



# 5 Minute Journal Club

*Hematologic Oncology*  
Issue 3, 2013

## **Results of the Pivotal BELIEF Phase II Trial of Single-Agent Belinostat in Relapsed or Refractory Peripheral T-Cell Lymphoma**

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## CME INFORMATION

### OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Clinical Oncology (ASCO) annual meeting and the International Conference on Malignant Lymphoma (ICML), to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they are aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because not only are they confronted almost overnight with thousands of new presentations and data sets, but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important ongoing trials and emerging data sets on novel agents in T-cell lymphoma from the latest ASCO and ICML meetings, including expert perspectives on how these new evidence-based concepts may 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

- Evaluate emerging efficacy and safety data with the anti-CD30 agent brentuximab vedotin and the novel histone deacetylase inhibitor belinostat as therapy for patients with relapsed or refractory T-cell lymphoma.
- Demonstrate knowledge of currently recruiting trials of the targeted agents brentuximab vedotin, belinostat and romidepsin as single agents or in combination with chemotherapy, and counsel appropriate patients with T-cell lymphoma for participation in these ongoing trials.

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**FACULTY** — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Advisory Committee: Allos Therapeutics, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Onyx Pharmaceuticals Inc, Spectrum Pharmaceuticals Inc;  
Consulting Agreements: Bristol-Myers Squibb Company, Celgene Corporation, Millennium: The Takeda Oncology Company.

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This activity is supported by educational grants from Genentech BioOncology/Biogen Idec, Onyx Pharmaceuticals Inc and Spectrum Pharmaceuticals Inc.

Hardware/Software Requirements:

A high-speed Internet connection

A monitor set to 1280 x 1024 pixels or more

Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later

Adobe Flash Player 10.2 plug-in or later

Adobe Acrobat Reader

(Optional) Sound card and speakers for audio

Last review date: October 2013

Expiration date: October 2014

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

One of the best examples of the recent transformation of clinical and translational science in the many variants of T-cell lymphoma (TCL) was a case presented by Dr Andrew Evens during a lymphoma think tank we hosted this summer in our Miami recording studio.

This 61-year-old man was diagnosed 2 years ago with Stage IV ALK-negative anaplastic large-cell lymphoma (ALCL) and received CHOEP — a common up-front choice among investigators — which resulted in a complete response (CR). Like many patients with peripheral T-cell lymphoma (PTCL) who hear the pros and cons of various forms of transplant, the patient balked at taking that difficult step and was followed expectantly for a year, when an obvious and significant recurrence was detected. Until recently this man's treatment options would have been confined to intensive salvage chemotherapy regimens, like ICE, DHAP and ESHAP, and other less intense options, including romidepsin, pralatrexate and other agents, but in 2013 we know that ALCL is uniformly CD30-positive and, as with about 60% of individuals with this disease who receive the antibody-drug conjugate (ADC) brentuximab vedotin (BV), this patient experienced a rapid CR and no significant toxicity. He then reconsidered his decision and elected to receive an autologous stem cell transplant and remains in CR 6 months later.

Unlike many other corners of oncology, including B-cell lymphomas, for which novel agents and strategies abound, TCL has until recently been devoid of these hopeful entities and the unfortunate result is painfully evident in a recent [JCO paper](#). This retrospective study of 153 patients in British Columbia who underwent treatment for PTCL (mostly PTCL NOS, angioimmunoblastic TCL [AITL] or ALCL) from 1976 to 2010 demonstrated a dismal median time from diagnosis to first relapse of 6.7 months and an even worse 5.5 months from first relapse to death. However, as seen with Dr Evens' patient, critical inroads have now been made, and equally as important, an effective clinical research infrastructure has emerged that is generating well-designed and executed studies. The ASCO and Lugano TCL papers summarized on this issue of *5-Minute Journal Club* typify recent steps forward and shine a light on where we might be in a few years.

