



Key ASH Presentations

Issue 6, 2012

Phase II Trials in T-Cell Lymphoma: Romidepsin and Pegylated Liposomal Doxorubicin/Bexarotene

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.

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Phase II Trials in T-Cell Lymphoma: Romidepsin and Pegylated Liposomal Doxorubicin/Bexarotene

Presentations discussed in this issue

Coiffier B et al. **Analysis of patients with common peripheral T-cell lymphoma subtypes from a Phase 2 study of romidepsin in relapsed or refractory peripheral T-cell lymphoma.** *Proc ASH* 2011; **Abstract 591**.

Coiffier B et al. **Results from a pivotal, open-label, Phase II study of romidepsin in relapsed or refractory peripheral T-cell lymphoma after prior systemic therapy.** *J Clin Oncol* 2012;30(6):631-6. **Abstract**

Straus DJ et al. **Final results of Phase II trial of pegylated liposomal doxorubicin (PLD) followed by bexarotene (Bex) in advanced cutaneous T-cell lymphoma (CTCL).** *Proc ASH* 2011; **Abstract 882**.

Slides from presentations at ASH 2011 and transcribed comments from a recent interview with Owen A O'Connor, MD, PhD (2/3/12) and from Steven M Horwitz, MD at a recent closed roundtable recording (3/9/12)

Results from a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy¹

Final Results of Phase II Trial of Pegylated Liposomal Doxorubicin (PLD) Followed by Bexarotene (Bex) in Advanced Cutaneous T-Cell Lymphoma (CTCL)²

¹Coiffier B et al.

J Clin Oncol 2012;30(6):631-6.

Proc ASH 2011;Abstract 591.

²Straus DJ et al.

Proc ASH 2011;Abstract 882.

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Results from a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma after Prior Systemic Therapy

Coiffier B et al.

J Clin Oncol 2012;30(6):631-6.

Proc ASH 2011;Abstract 591.

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Background

- Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare disorders resulting from clonal proliferation of mature post-thymic lymphocytes (*Ann Oncol* 1998;9:849).
- Currently, no agents are approved for use as first-line treatment of PTCL.
- Romidepsin is a structurally unique, selective inhibitor of histone deacetylase (HDAC) approved for the treatment of patients with cutaneous T-cell lymphoma following ≥ 1 prior systemic therapies.
- Prior Phase I and II trials showed clinical activity of romidepsin in PTCL (*Blood* 2011;117:5827; *Blood* 2001;98:2865).
- **Objective:**
 - Confirm the efficacy of romidepsin in patients with relapsed or refractory PTCL.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

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Trial Design

Eligibility (n = 130)

Histologically confirmed PTCL by central review for PTCL subtypes

Relapsed disease or refractory to ≥ 1 systemic therapies

No use of any investigational therapy within 4-6 weeks of study entry

Romidepsin
14 mg/m² IV d1, 8, 15
q4wk x 6 cycles*

* Patients with stable disease (SD), partial response (PR) or complete response/unconfirmed complete response (CR/CRu) could elect to extend therapy until progressive disease or another withdrawal criterion was met.

Primary endpoint:

- Rate of CR/CRu as determined by an independent review committee (IRC)

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

Response Rates: Overall IRC and Investigators' Assessments (INA)

Best response rate	IRC (n = 130)	INA (n = 130)
ORR (CR/CRu + PR)*	25%	29%
CR/CRu [†]	15%	16%
CR	10%	15%
CRu	5%	2%
PR	11%	13%
SD	25%	17%
PD or N/E	49%	54%

ORR, objective response rate; PD, progressive disease; N/E, not evaluable

* Median time to response was 1.8 mo; duration of response was 16.6 mo by IRC.

[†] Median time to response was 3.7 mo; duration of response was 16.6 mo by IRC.

