

# Non-Hodgkin's Lymphoma™

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U P D A T E

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

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# *Non-Hodgkin's Lymphoma Update*

## A Continuing Medical Education Audio Series

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### STATEMENT OF NEED/TARGET AUDIENCE

Non-Hodgkin's lymphoma is increasing in incidence in the United States and is the most commonly occurring hematologic malignancy. This treatment arena continues to evolve, and published results from ongoing clinical trials lead to the continuous emergence of new therapeutic agents and changes in the indications for existing treatments. In order to offer optimal patient care — including the option of clinical trial participation — practicing hematologists and oncologists must be well informed of these advances. To bridge the gap between research and patient care, *Non-Hodgkin's Lymphoma Update* utilizes one-on-one discussions with leading hematologic oncology investigators. By providing access to the latest research developments and expert perspectives, this CME activity assists hematologists and oncologists in the formulation of up-to-date clinical management strategies.

### GLOBAL LEARNING OBJECTIVES

- Critically evaluate the clinical implications of emerging clinical trial data in non-Hodgkin's lymphoma (NHL) treatment and incorporate these data into management strategies for patients with NHL.
- Counsel appropriately selected patients about the availability of ongoing clinical trials.
- Utilize individual patients' risk factors and disease classification to tailor therapy for subgroups of patients with NHL.
- Describe and implement an algorithm for sequencing of clinical management options for indolent and aggressive NHL, including “watch and wait” and maintenance monoclonal antibody therapy.
- Discuss the risks and benefits of monoclonal antibody therapy and radioimmunotherapy alone and in combination with chemotherapy for patients with NHL, and counsel appropriately selected patients about the risks and benefits of these agents.

### PURPOSE OF THIS ISSUE OF *NON-HODGKIN'S LYMPHOMA UPDATE*

The purpose of Issue 1 of *Non-Hodgkin's Lymphoma Update* is to support these global objectives by offering the perspectives of Drs Zelenetz, Leonard and Maloney on the integration of emerging clinical research data into the management of non-Hodgkin's lymphoma.

### ACCREDITATION STATEMENT

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**Dr Zelenetz** — Consulting Fees: Favrilie, GlaxoSmithKline, Sanofi-Aventis; Contracted Research: Amgen Inc, Biogen Idec, Genentech BioOncology, GlaxoSmithKline. **Dr Leonard** — Consulting Fees: Biogen Idec, Genentech BioOncology. **Dr Maloney** — Consulting Fees: Biogen Idec, Favrilie, Genentech BioOncology, Genitope Corporation, Genmab A/S, GlaxoSmithKline, Millennium Pharmaceuticals Inc.

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## UPCOMING EDUCATIONAL EVENTS

### NCCN Second Annual Congress: Hematologic Malignancies

September 14-15, 2007  
New York, New York  
Website: [www.nccn.org](http://www.nccn.org)

### ECCO 14 — The European Cancer Conference

September 23-27, 2007  
Barcelona, Spain  
Website: [www.fecs.be](http://www.fecs.be)

### SWOG Group Meeting

October 4-7, 2007  
Huntington Beach, California  
Website: [www.swog.org](http://www.swog.org)

### ECOG Group Meeting

November 9-11, 2007  
Fort Lauderdale, Florida  
Website: [www.ecog.org](http://www.ecog.org)

### CALGB Fall Expanded Committee Meetings

November 29-December 2, 2007  
Chicago, Illinois  
Website: [www.calgb.org](http://www.calgb.org)

### The American Society of Hematology 49<sup>th</sup> Annual Meeting and Exposition

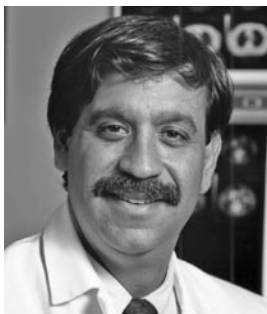
December 8-11, 2007  
Atlanta, Georgia  
Website: [www.hematology.org](http://www.hematology.org)

### ASCO 2008 Annual Meeting

May 30-June 3, 2008  
Chicago, Illinois  
Website: [www.asco.org](http://www.asco.org)

### 10<sup>th</sup> International Conference on Malignant Lymphoma

June 4-7, 2008  
Lugano, Switzerland  
Website: [www.lymphcon.ch](http://www.lymphcon.ch)



## INTERVIEW

### Andrew D Zelenetz, MD, PhD

Dr Zelenetz is Chief of Lymphoma Service at Memorial Sloan-Kettering Cancer Center in New York, New York.

