5 Minute JournalClub

POST-ASH Issue 4, 2013

Updated Results of Phase II Study GPI-006-02 of Single-Agent Romidepsin in Relapsed/Refractory PTCL

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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

- Appraise recent clinical research findings on the use of PET scans after initial chemotherapy to identify patients with early-stage Hodgkin lymphoma who can avoid additional radiation therapy, and apply this information in the management of patients' disease.
- Recall emerging clinical research data with combined proteasome and histone deacetylase inhibition in patients with peripheral T-cell or NK/T-cell lymphoma.
- Evaluate the benefits and risks of novel therapeutic approaches under evaluation with brentuximab vedotin as front-line or later-line therapy in advanced and relapsed/refractory Hodgkin and T-cell lymphomas.
- Consider patient characteristics associated with long-term responses to single-agent romidepsin in the care of patients with relapsed/refractory peripheral T-cell lymphoma.

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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:

Bruce D Cheson, MD
Professor of Medicine
Deputy Chief, Division of Hematology-Oncology
Head of Hematology
Georgetown University Hospital
Lombardi Comprehensive Cancer Center
Washington, DC

Advisory Committee: Celgene Corporation, Cephalon Inc, Gilead Sciences Inc, Mundipharma International Limited, Onyx Pharmaceuticals Inc, Pharmacyclics Inc, Sanofi; Consulting Agreements: Celgene Corporation, Cephalon Inc, Genentech BioOncology, Mundipharma International Limited.

Steven M Horwitz, MD
Assistant Attending
Lymphoma Service
Division of Hematologic Oncology
Memorial Sloan-Kettering Cancer Center
New York, New York

Consulting Agreements: Allos Therapeutics, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Janssen Pharmaceuticals Inc, Johnson & Johnson Pharmaceuticals, Kyowa Hakko Kirin Co Ltd, Millennium: The Takeda Oncology Company, Seattle Genetics; Contracted Research: Allos Therapeutics, Celgene Corporation, Infinity Pharmaceuticals Inc, Kyowa Hakko Kirin Co Ltd, Millennium: The Takeda Oncology Company, Seattle Genetics, Spectrum Pharmaceuticals Inc.

Brad S Kahl, MD
Skoronski Chair of Lymphoma Research
Associate Professor
University of Wisconsin School of Medicine and Public Health
Associate Director for Clinical Research
UW Carbone Cancer Center
Madison, Wisconsin

Advisory Committee: Celgene Corporation, Cephalon Inc, Genentech BioOncology, Millennium: The Takeda Oncology Company, Roche Laboratories Inc; Contracted Research: Abbott Laboratories, Cephalon Inc, Genentech BioOncology.

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

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: March 2013
Expiration date: March 2014

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POST-ASH Issue 4, 2013

Will brentuximab vedotin increase the cure rate of advanced Hodgkin lymphoma?... and more

To go directly to slides and commentary for this issue, **click here**.

Vincent T DeVita Jr, MD
NCI Director 1980-88

On a crisp autumn afternoon in 1990, I timidly entered the office of the Physician-in-Chief of Memorial Sloan-Kettering Cancer Center and former NCI Director Dr Vincent DeVita. My journey to the Big Apple was for our nascent breast cancer audio series (on cassette tapes!) and specifically focused on Dr DeVita's perspectives on the controversial "NCI Clinical Alert" he helped launch, defining the duration of adjuvant tamoxifen (discussed in our **recent breast cancer email**). Throughout the interview, Dr DeVita nibbled from a jar of chocolate-covered coffee beans, which seemed to further stimulate the conversation, and he became particularly animated when discussing his vision for combination chemotherapy exemplified by his prototypical MOPP regimen in Hodgkin lymphoma (HL) — or Hodgkin's disease, as it was known then. He then went on to describe for our listeners the principles of tumor cell kinetics and noncross-resistant combination regimens that spawned an entire generation of oncologic research.