- Baseline disease characteristics, prior therapeutic regimen or number of prior therapies had no impact on the ability of patients to respond to romidepsin.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

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Response Rates by Overall IRC Assessments in Patient Subgroups

Subgroup (n = 130)	CR/CRu rate		ORR	
	%	p-value	%	p-value
PTCL subtype		0.83*		0.92*
PTCL NOS (n = 69)	14		29	
AITL (n = 27)	19		30	
ALK-1-neg ALCL (n = 21)	19		24	
Others (n = 13)	0		0	

PTCL NOS, PTCL not otherwise specified; AITL, angioimmunoblastic T-cell lymphoma; ALK-1-neg-ALCL, ALK-1-negative anaplastic large-cell lymphoma

* Based on PTCL NOS, AITL and ALK-1-negative ALCL (n = 117)

- No meaningful differences were seen in ORR or CR/CRu rates based on sex, age, baseline disease characteristics, prior therapeutic regimen or number of prior therapies.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

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Progression-Free Survival (PFS)

Median PFS	IRC
Overall (n = 130)	4 months
Achieved CR/CRu (n = 19)	18 months
With PR (n = 14)	7 months
With SD (n = 33)	6 months
With PD or N/E (n = 64)	<2 months

- Patients who had achieved CR/CRu had substantially longer PFS than those in all other response categories.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

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Selected Drug-Related Adverse Events (AEs)

Event (n = 131)*	All grades	Grade ≥3
Nausea	54%	2%
Infections SOC [†]	18%	6%
Asthenia/fatigue	52%	5%
Thrombocytopenia	40%	23%
Vomiting	34%	4%
Diarrhea	23%	2%
Pyrexia	17%	4%
Neutropenia	29%	18%
Anemia	21%	5%

* Inclusive of 1 patient with a diagnosis of diffuse large B-cell lymphoma

[†] System organ class according to the Medical Dictionary for Regulatory Activities

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

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Author Conclusions

- Romidepsin, as a single-agent, induced complete and durable responses in patients with relapsed or refractory PTCL.
- Romidepsin improved outcomes across all major PTCL subgroups, regardless of the number or type of prior therapies.
- These data demonstrated that romidepsin produced manageable toxicity in patients with relapsed or refractory PTCL.
- Based on the results from this Phase II study, romidepsin was approved by the US Food and Drug Administration for the treatment of patients with relapsed or refractory PTCL.

Coiffier B et al. *J Clin Oncol* 2012;30(6):631-6.

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Investigator Commentary: Results from a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory PTCL

Romidepsin is one of 3 drugs that were approved for the treatment of T-cell lymphoma in the past 1 or 2 years. The original presentation of the investigators that led to the approval of romidepsin was based on 130 patients with relapsed or refractory PTCL. By IRC assessments, the ORR was 25% and 10% of the patients had CR.

However, the response rates presented in the abstracts at the recent ASH meeting were a lot higher than what was observed in the original presentation. This is because the meeting abstract presents a subset ORR analysis of the larger registration-directed study in the 3 most common PTCL subtypes (n = 117): PTCL NOS (29%), AITL (30%) and ALK-1-negative ALCL (24%). In the total patient population analysis (n = 130), the ORR is slightly lower. Overall, the data suggest that romidepsin may have more activity in the more common PTCL subtypes than what one may be led to believe by the larger data set of 130 patients.

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

Final Results of Phase II Trial of Pegylated Liposomal Doxorubicin (PLD) Followed by Bexarotene (Bex) in Advanced Cutaneous T-Cell Lymphoma (CTCL)

Straus DJ et al.

Proc ASH 2011;Abstract 882.