#### Tracks 1-19

- Track 1** Long-term results from GELA: R-CHOP versus CHOP in older patients with diffuse large B-cell lymphoma (DLBCL)
- Track 2** Intergroup study of maintenance rituximab following R-CHOP or CHOP in older patients with DLBCL
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- Track 15** RICOVER-60 trial: Six versus eight cycles of dose-dense CHOP-14 with or without rituximab in DLBCL
- Track 16** Tolerability of the R-CHOP-14 regimen
- Track 17** Tositumomab and I-131 tositumomab (Bexxar<sup>®</sup>) in combination with stem cell transplantation for relapsed DLBCL
- Track 18** Role of radioimmunotherapy in patients with mantle-cell lymphoma
- Track 19** Treatment strategies for patients with mantle-cell lymphoma

#### Select Excerpts from the Interview

#### Tracks 1-2

- ▶ **DR LOVE:** Can you discuss some of the important clinical trial results presented at ASCO this year?

► **DR ZELENETZ:** ASCO included several updates of groundbreaking studies. One was a seven-year update on the GELA (Groupe d'Etude des Lymphomes de l'Adulte) study (Coiffier 2007; [1.1]), which compared CHOP to rituximab and CHOP (R-CHOP).

The eligibility criteria were age older than 60 and younger than 80 with diffuse large B-cell lymphoma (DLBCL) and lacking any significant comorbid conditions that would preclude the use of anthracycline-based chemotherapy. Patients received rituximab and CHOP in the hospital, and they were premedicated with steroids so that infusion toxicities were extremely low. It was well tolerated.

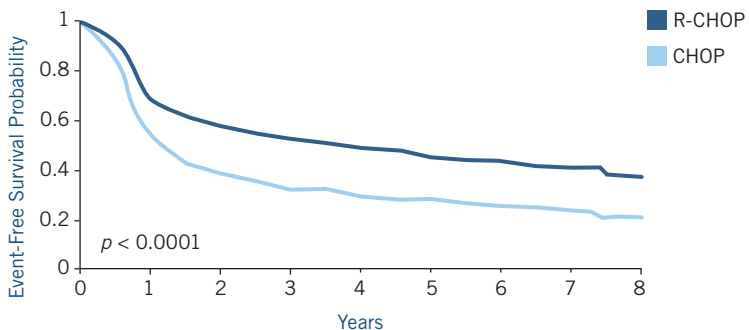
The biggest surprise is how the data have held up over time. The survival advantage continues to be maintained. There's even a slight increase in the separation between the curves over time, which is surprising in a study with patients aged 60 to 80 and with seven years' median follow-up — we would have expected people to start to die of other causes. The importance of rituximab and the clear breakthrough it adds to CHOP are confirmed.

Another presentation from Intergroup E4494/C9793 was a two-by-two randomized trial that compared R-CHOP to CHOP for patients with DLBCL and, in a second randomization, rituximab maintenance to observation. An initial four-arm analysis suggested that R-CHOP was clearly superior to CHOP but that maintenance after R-CHOP added no benefit whatsoever (Habermann 2006).

For a long time, maintenance rituximab appeared to be essentially equivalent to adding rituximab to CHOP. Patients who received CHOP initially and then received maintenance rituximab appeared to have almost the same outcome over the long term.

## 1.1

### Seven-Year Event-Free Survival Following R-CHOP versus CHOP in DLBCL Patients Aged 60-80 in the GELA Trial



CHOP = cyclophosphamide, doxorubicin, vincristine and prednisone; DLBCL = diffuse large B-cell lymphoma; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone

SOURCE: With permission from Coiffier B et al. *Proc ASCO* 2007; [Abstract 8009](#).

Vicky Morrison presented an updated analysis focused on the second randomization, and a relatively big surprise was that even though maintenance rituximab in those patients who were initially treated with CHOP clearly delayed time to progression, it did not eradicate disease (Morrison 2007). So in the final analysis, no statistically significant superiority for overall survival was evident for maintenance rituximab over observation. Based on these data, patients should receive rituximab and CHOP in combination.

## Track 5

► **DR LOVE:** What are the key data sets evaluating maintenance rituximab in the low-grade lymphomas?

► **DR ZELENETZ:** The first data set is from the HOVON-26 trial. It was also a two-by-two randomization comparing CHOP to R-CHOP with a second randomization for maintenance rituximab versus no maintenance. That first randomization was stopped because of the superiority of the R-CHOP arm. Patients who received R-CHOP as induction showed an improvement in progression-free survival with the maintenance rituximab (van Oers 2006).

The second data set, from the German Low Grade Lymphoma Study Group (GLSG), was also a two-by-two randomized trial, comparing FCM (fludarabine, cyclophosphamide and mitoxantrone) to R-FCM. Again, the first randomization was stopped because of the clear superiority of adding rituximab to the chemotherapy (Forstpointner 2004).

The second randomization showed a highly significant improvement in progression-free survival with maintenance rituximab, even in the group of patients who received rituximab in the induction (Hiddemann 2005).

So in low-grade lymphoma, particularly in follicular lymphomas, I believe we have a different answer regarding maintenance rituximab. In that situation, maintenance can certainly delay the time to the next treatment and may in fact have an impact on overall survival. Any indolent lymphoma study requires long follow-up to reflect all the events. When you start to see survival advantages relatively early in a follicular lymphoma trial, your interest perks up. If the advantage appears early, it will probably hold up as time goes on.

