. Additionally, both treatment groups achieved similar efficacy with second-line therapy, and although the efficacy was somewhat diminished in the bendamustine group, the difference between the two treatment groups was not statistically significant (Knauf 2010).

DR LOVE: Andy, you mentioned the median age of 61 for patients on the CLL-8 trial (2.2). What are your thoughts on the study by Mulligan and colleagues reported at ASH 2010 on the safety and tolerability of FCR in patients age 65 or older with previously untreated CLL?

DR ZELENETZ: This was an early report of a study evaluating three different regimens — FR, "FCR lite" and an FCR regimen that approximated the standard IV FCR treatment in CLL-8. Efficacy was reported across the arms and the treatments were tolerable (Mulligan 2010).

2.2

CLL-8 — Effect of the Addition of Rituximab (R) to Fludarabine (F) and Cyclophosphamide (C) on Survival for Patients with Chronic Lymphocytic Leukemia: A Phase III Trial

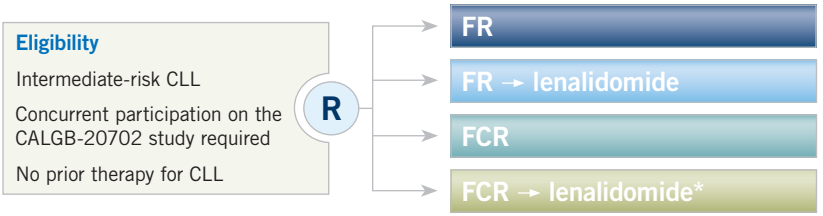
	FCR (n = 408)	FC (n = 409)	Hazard ratio	*p*-value
Three-year progression-free survival	65%	45%	0.56	<0.0001
Three-year overall survival	87%	83%	0.67	0.01
Grade 3 or 4 neutropenia	34%	21%	—	<0.0001
Grade 3 or 4 leukocytopenia	24%	12%	—	<0.0001

Hallek M et al. *Lancet* 2010;376(9747):1164-74.

2.3

CALGB-10404 Study: Fludarabine (F) and Rituximab (R) with or without Lenalidomide or Cyclophosphamide (C) for Patients with Symptomatic Chronic Lymphocytic Leukemia (CLL)

Protocol IDs: ECOG-10404, NCT00602459 **Target Accrual:** 405



* Patients with del(11q22.3)

NCI Physician Data Query, July 2011.

DR FRIEDBERG: It is important to note that the current Intergroup trial comparing FR to FCR followed by lenalidomide maintenance for CLL (2.3) underwent a modification to its design so that patients who were randomly assigned to FR would be reassigned to the FCR arm if they were found to have deletion 11q. Enough compelling data for adding an alkylating agent in this subset swayed the trial leaders to make that change.

NEW CLINICAL TRIALS IN CHRONIC LYMPHOCYTIC LEUKEMIA

DR LOVE: Can you talk about the background of the CALGB-10404 study?

DR CHESON: We currently have a trial evaluating FR followed by lenalidomide. Approximately 20 patients have received treatment on that study (Ujjani 2011). Additionally, we have a Phase I study in the relapsed setting evaluating the combination of bendamustine with lenalidomide, and when the maximum tolerated dose is reached, rituximab will be added. Other researchers are combining lenalidomide with ofatumumab. For the most part, when lenalidomide is added to cytotoxic therapy, it is generally administered as consolidation or maintenance because it can compromise the dose of other agents.

Lenalidomide is an interesting agent. Two major studies evaluating this agent have been published in CLL. One from Roswell Park reported about a 45 percent response rate in patients with relapsed/refractory CLL (Chanan-Khan 2006). The researchers started at a high dose of 25 mg and worked their way down.

In a study conducted at MD Anderson, they started at a low dose and worked their way up and reported about a 30 to 35 percent response rate in relapsed/refractory CLL (Ferrajoli 2008). Lenalidomide is also active in the front-line setting, but the response rates aren't terribly different than those seen in the relapsed setting.