## **1. Belinostat: The BELIEF Phase II trial**

The big T-cell story out of ASCO was this report of significant single-agent activity with a 26% response rate with this novel pan-histone deacetylase inhibitor (HDACi) in patients with relapsed/refractory (R/R) PTCL. Although on the surface some might review the data and think this is just another HDACi, during a recent interview for our audio series BELIEF principal investigator Dr Owen O'Connor discussed the potential game-changing difference of this drug. Specifically, unlike other agents with significant activity in PTCL, including romidepsin, the rate of myelosuppression is relatively low with belinostat and as such it can be administered to patients with platelet counts above 50,000.

From a clinical perspective this unique attribute may prove invaluable in the R/R setting, in which many patients have poor marrow reserve because of prior chemotherapy and in some cases transplant. Similarly, in terms of clinical research belinostat may be safer and easier to combine with chemotherapy, potentially allowing for more effective drug delivery — a strategy now being tested in up-front trials. The news did not stop at ASCO, as in Lugano Dr Steven Horwitz presented further data from BELIEF demonstrating that patients with AITL were particularly likely to benefit from the drug (46% response rate). These data have led many to become “believers” that belinostat may have real value and perhaps a role soon in clinical practice.

## **2. CD30 and BV**

We've talked a lot about this fascinating ADC in past programs, but the database continues to build and at Lugano we saw an interesting report from a Phase II US trial of 29 patients with mature T-/NK-cell lymphomas. Importantly, of 17 patients with postbaseline assessments, all but 3 experienced tumor size decreases and CRs were observed in 4 of 10 patients with AITL and 2 of 12 patients with PTCL NOS. These and prior data sets suggest that clinicians might want to consider CD30 testing for all patients with PTCL and maybe **some B-cell cancers** like diffuse large B-cell lymphoma along with cutaneous TCL, in which an ongoing Phase III trial is evaluating the efficacy of BV and anecdotal benefit has been observed. Interestingly, the correlation between CD30 status and response to BV is not as clear as one might think, and this paper like others before it reports durable responses in patients with low or undetectable CD30 expression.

Last week in the Big Apple during the first of our 4 daylong regional Year in Review (YIR) symposia, Dr Bruce Cheson commented on the challenge of using this marker and cited the example of Hodgkin lymphoma, in which most cells in the tumor mass are stroma and are CD30-negative but virtually all Reed-Sternberg cells have the antigen, thus explaining the impressive clinical activity in these patients. Another YIR faculty member, Dr Lauren Pinter-Brown, commented on 2 other factors confounding current CD30 evaluation, namely tumor heterogeneity and the evolution of newer, more sensitive assays, including quantitative image analysis, that may be able to identify

many more patients than the estimated 30% with PTCL currently considered to have CD30-positive tumors. Where this leads in the future is uncertain, but it's possible that BV and other ADCs will eventually be utilized in most patients with TCL.

### **3. The next generation of TCL clinical trials**

Despite the many advances in TCL treatment, continued research is of course needed, and at ASCO Dr O'Connor presented a Trials in Progress poster (TPS) featuring the newly launched and much anticipated Phase III ECHELON-2 study. This critical effort compares up-front CHOP to CHBVP, in which BV replaces vincristine in the front-line treatment of patients with CD30-positive mature TCLs, and should be widely embraced by clinicians who otherwise must turn to suboptimal standard options. In a similar manner, another relevant ASCO TPS focused on the Phase III RoCHOP trial, which adds the HDACi romidepsin to CHOP in patients with previously untreated PTCL. In terms of new agents, Dr Anas Younes, the new Chief of the Memorial Sloan-Kettering Lymphoma Service, in a brilliant ASCO review of many exciting ADCs in development said it's "prime time" for these agents in lymphoid cancers. He then underscored the immense value of this therapeutic concept by noting the important example of ALCL, where the unconjugated anti-CD30 antibody produced a 17% response rate that increased to 86% when the same naked antibody was conjugated to monomethyl auristatin E (MMAE).

Many other novel agents and strategies are being actively investigated in TCL, and Dr Pinter-Brown told our highly attentive and knowledgeable New York audience that TCL needs a "rituximab." In that regard, she is intrigued by mogamulizumab, a defucosylated humanized monoclonal antibody targeting C-C chemokine receptor 4 (CCR4) that is approved in Japan for R/R adult T-cell leukemia/lymphoma and is currently working its way through trials in North America, where the face of this disease is considerably different.

