



Key ASH Presentations
Issue 6, 2012

**Rituximab/BEAM versus
¹³¹Iodine-Tositumomab/BEAM
prior to SCT for Relapsed DLBCL**

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Consider the inclusion of single-agent romidepsin in the treatment algorithm for relapsed or refractory peripheral T-cell lymphoma.
- Integrate new and existing therapeutic strategies into the best-practice management of diffuse large B-cell lymphoma.
- Apply the results of emerging clinical research to the selection of optimal systemic therapy for patients with relapsed/refractory mantle-cell lymphoma.
- Recall new data with investigational agents demonstrating promising activity in non-Hodgkin lymphomas.

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To go directly to slides and commentary for this issue, [click here](#).

This past Friday 8 clinical investigators ventured to Miami for our annual post-ASH lymphoma Think Tank. Over the course of more than 6 fascinating hours together we focused on a multitude of topics and as always recorded the proceedings, which will be available as an enduring activity in the coming months. While our engineers are busy de-umming (our little secret) and editing the audio, we thought we would hold you over with a taste of some of the new ASH NHL papers that were fodder for discussion and debate during Friday's lymphoma extravaganza.

1. [Lenalidomide/rituximab](#)

The so-called R-squared regimen of the immunomodulatory agent lenalidomide (len) and rituximab (R) has generated considerable excitement among investigators, and at ASH we saw the results from a Phase II trial evaluating this combination alone or with dexamethasone for patients with relapsed indolent NHL or mantle-cell lymphoma (MCL) considered to be resistant to R. Of the 48 patients treated on the trial more than a third had a response, and the median progression-free survival was 18 months. These findings have raised hopes that len might help overcome R resistance and that in select populations such as the elderly this combination might become an alternative to aggressive treatment of relapsed disease — for example, with autologous stem cell transplant (ASCT).

2. [Two papers on MCL](#)

Another ASH NHL highlight was the presentation of a Phase II study of PCI-32765, an oral irreversible Bruton's tyrosine kinase inhibitor, as a single agent in relapsed/refractory MCL. The results are compelling, as two thirds of the 39 patients in the study had objective responses and 35 remain on treatment. Importantly, none stopped therapy due to toxicity. Many investigators now have patients in their practices on trials who have experienced obvious prolonged benefit with this agent, and as a result significant excitement surrounds it and other small molecules, like the PI3 kinase inhibitor CAL-101 that is also under active investigation in a variety of NHL subtypes.

The rarity of MCL has made the definition of treatment benefits a challenge, and another important study reported at ASH attempted to better establish the effects of R in this disease. This effort from the UK evaluated the combination of fludarabine and cyclophosphamide with or without R, and while a high rate of infection was observed in these patients receiving fludarabine, substantial improvements in response rate and an almost doubling of progression-free survival reinforced the value of adding the CD20 antibody, which is now used routinely up front and often as maintenance treatment.

3. Two studies of diffuse large B-cell lymphoma (DLBCL)

Previous research with dose-adjusted EPOCH with R has shown promising results in untreated DLBCL, and this [Phase IV trial](#) of 81 patients with poor-prognosis disease (age-adjusted IPI of 1 or higher) reported an encouraging 62% 5-year progression-free survival rate. An ongoing Phase III Intergroup trial is comparing EPOCH-R to R-CHOP.

One of the biggest disappointments at ASH came from the much-awaited [Phase III SWOG study](#) comparing conditioning R/BEAM (carmustine, etoposide, cytarabine, melphalan) to ¹³¹I-tositumomab/BEAM for patients with DLBCL about to undergo ASCT. The trial results were flat-out negative, confounding the positive findings observed in the Phase II setting and forcing investigators back to the drawing board to look at higher doses of radioimmunotherapy as pretransplant conditioning.