DR KAHL: I believe maintenance lenalidomide could be an attractive strategy in CLL, analogous to indolent lymphomas, especially in the relapsed setting. Getting patients into remission isn't the hardest part, but keeping them there can be a challenge. So an oral therapy with a favorable toxicity profile is an attractive maintenance strategy. Lenalidomide has a lot of issues in terms of dose and schedule that need to be optimized.

TREATMENT-ASSOCIATED TUMOR FLARE AND TUMOR LYSIS SYNDROME IN CLL

DR LOVE: Would you comment on the tumor flare and tumor lysis syndrome that have been reported with lenalidomide in CLL?

DR CHESON: These are interesting, albeit uncommon, phenomena — fewer than 15 percent of patients will experience tumor flare or Grade 3 or higher tumor lysis syndrome. Tumor flare occurs a week or two after you initiate lenalidomide therapy. It's been reported with doses as low as 2.5 mg of lenalidomide, which is a dose so low that it's not even commercially available.

DR LOVE: What are some of the agents available for the treatment of tumor lysis syndrome?

DR CHESON: Allopurinol is a xanthine oxidase inhibitor. It prevents the body from making uric acid, but it doesn't get rid of the uric acid that already exists. Rasburicase, however, is a recombinant urate oxidase, which rids the body of the uric acid that's already been made by converting it to the highly soluble compound allantoin, which is excreted in the urine.

We tend to administer rasburicase for patients at high risk, such as those with lymphoblastic leukemia or some of the acute lymphoid leukemias, and for patients who present with high uric acid levels who we believe are likely to develop rapid tumor lysis from therapy.

DR ZELENETZ: We should address one other consideration as it applies to rasburicase because rasburicase has an FDA approval, but it's generally not administered as indicated. A disconnect exists between the package insert and what's usually done. The package insert recommends multiday therapy, but we typically administer rasburicase as a single-day fixed dose. An interesting retrospective analysis of administration of a single 4.5-mg dose of rasburicase for tumor lysis was presented at ASH (Yim 2010). This approach turned out to be effective, and I believe that's an important message.

Rasburicase is expensive and can cause hypersensitivity reactions. It's exciting to know it can be effectively administered as a single dose with favorable results. You can then follow the patient and administer a second dose if needed. In their experience with 25 patients, two patients needed a second dose. So the dosing regimen as recommended and approved is probably much more drug than is necessary. ■

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Ding W, Ferrajoli A. **Evidence-based mini-review: The role of alkylating agents in the initial treatment of chronic lymphocytic leukemia patients with the 11q deletion.** *Hematology Am Soc Hematol Educ Program* 2010;2010:90-2.

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Knauf W et al. **Bendamustine induces higher remission rates, prolongs progression free survival as well as time to next treatment, and improves overall survival for patients in complete remission without compromising quality of life when compared to chlorambucil in first line treatment of chronic lymphocytic leukemia.** *Proc ASH* 2010;**Abstract 2449**.

Mulligan SP et al. **The safety and tolerability of oral fludarabine, ± oral cyclophosphamide and IV rituximab therapy in previously untreated patients with chronic lymphocytic leukaemia (CLL) aged ≥65 years — Interim analysis from the Australasian Leukaemia and Lymphoma Group (ALLG) and CLL Australian Research Consortium (CLLARC) CLL5 study.** *Proc ASH* 2010;**Abstract 699**.

O'Brien S, Kay NE. **Maintenance therapy for B-chronic lymphocytic leukemia.** *Clin Adv Hematol Oncol* 2011;9(1):22-31.

Pinto A et al. **Tumor flare reaction associated with lenalidomide treatment in patients with chronic lymphocytic leukemia predicts clinical response.** *Cancer* 2011;[Epub ahead of print].

Ujjani CS et al. **Lenalidomide following rituximab and fludarabine in untreated CLL.** *Proc ASCO* 2011;**Abstract 6558**.