## Tracks 15-16

► **DR LOVE:** Are there any newly emerging data in dose-dense therapy?

► **DR ZELENETZ:** The RICOVER-60 trial was important from two points of view (Pfreundschuh 2006). One is that it finally put to rest the question of six versus eight cycles of CHOP. With both CHOP and R-CHOP, six cycles were as good as eight. Many of the patients with large cell lymphoma are older than age 60. Sparing them an additional 100 mg/m<sup>2</sup> of doxorubicin is not a trivial undertaking. If it's not necessary to administer eight cycles, eight shouldn't be administered.

That was a secondary finding from the study. The GLSG had previously demonstrated that CHOP administered on a 14-day schedule compared to a 21-day schedule provided a superior outcome (Pfreundschuh 2004). In fact, the suggestion was that CHOP-14 was similar to R-CHOP-21 in the GELA results. So it raised a significant question: Does increasing the dose density overcome the need for adding rituximab to the regimen?

The RICOVER-60 trial asked that question directly. Patients older than age 60 were randomly assigned to receive CHOP-14 or R-CHOP-14. A statistically significant improvement in event-free and overall survival occurred in favor of dose-dense rituximab-based therapy.

Of course, this raises a third question: Is R-CHOP-14 better than R-CHOP-21? You can't find out by inference — you need to find out by direct comparison. Approximately 400 of the 640 patients necessary have already been accrued and randomly assigned to a GELA study that is evaluating that question of R-CHOP-14 versus R-CHOP-21 (1.2). We're hopeful that the data will accrue fast enough that we'll find out in 2008.

► **DR LOVE:** Any predictions?

► **DR ZELENETZ:** It's hard to know. The R-CHOP-14 data look good, but it's difficult to compare data sets, even when you normalize for prognostic factors. My feeling is that it's best to wait for the trial results. At Memorial, we chose to use R-CHOP-14 for our clinical study because of some retrospective data we generated showing that R-CHOP-14 seemed to improve outcome by approximately 10 or 15 percent.

R-CHOP-14 built on another large dose-dense trial that we had conducted called the NHL-15 (Portlock 2004). Our 01142 treatment regimen, sequential