Next, for our final issue of this series on summer heme-onc data sets we flip back to the "B" side and check out papers on follicular, mantle-cell and diffuse large B-cell lymphoma.

Neil Love, MD

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Miami, Florida

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# Results of the Pivotal BELIEF Phase II Trial of Single-Agent Belinostat in Relapsed or Refractory Peripheral T-Cell Lymphoma

## Presentations discussed in this issue

Horwitz S et al. **Belinostat in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL) subtype angioimmunoblastic T-cell lymphoma (AITL): Results from the pivotal BELIEF trial.** *Proc ICML 2013*; **Abstract 153.**

O'Connor OA et al. **Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial.** *Proc ASCO 2013*; **Abstract 8507.**

Slides from presentations at ASCO 2013 and ICML 2013 and transcribed comments from a recent interview with Owen A O'Connor, MD, PhD (8/20/13)

**Belinostat, a Novel Pan-Histone Deacetylase Inhibitor (HDACi), in Relapsed or Refractory Peripheral T-Cell Lymphoma: Results from the BELIEF Trial<sup>1</sup>**

**Belinostat in Angioimmunoblastic T-Cell Lymphoma: Results from the Pivotal BELIEF Trial<sup>2</sup>**

**<sup>1</sup> O'Connor OA et al.**

*Proc ASCO 2013*; Abstract 8507.

**<sup>2</sup> Horwitz S et al.**

*Proc ICML 2013*; Abstract 153.

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# Belinostat, a Novel Pan-Histone Deacetylase Inhibitor (HDACi), in Relapsed or Refractory Peripheral T-Cell Lymphoma: Results from the BELIEF Trial

**O'Connor OA et al.**

*Proc ASCO 2013;Abstract 8507.*

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## Background

- Currently approved therapies for relapsed or refractory PTCL have overall response rates of 25% to 29% (*JCO* 2011;29(9):1182-9; *JCO* 2012;30(6):631-6).
- Previously, a Phase II CLN-6 trial demonstrated that belinostat monotherapy yielded an overall response rate of 25% in relapsed/refractory PTCL (*Proc ASH* 2009;Abstract 920).
  - Belinostat was well tolerated, with the most common toxicities being Grade 1/2 gastrointestinal and constitutional side effects.
- **Study objective:** To assess the safety and efficacy of single-agent belinostat for patients with relapsed or refractory PTCL.

O'Connor OA et al. *Proc ASCO 2013;Abstract 8507.*

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# Phase II BELIEF Trial Design

## Eligibility (n = 129)

Relapsed or refractory PTCL\*  
 ≥1 prior systemic therapy  
 Platelet counts ≥50,000/uL  
 No prior HDACi therapy  
 No relapse within 100 days of autologous or allogeneic bone marrow transplant

**Belinostat**  
 1,000 mg/m<sup>2</sup> (IV), d1-5 q3wk

\* Confirmed by central pathology review (CPRG)

- **Primary endpoint:** Objective response rate (ORR)
- Secondary endpoints include: Safety, time to response, progression-free and overall survival and duration of response
- Exploratory analyses were conducted to determine response by PTCL subtypes

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

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# Response by Central Review

Response rate	n = 120
ORR	26%
Complete response (CR)	11%
Partial response (PR)	15%
Stable disease	15%
Progressive disease	40%
Not evaluable*	19%

\* Prior to first radiologic assessment due to death (n = 7); clinical progression (n = 10); patient withdrawal (n = 5); lost to follow-up (n = 1)

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

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## Response Rates According to Disease Characteristics

Characteristic	Response rate
Bone marrow involvement (n = 120)	
No (n = 65)	31%
Yes (n = 35)	23%
Indeterminate (n = 8)	25%
Not assessed (n = 12)	8%
Platelet counts (n = 120)	
≥100,000/uL (n = 100)	28%
<100,000/uL (n = 20)	15%

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

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## Response Rates by CPRG Lymphoma Diagnosis

Diagnosis	ORR
PTCL-NOS (n = 77)	23%
AITL (n = 22)	46%
ALCL, ALK-negative (n = 13)	15%
ALCL, ALK-positive (n = 2)	0%
Enteropathy-associated TCL (n = 2)	0%
Extranodal NK/TCL, nasal type (n = 2)	50%
Hepatosplenic TCL (n = 2)	0%