Yim B et al. **Single 4.5mg dose of rasburicase for tumor lysis syndrome in adults.** *Proc ASH* 2010;**Abstract 1779**.

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

CLINICAL CONTROVERSIES IN THE MANAGEMENT OF DLBCL

DR LOVE: Jonathan, can you comment on primary mediastinal large B-cell lymphoma (PMBL)?

DR FRIEDBERG: I believe it's important to note that PMBL is both a syndrome and a disease. When we're trying to interpret data sets, we have to remember that. For years, this has been a syndrome that occurs in young women. It tends to involve mediastinal structures, has a propensity to go to extranodal sites and causes effusions, both pericardial and pleural. We now know from gene expression profiling that primary mediastinal lymphoma is a disease. Not everybody who presents with the syndrome has the disease and, in fact, some people who don't present with the syndrome have the disease.

DR FOSS: We know that these patients should be approached differently than the "garden variety" patients with DLBCL.

DR LOVE: Bruce, what clinical trials are available for patients with PMBL?

DR CHESON: CALGB-50303 is a national high-priority trial that compares R-CHOP to R-EPOCH in patients with PMBL as well as other subtypes of Stage II to IV DLBCL.

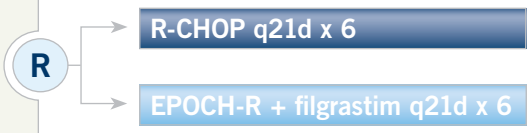
3.1

CALGB-50303: A Phase III Study of R-CHOP versus Dose-Adjusted EPOCH-R with Molecular Profiling in Untreated de Novo Diffuse Large B-Cell Lymphomas (DLBCL)

Protocol IDs: CALGB-50303, NCT00118209 **Target Accrual:** 478

Eligibility

Previously untreated histologically documented de novo Stage I mediastinal (thymic) DLBCL or any Stage II, III or IV DLBCL



A frozen tumor biopsy equivalent to a minimum of four 16 gauge or higher needle cores is an important component of this study. Patients without adequate frozen material should have a biopsy performed to obtain material.

For patients registered on the optional FDG-PET/CT imaging companion (CALGB-580603), PET/CT of the abdomen/chest/pelvis will be collected at baseline and after cycles 2 and 6.

NCI Physician Data Query, July 2011.

It has accrued approximately 340 of a planned 440 patients (3.1). This study is particularly interesting in that it does not permit radiation therapy after the chemotherapy. The standard in the past has been R-CHOP followed by involved-field radiation therapy. Data from the NCI with a relatively small number of patients who had PMBL indicate that all patients except one fared well without radiation therapy, and that patient was salvaged with radiation therapy. So we are attempting to determine whether we can eliminate the need for radiation therapy.

Another critical question under investigation is prospective validation of FDG-PET and, most important, tumor biopsies are taken for DNA microarray analysis. This study will teach us a lot about whether one subtype of lymphoma is preferentially sensitive to an infusional regimen versus a bolus regimen. So we encourage our patients to enroll on this trial so that we can answer these important clinical questions and complete the correlative studies.

DR LOVE: Another area where there is some controversy is the use of CNS prophylaxis for patients with DLBCL. Brad, what are your thoughts about this issue?

DR KAHL: That's a murky issue right now in large cell lymphoma. My review of the literature suggests that the risk factors for CNS relapse are number of extranodal sites and a high LDH. So if I have patients with multiple extranodal sites and a high LDH, those are the patients for whom I believe some form of CNS prophylaxis might be indicated.

DR CHESON: Regarding CNS prophylaxis, a large study was presented at ASH 2010 from Norbert Schmitz of the German High Grade Lymphoma Study Group evaluating thousands of patients with large cell lymphoma who underwent treatment on a series of successive clinical protocols.