**1.2** **A Phase III, Multicenter, Randomized, Open-Label Trial of Dose-Dense versus Conventionally Scheduled R-CHOP**

Protocol ID: LNH03-6B  
Target Accrual: 600

Study Initiated: December 2003  
Expected Completion: December 2008

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graph LR; R((R)) --> A[R-CHOP-14 ± darbepoetin alpha]; R --> B[R-CHOP-21 ± darbepoetin alpha];
```

**Select Eligibility Criteria**

- 66 to 80 years old
- Previously untreated CD20+ diffuse large B-cell lymphoma with age-adjusted IPI = 1, 2 or 3
- ECOG PS 0 to 2

**Trial Lead Organization**

Groupe d'Etudes de Lymphomes de L'Adulte (GELA)

SOURCE: NCI Physician Data Query, July 2007.



dose-dense CHOP followed by ICE (ifosfamide, carboplatin and etoposide), was designed for younger patients who are transplant eligible. For the older patient, our standard is still R-CHOP-21.

► **DR LOVE:** When you use R-CHOP-14, how do patients respond to it?

► **DR ZELENETZ:** It's surprising how well people tolerate it. It's easy, and a lot of people like the idea that they'll be done in 12 weeks. We virtually never have to back off to 21 days due to toxicity. We've successfully treated patients through their late sixties and up to age 70 with this dose-dense regimen.

In lymphoma, it's a more involved treatment because we're administering dose-dense prednisone and we have to remember to add prophylactic medications, so patients receive fluconazole, acyclovir, sulfamethoxazole and trimethoprim. Otherwise, we see an excess risk of shingles, fungal infection — thrush, in particular — and pneumocystic pneumonia. Ever since we observed that increasing dose density increases the infectious risk, we've been able to control that risk with prophylaxis. ■

## SELECT PUBLICATIONS

Coiffier B et al. **Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor-risk patients.** *Proc ASCO* 2007; [Abstract 8009](#).

Forstpointner R et al. **The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group.** *Blood* 2004;104(10):3064-71. [Abstract](#)

Habermann TM et al. **Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma.** *J Clin Oncol* 2006;24(19):3121-7. [Abstract](#)

Hiddemann W et al. **Rituximab maintenance prolongs response duration after salvage therapy with R-FCM in patients with relapsed follicular lymphomas and mantle cell lymphomas: Results of a prospective randomized trial of the German Low Grade Lymphoma Study Group (GLSG).** *Proc ASH* 2005; [Abstract 920](#).

Morrison VA et al. **Maintenance rituximab (MR) compared to observation (OBS) after R-CHOP or CHOP in older patients (pts) with diffuse large B-cell lymphoma (DLBCL): An Intergroup E4494/C9793 update.** *Proc ASCO* 2007; [Abstract 8011](#).

Pfreundschuh M et al. **Six vs eight cycles of bi-weekly CHOP-14 with or without rituximab for elderly patients with diffuse large B-cell lymphoma (DLBCL): Results of the RICOVER-60 trial of the German High-Grade Non-Hodgkin's Lymphoma Study Group (DSHNHL).** *Proc ASH* 2006; [Abstract 205](#).

Pfreundschuh M et al. **Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of young patients with good-prognosis (normal LDH) aggressive lymphomas: Results of the NHL-B1 trial of the DSHNHL.** *Blood* 2004;104(3):626-33. [Abstract](#)

Portlock CS et al. **The NHL-15 protocol for aggressive non-Hodgkin's lymphoma: A sequential dose-dense, dose-intense regimen of doxorubicin, vincristine and high-dose cyclophosphamide.** *Ann Oncol* 2004;15(10):1495-503. [Abstract](#)

Van Oers MH et al. **Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial.** *Blood* 2006;108(10):3295-301. [Abstract](#)



## INTERVIEW

### John P Leonard, MD

Dr Leonard is Clinical Director of the Center for Lymphoma and Myeloma and Professor of Medicine at Weill Medical College of Cornell University and New York Presbyterian Hospital in New York, New York.

### Tracks 1-18

- |                 |  |                 |   |
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| <b>Track 1</b>  | Phase II trial of bortezomib in combination with R-CHOP in patients with DLBCL | <b>Track 11</b> | Management of mantle-cell lymphoma  |
| <b>Track 2</b>  | Ongoing clinical trials for patients with DLBCL                                | <b>Track 12</b> | Vaccine trials for patients with indolent lymphoma                            |
| <b>Track 3</b>  | Clinical trials of bevacizumab in patients with lymphoma                       | <b>Track 13</b> | Management of indolent lymphoma   |
| <b>Track 4</b>  | Rationale for combining bortezomib with R-CHOP                                 | <b>Track 14</b> | Current trials evaluating consolidation radioimmunotherapy after chemotherapy |
| <b>Track 5</b>  | Clinical use of PET scans for patients with lymphoma                           | <b>Track 15</b> | Clinical use of radioimmunotherapy  |
| <b>Track 6</b>  | Clinical trials with galiximab and lumiliximab                                 | <b>Track 16</b> | Advances in the treatment of chronic lymphocytic leukemia                     |
| <b>Track 7</b>  | Non-Hodgkin's lymphoma: Highlights from ASCO 2007                              | <b>Track 17</b> | Challenging issues in the management of lymphoma                              |
| <b>Track 8</b>  | Clinical use of maintenance rituximab in patients with follicular lymphoma     | <b>Track 18</b> | Approach to patients with relapsed large B-cell lymphoma                      |
| <b>Track 9</b>  | Novel agents in the treatment of mantle-cell lymphoma                          |                 |   |
| <b>Track 10</b> | Ongoing clinical trials in mantle-cell lymphoma                                |                 |   |