4. [Two papers on T-cell lymphoma](#)

At ASH Dr Bertrand Coiffier presented an update of the Phase II pivotal study evaluating the selective inhibitor of histone deacetylase romidepsin in relapsed or refractory peripheral T-cell lymphoma (PTCL). This trial, which led to the FDA approval in this setting, evaluated 130 patients across PTCL subgroups, and these findings reveal higher response rates among individuals with the most common forms of the disease. This suggests that romidepsin may perhaps have more activity in common PTCL subtypes than initial data suggested.

In cutaneous T-cell lymphoma we saw the results of a Phase II trial investigating the interesting sequence of pegylated liposomal doxorubicin (PLD) — which has been shown to have high response rates and is known to concentrate in the skin — followed by the synthetic retinoid bexarotene (Bex). Perhaps because the study selected for patients with more aggressive disease, a 41% response rate (lower than reported in other trials) was observed with PLD and Bex did not increase the rate or duration of response. With the current shortage of PLD, not many patients are being treated with this agent.

Next up on this ASH series we go back to multiple myeloma and new reports on effective long-term disease control in older patients on continuing therapy.

Neil Love, MD

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Rituximab/BEAM versus ¹³¹Iodine-Tositumomab/BEAM prior to SCT for Relapsed DLBCL

Presentation discussed in this issue

Vose JM et al. Randomized Phase III trial of ¹³¹-iodine-tositumomab/carmustine, etoposide, cytarabine, melphalan (BEAM) vs rituximab/BEAM and autologous stem cell transplantation for relapsed diffuse large B-cell lymphoma (DLBCL): No difference in progression-free (PFS) or overall survival (OS). *Proc ASH* 2011; [Abstract 661](#).

Slides from a presentation at ASH 2011 and transcribed comments from recent interviews with Owen A O'Connor, MD, PhD (2/3/12) and Craig Moskowitz, MD (1/11/12)

BMT CTN Protocol 0401: Results of a Phase III Randomized Multicenter Trial of Rituximab/BEAM vs ¹³¹-Iodine Tositumomab/BEAM Conditioning Regimen for Relapsed Diffuse Large B-Cell Lymphoma

Vose JM et al.

Proc ASH 2011;Abstract 661.

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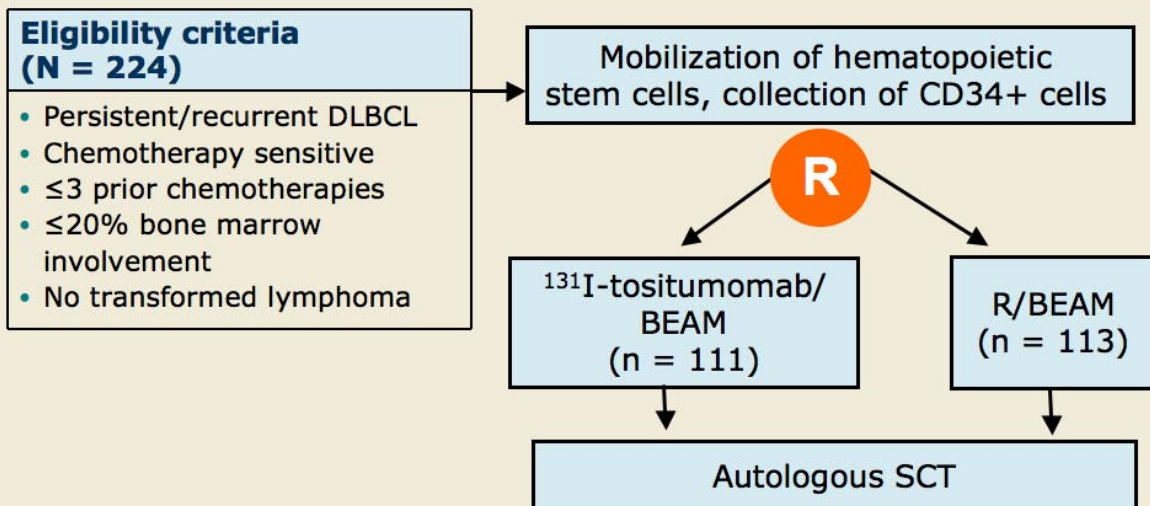
Background