The authors evaluated incidence of CNS relapse. Out of thousands of patients, two and a half percent developed CNS recurrences at a median of seven months, suggesting that CNS disease was probably there to begin with.

Survival of these patients was dismal, and the authors were unable to identify any factor that correlated with the occurrence of CNS relapse — they examined LDH and advanced stage.

This was a group of patients at high risk, but their likelihood of developing CNS recurrence was only 6.5 percent, and it didn't differ with one regimen versus another. It was a little lower in patients who received rituximab but not that much lower. It also didn't matter whether prophylaxis was administered.

Whether or not the patient received intrathecal methotrexate, the likelihood of developing a CNS relapse was not different (Schmitz 2010). ■

SELECT PUBLICATION

Schmitz N et al. **CNS disease in younger patients (≤60 years) with aggressive lymphoma treated in trials of the German High Grade Non Hodgkin Lymphoma Study Group (DSHNHL) and the MabThera International Trial (MInT).** *Proc ASH* 2010;**Abstract 112**.

MANTLE-CELL LYMPHOMA (MCL)

FRONT-LINE THERAPY FOR MCL

DR LOVE: What are some of the ongoing clinical research efforts right now for patients with newly diagnosed MCL?

DR KAHL: Two front-line trials are being planned by the US Intergroup, one for younger patients and one for older patients. In the trial for younger patients, all patients receive autologous stem cell transplantation as part of their initial therapy.

It poses the question, does it matter which induction treatment precedes stem cell transplant? Half the patients receive conventional hyper-CVAD for four cycles and the other half receive BR for six cycles, and both treatments are followed by stem cell transplant.

Progression-free survival, toxicity and quality of life will be analyzed. It's an appealing front-line trial for younger patients who can tolerate intensive therapies.

A trial being initiated now for older patients has BR induction followed by rituximab maintenance as a baseline arm. Another arm will add bortezomib to the induction therapy, one arm will add lenalidomide to the postremission therapy and the final arm will add both bortezomib to the induction therapy and lenalidomide to the postremission therapy.

DR LOVE: We've seen positive results with lenalidomide maintenance in myeloma. Is this what you would call lenalidomide maintenance?

DR KAHL: Yes, low-dose lenalidomide and rituximab maintenance for two years.

DR CHESON: I believe it's an excellent trial. Regimens such as BR have high response rates (Rummel 2009), so it may be tricky to demonstrate a difference in outcomes among the arms without considerable numbers of patients.

It may also be complicated because it's basically a four-arm study. To explain that to patients and to convince them to enroll is a challenge.

MAINTENANCE THERAPY FOR MCL

DR LOVE: Would you discuss the recent results reported with rituximab maintenance in elderly patients with MCL?

DR KAHL: In this large European trial, rituximab maintenance therapy conferred enough clinical benefit that the data safety monitoring board closed it early. The trial was almost fully enrolled. These data suggest that maintenance rituximab should become a standard option for older patients with MCL (Kluin-Nelemans 2011; [4.1]).

I've been a proponent of this approach for a few years and have studied it at the University of Wisconsin. We conducted a trial years ago of modified hyper-CVAD, which is sort of a watered-down conventional hyper-CVAD, but we administered two years of maintenance rituximab after that, and I've always believed that the maintenance therapy is what made the difference.

With this regimen, the median progression-free survival was approximately three years in a representative population with MCL, which is about twice as long as what you observe with R-CHOP.

The follow-up study we conducted added maintenance rituximab, and then we collaborated with ECOG and conducted another study with maintenance rituximab.

The mature results of the ECOG study have not yet been reported, but in the second study from Wisconsin, at three years more than 60 percent of our patients are in remission with maintenance rituximab (Kenkre 2011). ■

4.1

Rituximab (R) Maintenance After Induction Therapy with R-CHOP or R/FC for Elderly Patients with MCL: First Results from the European Mantle Cell Lymphoma Network Study*

Response	R maintenance	IFN maintenance	Hazard ratio	*p*-value
Median remission duration	51 months	24 months	0.56	0.0117
Select Grade 3/4 toxicities				
Leukocytopenia	17%	36%	—	—
Thrombocytopenia	7%	16%	—	—

* Randomization closed October 2010. Data were reported for 223 of 308 responding patients randomly assigned to maintenance.