## Select Excerpts from the Interview

### Track 2

► **DR LOVE:** What are some of the questions being studied right now in diffuse large B-cell lymphoma research?

► **DR LEONARD:** Number one, will CHOP remain the standard therapy? We're conducting a randomized trial of R-CHOP versus R-EPOCH (2.1) based on Wyndham Wilson's data and some Phase II data that the CALGB generated (Gutierrez 2000; Wilson 2001).

The GELA is evaluating R-CHOP-21 versus R-CHOP-14. Their data supporting the 14-day schedule were generated primarily in the prerituximab era, so whether or not the 14-day, dose-dense treatment will be useful in lymphoma in the rituximab era remains to be seen. Some people in practice are using R-CHOP-14, but most are using R-CHOP-21, and I believe that's an important question.

Finally, evaluating new biologic agents and antibodies is another issue. Bevacizumab is being considered in lymphoma. And we have enzastaurine, a protein kinase-C inhibitor. Those are questions that people are considering, and the challenge is that many of these agents may have only marginal, single-agent activity in large cell lymphoma.

Do you go forward and conduct a large trial with hundreds of patients without much single-agent activity because you believe the agents will be chemosensitizers?

**2.1 Phase III Randomized Study of R-CHOP versus R-EPOCH for Patients with Previously Untreated de Novo Diffuse Large B-Cell Non-Hodgkin's Lymphoma**

Protocol ID: CALGB-50303  
Target Accrual: 478 (Open)

**R-CHOP**  
Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisone

**R-EPOCH**  
Rituximab + doxorubicin + etoposide + vincristine + cyclophosphamide + prednisone + filgrastim

In both study arms, treatment repeats q21d x 6 courses in the absence of disease progression or unacceptable toxicity.

**Select Eligibility Criteria**

- Histologically confirmed de novo B-cell non-Hodgkin's lymphoma
- CD20-positive disease
- Stage I primary mediastinal (thymic) or Stage II to IV disease
- No known lymphomatous CNS involvement

**Study Contacts**

*Cancer and Leukemia Group B*  
Wyndham Wilson, MD, PhD  
Protocol Chair  
Tel: 301-435-2415  
Andrew D Zelenetz, MD, PhD  
Protocol Co-Chair  
Tel: 212-639-2656

SOURCE: NCI Physician Data Query, July 2007.

**Track 3**

▶ **DR LOVE:** What is known about bevacizumab in lymphoma?

► **DR LEONARD:** We're planning a Phase II trial in mantle-cell lymphoma with CHOP, rituximab and bevacizumab as up-front therapy. We have a lot of interest in angiogenesis and lymphomas. The data with bevacizumab in lymphoma have been generated primarily from two studies.

One was from the Southwest Oncology Group and was presented previously at ASCO (Stopeck 2005). The other was a small pilot trial from ECOG that evaluated R-CHOP with bevacizumab (Ganjour 2006). They demonstrated activity, but obviously, learning what the bevacizumab added to the R-CHOP would require a randomized trial.

## Track 11

► **DR LOVE:** What is your clinical approach to patients with mantle-cell lymphoma?

► **DR LEONARD:** I observe patients with mantle-cell disease for a while if they're asymptomatic. Mantle cell is almost like a FLIPI high-risk follicular lymphoma in that the patients have incurable disease, but in some cases it can be indolent and they can go off therapy. We've been studying R-CHOP with bortezomib.

You must decide whether a patient is a transplant candidate and whether a more aggressive approach will be part of your treatment plan. If not, with a 75- or 80-year-old patient with mantle-cell disease you can obtain reasonably good mileage out of an R-CHOP-type regimen.

However, these are patients for whom I believe bortezomib will also play an important role because with it, you can achieve good disease control without the toxicity of the more aggressive regimens.

► **DR LOVE:** What are your thoughts on Brad Kahl's modified R-hyper-CVAD regimen?

► **DR LEONARD:** R-hyper-CVAD is a challenging regimen for patients because of the toxicities. The data have been impressive, but we have to be mindful of patient selection issues.

The idea of being in the hospital for six months to receive hyper-CVAD for the possibility of a progression-free survival benefit or an overall survival benefit is difficult to weigh.

The idea with the modified regimen has been to reduce the toxicity and cut out the methotrexate/ARA-C, which is the more toxic portion of the regimen. I've seen reports of two- to three-year progression-free survival, which certainly appears reasonable.

## Track 13

► **DR LOVE:** How do you approach the off-protocol clinical management of the patient with indolent lymphoma?

► **DR LEONARD:** I feel strongly about observing these patients for a while. I try to watch for three to four months because that provides the clinician a sense of what to expect out of the disease and allows the patient to become comfortable with the disease. It's counterintuitive that you can be diagnosed with cancer and your doctors want to simply watch and wait, and certainly clinicians know the challenges of spending an hour explaining to a patient why he or she does not need treatment.

When I treat patients, I tend to use concurrent R-chemotherapy regimens. I am more in the R-CVP camp than anything. I tend to use the anthracycline later in case the disease transforms. Certainly a number of people use fludarabine-based regimens, but I use those more sparingly.

## Track 14

► **DR LOVE:** What is currently happening in terms of clinical research of radioimmunotherapy (RIT) for lymphoma?

► **DR LEONARD:** Most of the data coming out now have been from Phase II trials evaluating chemotherapy combinations — largely in indolent lymphoma, some in aggressive lymphoma — with R-chemotherapy followed by RIT. These studies have all suggested that you can use these combinations. They have acceptable toxicity and high response rates, but they're all incorporating chemotherapy regimens that have high response rates.