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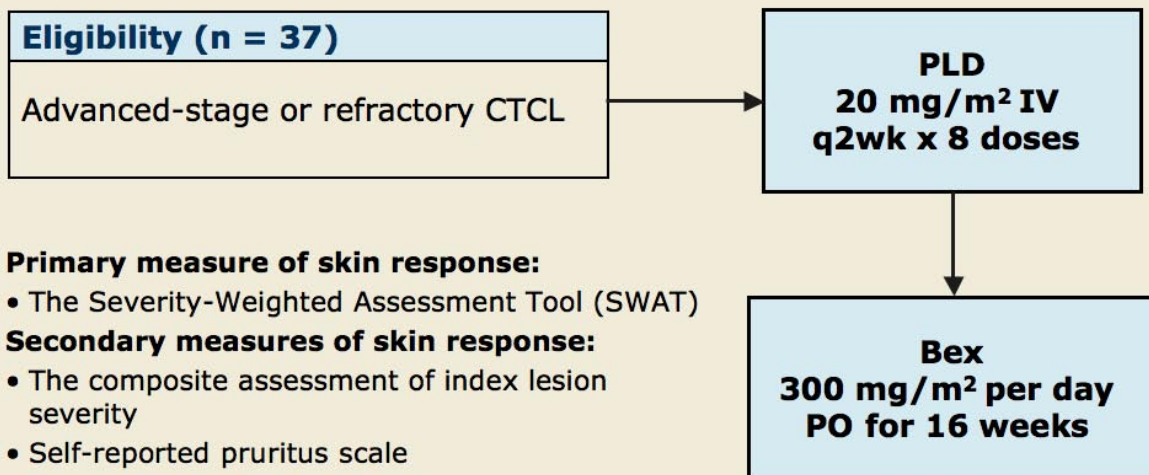
Background

- Pegylated liposomal doxorubicin (PLD) is approved for the treatment of Kaposi's sarcoma and concentrates highly in the skin.
- Previous studies have demonstrated the effectiveness of PLD in patients with advanced cutaneous T-cell lymphoma (CTCL) but without a strictly defined response criteria (*Arch Dermatol* 2008;144:727; *Cancer* 2003;98:993).
- Bexarotene (Bex) is a synthetic retinoid that has been reported to have an objective response rate (ORR) of about 50% in patients with relapsed or refractory CTCL (*JCO* 2001;19:2456; *Arch Dermatol* 2001;137:581).
- **Objective:**
 - Determine the true ORR for PLD and assess if the ORR and remission durations can be improved by sequential Bex following PLD in advanced or refractory CTCL.

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

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Trial Design



Response assessments were performed after 8 weeks (PLD) and 16 weeks (Bex).

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

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Efficacy Results (Abstract Only)

Clinical parameter	n = 34
ORR*	41%
Clinical complete response (CCR)	6%
Partial response (PR)	35%
Median PFS	4.82 months

CCR: Complete disappearance of skin lesions on examination

* Maximum responses were all seen after 16 weeks of PLD.

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

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Adverse Events (AEs) and Deaths (Abstract Only)

Event, n	
Grade 3/4 serious AEs	9
Tumor pain	4
Grade 3 hand-foot syndrome	2
Infection — unknown ANC-skin (cellulitis)	1
Infection — normal ANC-skin (cellulitis)	1
Neutropenia	1
Deaths	19
Progressive disease	18
Congestive heart failure*	1

* Patient (n = 1) was pretreated for LVEF of 60%

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

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Author Conclusions

- With strict criteria, ORR for PLD is one of the highest reported for single agents in CTCL.
- However, the ORR for PLD determined in this study is lower than previously reported.
- The study population contained a high proportion of patients with advanced disease (data not shown) as reflected in the poor survival outcomes.
- Sequentially administering Bex did not increase the response rate or duration (data not shown).

Straus DJ et al. *Proc ASH* 2011;Abstract 882.

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Investigator Commentary: Final Results of a Phase II Trial of PLD followed by Bex in Advanced CTCL

This study, of which I was a part, was designed to determine whether clinical responses can be induced with a relatively safe chemotherapy and then maintained with a milder agent like Bex. The results showed a reasonable response rate of about 40% with liposomal doxorubicin, although others in the literature report a rate of about 80%.

This study did not demonstrate a benefit in terms of durability of response with Bex, although we have seen a couple of patients who have had long-term remissions after follow-up with maintenance therapy. I believe the study was rationally designed but it inadvertently selected for a highly aggressive, somewhat atypical patient population. This is because a patient with mycosis fungoides suitable for chemotherapy but never having received Bex is unusual. Such a patient tends to start off with an early aggressive disease. This may explain why the durability of responses to Bex was so short.

Overall, these data demonstrate that PLD is an active drug but it is uncertain whether maintenance therapy with Bex improves response.

Interview with Steven M Horwitz, MD, March 9, 2012