Kluin-Nelemans H et al. *Proc EHA* 2011;**Abstract 0504**.

SELECT PUBLICATIONS

Kenkre VP et al. **Maintenance rituximab following induction chemo-immunotherapy for mantle cell lymphoma: Long-term follow-up of a pilot study from the Wisconsin Oncology Network.** *Leuk Lymphoma* 2011;[Epub ahead of print].

Kluin-Nelemans J et al. **Rituximab maintenance significantly prolongs duration of remission in elderly patients with mantle cell lymphoma. First results of a randomized trial of the European MCL Network.** *Proc EHA* 2011;**Abstract 0504**.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to CHOP plus rituximab 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

RELAPSED DISEASE

DR LOVE: What are some of the new treatment options for a patient with relapsed T-cell lymphoma?

DR HORWITZ: The two approved HDAC inhibitors are an oral drug, vorinostat, and an intravenous drug, romidepsin. Those are both approved for relapsed cutaneous T-cell lymphoma (CTCL). Response rates with those two agents are fairly similar.

Romidepsin is approved in CTCL based on two studies — a multicenter study in just fewer than 100 patients (Whittaker 2010) and a slightly smaller NCI study (Piekarz 2009).

A study evaluating romidepsin in about 130 patients with relapsed peripheral T-cell lymphoma (PTCL) has recently been completed and was presented at ASH 2010 (Coiffier 2010). A response rate of approximately 26 percent was reported in that group of patients. The duration of complete responses is still ongoing at approaching a year.

The antifolate agent pralatrexate is also approved in PTCL based on a 115-patient study with slightly less than a 30 percent response rate (O'Connor 2011).

We've also performed a study in relapsed/refractory CTCL evaluating low doses of pralatrexate at half the dose administered for aggressive T-cell lymphomas and have seen about a 50 percent response rate in those patients (Horwitz 2010).

I believe another option would be the anti-CD52 antibody alemtuzumab, which has high response rates at particularly low doses in Sézary syndrome (Lundin 2003).

For CTCL, a number of single-agent chemotherapies, such as liposomal doxorubicin or gemcitabine, could be considered, although those are not as well studied and the response rates aren't as well characterized.

DR LOVE: What's been your experience in terms of tolerability of these agents?

DR FOSS: Many patients receiving HDAC inhibitors experience constitutional side effects in the form of

fatigue and asthenia. Some patients develop nausea, and some also have diarrhea.

With regard to pralatrexate, you have to remember that patients need vitamin supplementation with B_{12} and folic acid prior to receiving the agent because its major toxicity is mucositis. This is ameliorated to some degree in patients who receive vitamin supplementation.

The second major toxicity with pralatrexate is thrombocytopenia, although that's been fairly manageable in that it's short-lived.

NOVEL AGENTS IN T-CELL LYMPHOMA

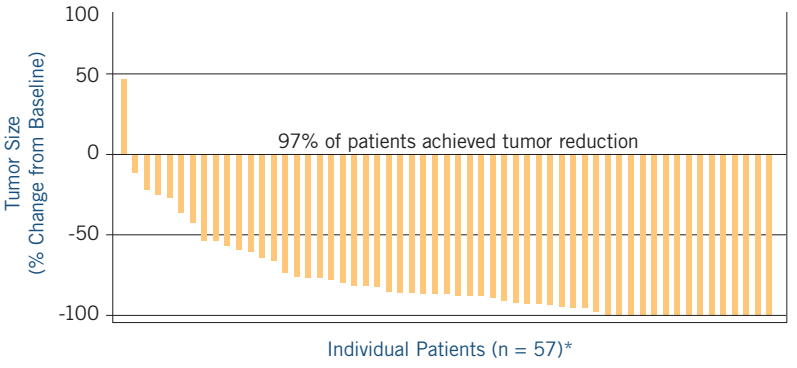
DR LOVE: What do we know about brentuximab vedotin in anaplastic large cell lymphoma (ALCL; [5.1])?