The primary trial that will answer the question of RIT consolidation after chemotherapy will be the SWOG-S0016 trial (2.2) of R-CHOP versus CHOP followed by Bexxar as initial treatment for follicular lymphoma.

In this study, R-CHOP is not followed by RIT, and if it were designed today, it probably would be designed to include that arm. I believe if it's a positive trial, some people may extrapolate to that. We have relatively few data on RIT after rituximab-containing regimens. Ollie Press has presented preclinical data that provide some insight into this combination. The concern is that if you have rituximab circulating from the R-CHOP at the time you administer the RIT, it will block out the radiolabeled antibody.

He presented some data suggesting that might be the case. One might argue that if you were going to use that strategy — let's say if you were administering six cycles of R-CHOP — maybe you'd administer R-CHOP the first four and then CHOP alone, so you'd clear the rituximab before coming in with RIT.

In clinical practice, RIT is an underused option for many patients, in part because people are just now becoming familiar with it. However, data suggest that it can be helpful for patients with rituximab-refractory disease and for patients with chemotherapy-refractory disease with indolent and transformed lymphomas. I tend to use it for people who have responsive disease but shorter remissions. ■

## Phase III Randomized Study of CHOP with Either Rituximab or Bexxar for Patients with Newly Diagnosed Follicular Non-Hodgkin's Lymphoma

Protocol IDs: SWOG-S0016, CALGB-50102  
Target Accrual: 500 (Open)

### Eligibility

- Stage II to IV follicular non-Hodgkin's lymphoma
- Bone marrow aspiration and biopsy within the past 42 days
- No prior monoclonal antibodies for cancer
- No prior radiation therapy for lymphoma

R

CHOP only (Closed to accrual  
12/15/2002)

CHOP + rituximab

CHOP → Bexxar

### Study Contacts

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SOURCE: NCI Physician Data Query, June 2007.

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## INTERVIEW

### David G Maloney, MD, PhD

Dr Maloney is Associate Member of the Clinical Research Division at the Fred Hutchinson Cancer Research Center and Associate Professor of Medicine in the Division of Oncology at the University of Washington in Seattle, Washington.

#### Tracks 1-20

- |                |   |                 |  |
|----------------|---|-----------------|--|
| <b>Track 1</b> | Clinical treatment strategy for advanced stage follicular lymphoma                                  | <b>Track 10</b> | Rituximab maintenance with front-line chemotherapy                             |
| <b>Track 2</b> | Benefit of adding rituximab to chemotherapy for patients with follicular lymphoma                   | <b>Track 11</b> | Side effects associated with maintenance rituximab                             |
| <b>Track 3</b> | “Watch and wait” versus treatment for patients with follicular lymphoma                             | <b>Track 12</b> | Autologous stem cell transplant for patients with relapsed follicular lymphoma |
| <b>Track 4</b> | Use of immune response signatures as an indicator of prognosis                                      | <b>Track 13</b> | Diagnosing transformation from indolent to aggressive lymphoma                 |
| <b>Track 5</b> | ECOG-E4402: Rituximab Extended Schedule Or Re-Treatment (RESORT) trial                              | <b>Track 14</b> | Allogeneic stem cell transplantation for follicular lymphoma                   |
| <b>Track 6</b> | Clinical utility of single-agent rituximab for patients with follicular lymphoma                    | <b>Track 15</b> | Treatment strategies for mantle-cell lymphoma                                  |
| <b>Track 7</b> | SWOG-S0016: CHOP with either rituximab or Bexxar in follicular lymphoma                             | <b>Track 16</b> | Allogeneic stem cell transplantation for mantle-cell lymphoma                  |
| <b>Track 8</b> | Clinical use of maintenance rituximab for follicular lymphoma                                       | <b>Track 17</b> | R-CHOP as induction therapy for DLBCL  |
| <b>Track 9</b> | PRIMA study: Maintenance rituximab after response to R-chemotherapy in advanced follicular lymphoma | <b>Track 18</b> | Clinical trial of dose-adjusted EPOCH-R  |
|                |   | <b>Track 19</b> | Role of PET scans in patients with DLBCL                                       |
|                |   | <b>Track 20</b> | ASCO 2007: Non-Hodgkin's lymphoma highlights                                   |

#### Select Excerpts from the Interview

##### Track 1

► **DR LOVE:** Can you talk about your approach to treating advanced-stage follicular lymphoma?

► **DR MALONEY:** My initial approach is to determine whether a patient needs to be treated or not. I'm still an advocate of watching and waiting, or benign

neglect, depending on what people call initial observation. I will observe patients unless they have symptoms of their disease or classic criteria requiring therapy. If they have high-volume disease, symptoms or low hemoglobin or blood counts, I'll certainly recommend therapy.

My sense is that an average doctor in the United States is more inclined to treat patients than to observe them, but no study has ever shown an advantage to treating people before they acquire symptoms. You can always argue “foul” because rituximab wasn't available during the early studies of initial therapy versus the watch-and-wait approach. That's one of the top questions I receive about lymphoma therapy: Is there still a role for watching patients with follicular lymphoma?