- High-dose chemotherapy and autologous stem cell transplant (SCT) are the standard of care for patients with relapsed DLBCL.
- Patients who have received prior rituximab (R) therapy have a 2-year PFS rate of 40%.
- A Phase II trial of ^{131}I -tositumomab with BEAM (carmustine/etoposide/cytarabine/melphalan) chemotherapy prior to autologous SCT showed a 3-year PFS rate of 70% for patients with relapsed and high-risk DLBCL (*Proc ASCO 2007*, Abstract 8013).
- **Current study objective:** Compare R/BEAM to ^{131}I -tositumomab/BEAM prior to SCT in patients with relapsed DLBCL.

Vose JM et al. *Proc ASH 2011*;Abstract 661.

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Phase III Study Schema



Vose JM et al. *Proc ASH 2011*;Abstract 661.

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Survival Rates

Outcome	¹³¹ I-tositumomab/ BEAM	R/BEAM	p-value
Two-year progression-free survival (PFS) rate			
All patients (n = 111, 113)	48.6%	49.0%	0.65
Patients in CR (n = 55, 52)	52.7%	61.9%	0.32
Patients not in CR (n = 56, 61)	44.6%	38.0%	0.88
Two-year overall survival (OS) rate			
All patients (n = 111, 113)	60.1%	66.3%	0.29
Second CR*	76.9%	79.9%	0.61

* Patients in CR after salvage chemotherapy

Multivariate analysis for PFS and OS rates:

- PFS: CR patients, HR = 1; Non-CR patients, HR = 1.63 ($p = 0.008$)
- OS: CR patients, HR = 1; Non-CR patients, HR = 2.42 ($p = 0.0005$)

Vose JM et al. *Proc ASH* 2011;Abstract 661.

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Causes of Death

Cause of death	¹³¹ I-tositumomab/BEAM (n = 103)	R/BEAM (n = 107)
Relapse/progression	83.8%	83.3%
Graft rejection/failure	2.7%	0
Organ failure	5.4%	5.4%
Secondary AML	0	2.8%
Acute respiratory distress syndrome	8.1%	0
Lung cancer	0	2.8%
Thromboembolic	0	2.8%

Vose JM et al. *Proc ASH* 2011;Abstract 661.

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Author Conclusions

- No difference in PFS, OS or relapse/progression was seen when tositumomab/BEAM was compared to R/BEAM.
- Disease state at transplant (ie, complete remission after salvage chemotherapy) was the most predictive of outcome.
- Mucositis was significantly increased in patients receiving tositumomab/BEAM conditioning compared to R/BEAM, and the hematologic recovery and other toxicities were similar between the 2 treatment arms (data not shown).

Vose JM et al. *Proc ASH* 2011;Abstract 661.

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Investigator Commentary: Rituximab/BEAM vs ¹³¹I-Tositumomab/BEAM for Relapsed DLBCL

The role of radioimmunotherapy is an area of significant debate, with many single-arm studies evaluating both tositumomab and ibritumomab tiuxetan integrated into BEAM-based chemotherapy regimens. I'm not sure that this particular trial puts to rest the issue of RIT for patients with DLBCL. Many follow-up studies will investigate higher doses of ibritumomab tiuxetan integrated into BEAM. These studies should shed additional light on the value of integrating radioimmunotherapy into the autologous stem cell transplant arena.

Interview with Owen A O'Connor, MD, PhD, February 3, 2012

This was the most disappointing study at the ASH meeting. It was a high-priority lymphoma study and "make or break" for radioimmunotherapy for transplant patients. If it was positive, it would have been great for patients with lymphoma and would have put tositumomab on the map. The Phase II results were phenomenal, but this study was completely negative with superimposable survival curves. This is sad for lymphoma patients and by far the most disappointing news of the meeting.

Interview with Craig Moskowitz, MD, January 11, 2012

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