DR HORWITZ: Brentuximab vedotin is an anti-CD30 antibody that's conjugated to a chemotherapy called monomethyl auristatin E. So this antibody basically targets the chemotherapy to the tumor cell. It gets endocytized and acts as an antitubulin agent. Unlabeled CD30 antibodies target well to ALCL, which is always CD30 expressing. They have almost no toxicity and little activity.

DR ZELENETZ: The idea is that the drug-antibody conjugate is not active by itself. If the agent is going to work, it has to get inside the cell. This agent is designed so that CD30 is removed from the cell surface through the mechanism of endocytosis.

5.1

Response and Maximum Tumor Reduction in Patients with Relapsed or Refractory Systemic Anaplastic Large Cell Lymphoma Treated with Brentuximab Vedotin (SGN-35)



* 57 of 58 patients with postbaseline CT assessments

Response	Independent review facility	Investigator
Overall response rate	86%	81%
Complete remission	53%	59%
Partial remission	33%	22%

With permission from Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

The linkage between the antibody and the drug is labile, and the drug is released, so now you have free drug that's delivered inside the tumor cell and is then trafficked to the nucleus.

DR LOVE: What's the spectrum of CD30 as a target in general?

DR HORWITZ: It's somewhat variable. About 10 percent of PTCLs have high CD30 expression. In a couple of T-cell lymphomas, such as ALCL, about 100 percent of the tumor cells express CD30, similar to most Hodgkin lymphomas.

A number of the other T-cell lymphomas have lower rates of expression — HTLV1-associated lymphomas have low levels of expression as do some mycosis fungoides. ■

SELECT PUBLICATIONS

Akilov OE, Geskin L. **Therapeutic advances in cutaneous T-cell lymphoma.** *Skin Therapy Lett* 2011;16(2):1-5.

Ansell SM. **Brentuximab vedotin: Delivering an antimitotic drug to activated lymphoma cells.** *Expert Opin Investig Drugs* 2011;20(1):99-105.

Coiffier B et al. **Final results from a pivotal, multicenter, international, open-label, Phase 2 study of romidepsin in progressive or relapsed peripheral T-cell lymphoma (PTCL) following prior systemic therapy.** *Proc ASH* 2010;**Abstract 114**.

Deutsch YE et al. **CD30: An important new target in hematologic malignancies.** *Leuk Lymphoma* 2011;[Epub ahead of print].

Foyil KV et al. **Brentuximab vedotin for the treatment of CD30+ lymphomas.** *Immunotherapy* 2011;3(4):475-85.

Horwitz SM et al. **Identification of an active, well-tolerated dose of pralatrexate in patients with relapsed or refractory cutaneous T-cell lymphoma (CTCL): Final results of a multicenter dose-finding study.** *Proc ASH* 2010;**Abstract 2800**.

Lundin J et al. **Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sézary syndrome.** *Blood* 2003;101(11):4267-72.

O'Connor OA et al. **Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: Results from the pivotal PROPEL study.** *J Clin Oncol* 2011;29(9):1182-9.

O'Connor O 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**.

Piekarz RL et al. **Phase 2 trial of romidepsin in patients with peripheral T-cell lymphoma.** *Blood* 2011;117(22):5827-34.

Piekarz RL et al. **Phase II multi-institutional trial of the histone deacetylase inhibitor romidepsin as monotherapy for patients with cutaneous T-cell lymphoma.** *J Clin Oncol* 2009;27(32):5410-7.

Serova M et al. **Single agent and combination studies of pralatrexate and molecular correlates of sensitivity.** *Br J Cancer* 2011;104(2):272-80.