Studies are now showing clear-cut survival advantages — especially among the patients at higher risk — to the use of rituximab with chemotherapy. We are also starting to see this, at least in the relapse setting, with maintenance use of rituximab following induction with rituximab and chemotherapy.

## Track 5

▶ **DR LOVE:** Can you describe a typical patient who would be observed with a watch-and-wait approach?

▶ **DR MALONEY:** The typical watch-and-wait candidate would be in his or her midsixties with involved lymph nodes, which might have been evident for a while and someone finally made a diagnosis. These patients feel fine, and they have absolutely no symptoms. They might have a palpable abnormality that was evaluated using a CAT scan, and then someone orders a biopsy. The disease is staged, usually with a bone marrow biopsy and CAT scans.

If they have particularly low-bulk or low-volume disease, I talk to them about watching and waiting as an option. I also talk to them about an approach like that of the ECOG RESORT study (3.1), which is treating this type of disease with single-agent rituximab — that is then extended using either a continuous maintenance type of approach or a watch-and-wait approach (ie, after the rituximab, wait until relapse and then re-treat at that time).

The danger of that study, from a scientific perspective, is that it might cause rituximab resistance to the single agent. Then you would not obtain the mileage that you would by using it in a chemoimmunotherapy regimen, with which you get “more bang for the buck.”

## Track 6

▶ **DR LOVE:** What are your thoughts on the use of rituximab monotherapy?

▶ **DR MALONEY:** I use it. I offer rituximab to patients as a single agent. Again, usually not for patients who are completely asymptomatic, but if patients have some evidence of disease progression, then I believe that's an option. We also



have a dexamethasone with rituximab study that we've developed based on some synergy observed in the lab.

► **DR LOVE:** What is your usual preferred treatment regimen?

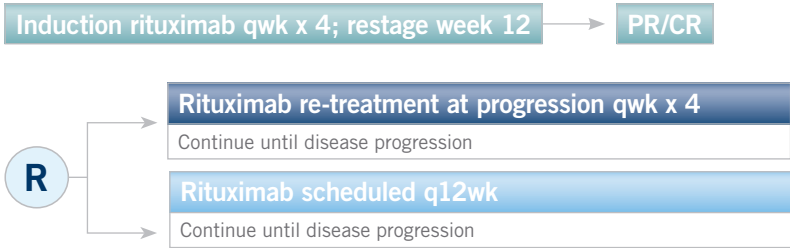
► **DR MALONEY:** For the oldest patients, I'm less inclined to administer an anthracycline. I'm more inclined to administer single-agent rituximab, and if I'm going to use chemotherapy, I'm more likely to use something like the CVP regimen.

For younger patients, I'm pretty convinced that the best option currently is rituximab with CHOP, based on the results of multiple studies that suggest that the longest progression-free survival occurs with that regimen (Buske 2006; Hiddemann 2003; Pfreundschuh 2006). That's an extremely controversial area.

### 3.1

#### RESORT Trial: A Phase III Randomized Study of Rituximab for Patients with Low Tumor Burden Indolent Non-Hodgkin's Lymphoma (NHL)

Protocol ID: ECOG-E4402  
Target Accrual: 389 (Open)



#### Select Eligibility Criteria

- Low-grade NHL, previously untreated
- Measurable disease
- Low tumor burden
- Stage III/IV disease
- ECOG PS 0 or 1

#### Study Contacts

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Michael Williams, MD, Tel: 434-924-9637

SOURCE: NCI Physician Data Query, July 2007.

### 🔊 Track 7

► **DR LOVE:** Describe the typical patient with follicular lymphoma who will receive treatment as opposed to a watch-and-wait approach.

► **DR MALONEY:** These patients will have symptoms — night sweats, weight loss. They'll have cytopenias associated with marrow involvement or splenomegaly or adenopathy causing compression of a ureter, et cetera. Those are the patients that I'm much more inclined to treat.

My first priority is to try to put them on a study. Our current study is SWOG-S0016 (2.2). This is a randomized, Phase III study of R-CHOP administered according to the Czuczman schedule versus CHOP followed by Bexxar.

Both of those regimens are based on some Phase II experience we had in the Southwest Oncology Group, in which the response and progression-free survival at five years among patients treated with CHOP followed by Bexxar are the highest we've ever seen — progression-free survival is around 70 percent (Press 2006).

That's one arm of the Phase III study. The other arm is the CHOP and rituximab regimen, which seems to be the current best single R-chemotherapy regimen.

## Track 8

► **DR LOVE:** Would you provide an update on the issue of rituximab maintenance in indolent lymphoma?

► **DR MALONEY:** The challenge with rituximab maintenance is essentially trying to extrapolate data from the relapse setting to the front-line setting.

One of the key studies was by van Oers (van Oers 2006), which randomly assigned patients with relapsed follicular lymphoma who had never received rituximab to CHOP versus R-CHOP with or without maintenance rituximab for two years.

In that study, a tremendous benefit was demonstrated from the addition of rituximab maintenance to either group, including the R-CHOP group, and that was the surprise of the study. So the temptation is to say, “Well, these people who relapsed were all rituximab naïve, and that can't be much different from the front-line setting.”

So the question is, should we begin using R-CHOP, for example, followed by two years of maintenance as the standard approach for the front-line patients? At least on the surface, it seems like a reasonable thing to do.

I would be cautious, though, because if you examine the data carefully, you see that rituximab maintenance probably works in relapsed disease because so many events are expected in the first couple of years. In a relapse setting, the benefit of your therapy is much shorter.