PTCL-NOS = PTCL-not otherwise specified; ALCL = angioimmunoblastic T-cell lymphoma; TCL = T-cell lymphoma

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

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## Clinical Outcomes

Outcome	All patients (n = 120)	Baseline platelet counts	
		≥100,000/uL (n = 100)	<100,000/uL (n = 20)
ORR by CPRG	25.8%	28.0%	15.0%
Median DoR	13.6 months	13.6 months	4.1 months
Median PFS	1.6 months	1.8 months	1.3 months
Median OS	7.9 months	9.2 months	4.3 months
Median TTR	5.6 weeks	5.6 weeks	6.4 weeks

DoR = duration of response; PFS = progression-free survival; OS = overall survival; TTR = time to response

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

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## Select Grade ≥3 Adverse Events

Event	All patients (n = 129)	Baseline platelet counts	
		≥100,000/uL (n = 105)	<100,000/uL (n = 24)
Thrombocytopenia	15%	6%	54%
Neutropenia	13%	10%	25%
Leukopenia	13%	9%	29%
Anemia	12%	8%	29%
Dyspnea	6%	Not reported	
Pneumonia	6%	Not reported	
Febrile neutropenia	5%	Not reported	
Fatigue	5%	Not reported	
Hypokalemia	4%	Not reported	

O'Connor OA et al. *Proc ASCO* 2013;Abstract 8507.

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## Author Conclusions

- Belinostat demonstrated activity in patients with relapsed/refractory PTCL.
  - All patients (n = 120), ORR: 26%
  - Baseline platelet counts  $\geq 100,000/\mu\text{L}$ , ORR: 28%
  - Baseline platelet counts  $< 100,000/\mu\text{L}$ , ORR: 15%
- Belinostat was well tolerated with a favorable safety profile.
  - This included patients who had previously undergone autologous or allogeneic stem cell transplantation.
- Patients with poor marrow reserve and low platelet counts tolerated and benefited from belinostat treatment.
- Further investigation of belinostat in combination with other therapies is warranted to develop new treatment paradigms for PTCL.

O'Connor OA et al. *Proc ASCO 2013*;Abstract 8507.

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## Discussant Conclusions

- Belinostat demonstrated a 26% to 28% ORR and was well tolerated with a favorable safety profile in patients with relapsed/refractory PTCL, including patients with a previous stem cell transplant.
- Patients with poor marrow reserve and low platelet counts due to marrow involvement and those who had undergone stem cell transplantation tolerated belinostat therapy.
  - This included 3 patients with baseline platelet counts of  $\leq 25,000/\mu\text{L}$ .
- The low incidence of myelosuppression observed warrants further investigation of belinostat combination therapy to develop new treatment paradigms for relapsed or refractory PTCL.

Gisselbrecht C et al. *Proc ASCO 2013*;Discussant.

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### **Investigator Commentary: Phase II BELIEF Trial of Belinostat in Relapsed/Refractory PTCL**

Many of the data from the BELIEF study are similar to what we've seen with other HDAC inhibitors. One of the most interesting observations of the BELIEF study was the activity of belinostat in patients with low platelet counts. Patients had a platelet count cutoff of 50,000/uL, with most having counts of >100,000/uL. Many of these patients get "beat up" and have counts of <100,000/uL and technically would not be eligible for the drug if it gets approved for those with a platelet count of  $\geq$ 100,000/uL. For many of the patients with platelet counts between 50,000/uL and 100,000/uL and even a few with counts <50,000/uL, the response rate was respectable. More importantly, belinostat was well tolerated irrespective of the pretreatment platelet count.

In this study, about 20 patients had platelet counts <100,000/uL. However, in clinical practice most patients with PTCL have platelet counts <100,000/uL. That's probably because they've gone through multiple lines of chemotherapy. Many would have received CHOP, oxaliplatin or gemcitabine and possibly autologous stem cell transplants. So the patients in the clinical trial are selected to meet certain eligibility criteria.