Shustov AR et al. **Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma.** *Proc ASH* 2010;**Abstract 961**.

Whittaker SJ et al. **Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma.** *J Clin Oncol* 2010;28(29):4485-91.

Younes A et al. **Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas.** *N Engl J Med* 2010;363(19):1812-21.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **In an Intergroup randomized trial of rituximab versus watch and wait for patients with Stage II to Stage IV asymptomatic, nonbulky FL, patients experienced a higher response rate if they received rituximab versus the watch-and-wait strategy.**
   a. True
   b. False

2. **In the LYM-3001 Phase III study for patients with relapsed FL, the addition of bortezomib to rituximab resulted in significant improvements in _____.**
   a. Overall response rate
   b. Progression-free survival
   c. Both a and b

3. **The Phase III German CLL-10 trial is evaluating combined immunochemotherapy with FCR versus _____ for patients with previously untreated CLL.**
   a. BR
   b. FR → lenalidomide
   c. R-CHOP

4. **A Phase III trial of fludarabine/cyclophosphamide with or without rituximab found that the addition of rituximab was associated with greater overall survival among patients with untreated, advanced CLL.**
   a. True
   b. False

5. **The CALGB-10404 trial is evaluating fludarabine/rituximab with or without _____ or cyclophosphamide for patients with symptomatic CLL.**
   a. Thalidomide
   b. Lenalidomide
   c. Pomalidomide

6. **The CALGB-50303 study is evaluating R-CHOP versus dose-adjusted EPOCH-R for patients with untreated de novo DLBCL.**
   a. True
   b. False

7. **A trial evaluating maintenance rituximab after induction therapy with R-CHOP or R-FC for elderly patients with MCL reported that the remission duration was more than doubled for patients receiving rituximab maintenance versus IFN maintenance.**
   a. True
   b. False

8. **A planned Intergroup study in MCL will evaluate R-hyper-CVAD followed by transplant versus _____ followed by transplant as initial therapy.**
   a. Bortezomib/rituximab
   b. BR
   c. Lenalidomide/rituximab

9. **What is the mechanism of action of romidepsin?**
   a. Antimetabolite
   b. Alkylating agent
   c. Histone deacetylase inhibitor
   d. None of the above

10. **A Phase II study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic ALCL reported that _____ of patients achieved tumor reduction.**
    a. 32 percent
    b. 64 percent
    c. 97 percent

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Recent Developments in Clinical and Translational Research in NHL and CLL

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
CLL-10: FCR versus BR in previously untreated CLL	4 3 2 1	4 3 2 1
PRIMA trial: Rituximab maintenance for FL after front-line induction therapy with rituximab-containing regimens	4 3 2 1	4 3 2 1
Clinical research with novel agents — bortezomib, galiximab, lenalidomide and bendamustine — in FL	4 3 2 1	4 3 2 1
NCCN comparison of initial treatment 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
Management of tumor lysis syndrome in CLL	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: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide one or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No

If no, please explain: .....

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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. . . . . 4 3 2 1 N/M N/A
- Integrate recent trial results with 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 CNS prophylaxis into the management of diffuse large B-cell lymphoma. . . . . 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

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

PART TWO — Please tell us about the faculty and moderator 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
Francine Foss, MD	4	3	2	1	4	3	2	1
Jonathan W Friedberg, MD, MMSc	4	3	2	1	4	3	2	1
Steven M Horwitz, MD	4	3	2	1	4	3	2	1
Brad S Kahl, MD	4	3	2	1	4	3	2	1
John P Leonard, MD	4	3	2	1	4	3	2	1
Peter McLaughlin, MD	4	3	2	1	4	3	2	1
Andrew D Zelenetz, MD, PhD	4	3	2	1	4	3	2	1
Moderator	**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 moderator for this activity:

.....

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Hematologic Oncology™ UPDATE

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Hematologic Oncology™

UPDATE

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