For example, in the van Oers study, the median time to progression in the CHOP arm was only 20 months, and even in the R-CHOP arm it was only 33 months. That's a lot less than what you would expect to see in the setting of up-front R-CHOP, in which the time to progression is nearly five years.

If you have a lot of events occurring in the first one or two years, then it isn't unreasonable to surmise that if the maintenance therapy does something, it might contribute to improved outcome.

I'm a little skeptical about whether maintenance will be easily shown as beneficial in the front-line setting, because you will see only 10 percent of your events happening in the first couple of years.

The PRIMA study — a study that has now accrued fully in Europe — is evaluating any one of a number of induction chemotherapy regimens with rituximab followed by rituximab maintenance or observation.

I still believe rituximab maintenance may be effective, but it won't be easy to prove in that front-line setting. ■

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Pfreundschuh M et al. **Six vs eight cycles of bi-weekly CHOP-14 with or without rituximab for elderly patients with diffuse large B-cell lymphoma (DLBCL): Results of the completed RICOVER-60 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL).** *Proc ASH* 2006; [Abstract 205](#).

Press OW et al. **Phase II trial of CHOP chemotherapy followed by tositumomab/iodine I-131 tositumomab for previously untreated follicular non-Hodgkin's lymphoma: Five-year follow-up of Southwest Oncology Group Protocol S9911.** *J Clin Oncol* 2006;24(25):4143-9. [Abstract](#)

Solal-Celigny P et al. **Follicular lymphoma international prognostic index.** *Blood* 2004;104(5):1258-65. [Abstract](#)

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Vose JM et al. **Phase II study of rituximab in combination with CHOP chemotherapy in patients with previously untreated, aggressive non-Hodgkin's lymphoma.** *J Clin Oncol* 2001;19(2):389-97. [Abstract](#)

## QUESTIONS (PLEASE CIRCLE ANSWER):

1. Following standard rituximab induction therapy, the RESORT trial will compare extended-schedule rituximab maintenance to rituximab re-treatment upon progression.
  - a. True
  - b. False
2. SWOG-S0016 is evaluating CHOP with \_\_\_\_\_ for patients with newly diagnosed non-Hodgkin's lymphoma.
  - a. Rituximab
  - b. Bexxar
  - c. Bortezomib
  - d. Both a and b
  - e. a, b and c
3. The LNH98-B3 GELA study evaluating the standard French dose-intense regimens of induction AC/ACE versus AC/VBP included \_\_\_\_\_.
  - a. Older patients with intermediate/high-risk mantle-cell lymphoma
  - b. Older patients with low-risk large B-cell lymphoma
  - c. Younger patients with intermediate/high-risk large B-cell lymphoma
4. In LNH98-B3 GELA, patients receiving maintenance rituximab after response to induction chemotherapy experienced a significant prolongation in progression-free survival.
  - a. True
  - b. False
5. The HOVON-26 trial evaluating rituximab for patients with low-grade lymphoma demonstrated that patients who received R-CHOP as induction therapy showed an improvement in \_\_\_\_\_ with maintenance rituximab.
  - a. Progression-free survival
  - b. Overall survival
  - c. Both a and b
6. CALGB-50303 will evaluate R-CHOP versus \_\_\_\_\_ for previously untreated patients with DLBCL.
  - a. R-CHOP/bortezomib
  - b. CHOP/bortezomib
  - c. R-EPOCH
7. The RICOVER-60 trial demonstrated that treatment with \_\_\_\_ cycles was as effective as \_\_\_\_ cycles of R-CHOP for event-free survival.
  - a. Two, four
  - b. Six, eight
  - c. Eight, 10
  - d. 10, 12
8. In the RICOVER-60 trial, the addition of rituximab to dose-dense CHOP resulted in a significant improvement in event-free and overall survival.
  - a. True
  - b. False
9. The NHL-15 trial evaluated dose-dense CHOP versus ICE (isofosfamide, carboplatin and etoposide) for younger patients eligible for transplant.
  - a. True
  - b. False
10. The PRIMA study is evaluating induction chemotherapy with rituximab followed by rituximab maintenance versus \_\_\_\_\_.
  - a. Etoposide
  - b. Bexxar
  - c. Bevacizumab
  - d. Observation

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- Critically evaluate the clinical implications of emerging clinical trial data in non-Hodgkin's lymphoma (NHL) treatment and incorporate these data into management strategies for patients with NHL. . . . . 5 4 3 2 1 N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trials. . . . . 5 4 3 2 1 N/A
- Utilize individual patients' risk factors and disease classification to tailor therapy for subgroups of patients with NHL. . . . . 5 4 3 2 1 N/A
- Describe and implement an algorithm for sequencing of clinical management options for indolent and aggressive NHL, including "watch and wait" and maintenance monoclonal antibody therapy. . . . . 5 4 3 2 1 N/A
- Discuss the risks and benefits of monoclonal antibody therapy and radioimmunotherapy alone and in combination with chemotherapy for patients with NHL, and counsel appropriately selected patients about the risks and benefits of these agents. . . . . 5 4 3 2 1 N/A

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John P Leonard, MD	5 4 3 2 1	5 4 3 2 1
David G Maloney, MD, PhD	5 4 3 2 1	5 4 3 2 1

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- Objectives were related to overall purpose/goal(s) of activity. . . . . 5 4 3 2 1 N/A
- Related to my practice needs. . . . . 5 4 3 2 1 N/A
- Will influence how I practice. . . . . 5 4 3 2 1 N/A
- Will help me improve patient care. . . . . 5 4 3 2 1 N/A
- Stimulated my intellectual curiosity. . . . . 5 4 3 2 1 N/A
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.....

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