***Interview with Owen A O'Connor, MD, PhD, August 20, 2013***

## **Belinostat in Angioimmunoblastic T-Cell Lymphoma: Results from the Pivotal BELIEF Trial**

**Horwitz S et al.**

*Proc ICML 2013;Abstract 153.*

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## Background

- Peripheral T-cell lymphoma (PTCL) is a heterogeneous, aggressive disease that is associated with poor prognosis.
  - 5-year overall survival rate: 32% (*JCO* 2013;31:240)
- Angioimmunoblastic T-cell lymphoma (AITL) is a subcategory of PTCL representing 15% to 20% of patients with PTCL (*JCO* 2008;26:4124).
- The current treatment for AITL is similar to that for other subtypes of PTCL.
- In a Phase II CLN-6 trial, single-agent belinostat, a novel hydroxamic-based HDACi, was well tolerated and yielded response rates of 25% in relapsed/refractory PTCL (*Proc ASH* 2009;Abstract 920).
- **Study objective:** To evaluate the efficacy of single-agent belinostat for patients with relapsed or refractory PTCL, with specific analysis of patients with the AITL subtype.

Horwitz S et al. *Proc ICML* 2013;Abstract 153.

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## Efficacy Summary

<b>All patients*</b>	<b>n = 120</b>
Overall response rate	26%
Median progression-free survival	1.6 months
<b>Patients with AITL*</b>	
Overall response rate	46%
Median progression-free survival (n = 22)	4.2 months

\* By central review

Horwitz S et al. *Proc ICML* 2013;Abstract 153.

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## Select Grade $\geq 3$ Adverse Events

<b>Hematologic</b>	<b>All patients (n = 129)</b>	<b>AITL (n = 22)</b>
Thrombocytopenia	15%	23%
Neutropenia	13%	9%
Leukopenia	13%	9%
Anemia	12%	27%
<b>Nonhematologic</b>	<b>n = 120</b>	<b>n = 22</b>
Dyspnea	6%	Not reported
Pneumonia	6%	Not reported
Febrile neutropenia	5%	Not reported
Fatigue	5%	Not reported
Hypokalemia	4%	Not reported

Horwitz S et al. *Proc ICML 2013*;Abstract 153.

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## Author Conclusions

- Belinostat was well tolerated with a favorable safety profile.
- Patients with poor marrow reserve and low platelet counts tolerated and benefited from belinostat therapy.
  - This included patients who had previously undergone stem cell transplantation.
- Belinostat demonstrated activity in:
  - Patients with relapsed or refractory PTCL (ORR: 26%)
  - Patients with relapsed or refractory AITL (ORR: 46%)
- This study demonstrates the need to collect tissue samples on future prospective trials.
- Future up-front trials in PTCL should:
  - Study uncommon diseases that are often lumped together
  - Maximize treatment effect to find differences

Horwitz S et al. *Proc ICML 2013*;Abstract 153.

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### **Investigator Commentary: Pivotal Phase II BELIEF Trial of Belinostat in AITL**

The BELIEF study evaluated a new hydroxamic acid analog, belinostat, in relapsed or refractory PTCL and reported an ORR of 26%. Belinostat is probably a little more potent than vorinostat but is probably not nearly as potent as romidepsin in terms of IC50 values that one might look at in in vitro assays. Interestingly, in the initial agreement with the FDA, the primary objective of the study was to have a response rate in excess of 20% in this patient population. This provides some insight into how low our expectations are for responses in this population.

BELIEF reaffirms that HDAC inhibitors have a unique single-agent class effect in PTCL. This is yet another example in which an ORR in the range of 25% to 30% is seen, similar to vorinostat, romidepsin or panobinostat. An important observation is that the ORR in AITL was markedly higher than in the overall study population and than that reported in the PROPEL study with pralatrexate. That was taken as a signal that belinostat may be targeting some interesting biology in AITL that's not being targeted by other HDAC inhibitors. This is a provocative finding, but I wouldn't make too much of it yet because we need more data. This is a relatively small study of about 120 patients. When you consider the individual number of patients, it's still between 10 and 20 with this particular PTCL subtype.

***Interview with Owen A O'Connor, MD, PhD, August 20, 2013***