A lot has happened since that fall day, and while tens of thousands of people have been cured of HL and other cancers with chemotherapy, for most patients in the advanced setting treatment has been palliative in nature and marred by toxicities. In that regard, most investigators, including the one who now occupies Dr DeVita's august Memorial office and title (Dr José Baselga), have concentrated their efforts on developing novel targeted agents designed to make cytotoxics obsolete. Unfortunately, we are not there yet and chemotherapy remains a mainstay in our treatment armamentarium, and at ASH we saw this dynamic play out as both new agents and tried-and-true chemotherapy grabbed headlines in HL and T-cell lymphomas:

1. Chemotherapy without radiation therapy (RT) in early-stage HL

According to another Memorial maven, Dr Andy Zelenetz, the ASH presentation of the much-awaited UK RAPID trial may set a new standard in this disease — specifically for patients with Stage IA and IIA HL or mediastinal bulky disease who have a negative PET scan after 3 cycles of ABVD. In RAPID, at 4 years more than 90% of patients were progression free with or without involved-field RT and, based in part on these findings, investigators are continuing to carefully consider treatment without RT in early PET-negative cases, particularly for younger women at risk for delayed secondary breast cancers.

2. Brentuximab vedotin (BV) as part of up-front treatment of advanced HL

Dr DeVita must be pleasantly surprised at the advent of antibody-drug conjugates (ADC) like BV and the just-approved (in metastatic breast cancer) T-DM1 (ado-trastuzumab emtansine) — agents that can deliver cytotoxics inside tumor cells with minimal normal cell kill. Although BV was approved only 18 months ago, ASH was a reminder that this ADC is here to stay for the long term. Phase II trials of BV in the relapsed/refractory (RR) HL setting revealed a 75% response rate (34% CR) and have helped foster attempts, including a randomized Phase II trial first reported at last year's ASH, to integrate this anti-CD30 ADC into up-front treatment of advanced HL. As part of last year's report, ABVD combined with BV yielded an unacceptable pulmonary toxicity rate. However, this was not seen with BV and AVD (ABVD without the bleomycin), and efficacy findings were encouraging enough to spawn a major ongoing multicenter Phase III trial comparing ABVD to BV + AVD. In this ASH update of the Phase II study, 24 of 26 patients had negative FDG-PET scans after 2 cycles of BV + AVD, which was well tolerated other than mostly reversible peripheral neuropathy.

3. BV as part of up-front treatment of systemic anaplastic large cell lymphoma (sALCL) and mature T- and NK-cell lymphomas

As with HL, encouraging findings in the RR setting (86% responses with 57% CR) have led to efforts to combine BV with up-front chemotherapy. At ASH we saw results from 2 arms of a Phase I study evaluating BV combined with CHP (the vincristine was omitted from CHOP to prevent neuropathy) in patients with sALCL or mature T- and NK-cell lymphomas. The regimen was well tolerated and response was observed in all 26 patients in the trial, including 23 CRs. These and other encouraging data have led to an ongoing Phase III trial comparing BV-CHP to CHOP.

4. BV in RR mycosis fungoides (MF)/Sézary syndrome

A small Phase II study reported at ASH evaluated single-agent BV in patients with previously treated MF/Sézary syndrome, and responses occurred in 13 of 19 patients. Importantly, activity was observed with all levels of CD30 expression, although the authors point out significant limitations with conventional immunohistochemical staining

compared to the multispectral image analysis used in this study. Based in part on these findings, a Phase III trial will compare BV to investigator's choice of bexarotene or methotrexate in these patients.

5. Histone deacetylase (HDAC) inhibition in T-cell lymphomas — bortezomib/ panobinostat (BP) and romidepsin

Two reports unveiled in Atlanta further contribute to the growing database on the effectiveness of HDAC inhibitors in T-cell lymphoma. **The first evaluated** the novel BP combination in 11 patients with RR PTCL and NK-cell lymphoma. The results from this effort were encouraging, and the investigators are interested in studying longer-term maintenance with this regimen.

The second important HDAC paper was an update of the pivotal Phase II trial of romidepsin in 130 patients with RR PTCL. Previous data from that study demonstrated a 25% response rate (and led to the FDA approval of this agent in this setting), and the ASH data set is noteworthy in that more follow-up reveals that responses are often durable, lasting on average more than a year, and up to 4 years, further solidifying the role of this agent in these patients.

The shift in research emphasis in HL, T-cell lymphomas and most other corners of oncology away from chemotherapy and toward novel agents clearly is in full swing, and it will be interesting to look back in a quarter of a century when we know whether this strategy delivers or if it repeats the limitations of chemotherapy that crushed the hopes of oncology leaders of the past generation.

Next…Another cancer for which biological treatment has yielded results never dreamed of in the cytotoxic era — multiple myeloma and a series of ASH papers evaluating two exciting novel proteasome inhibitors — the oral investigational compound ixazomib (formerly MLN9708) and the recently approved irreversible agent carfilzomib.

Neil Love, MD
Research To Practice
Miami, Florida

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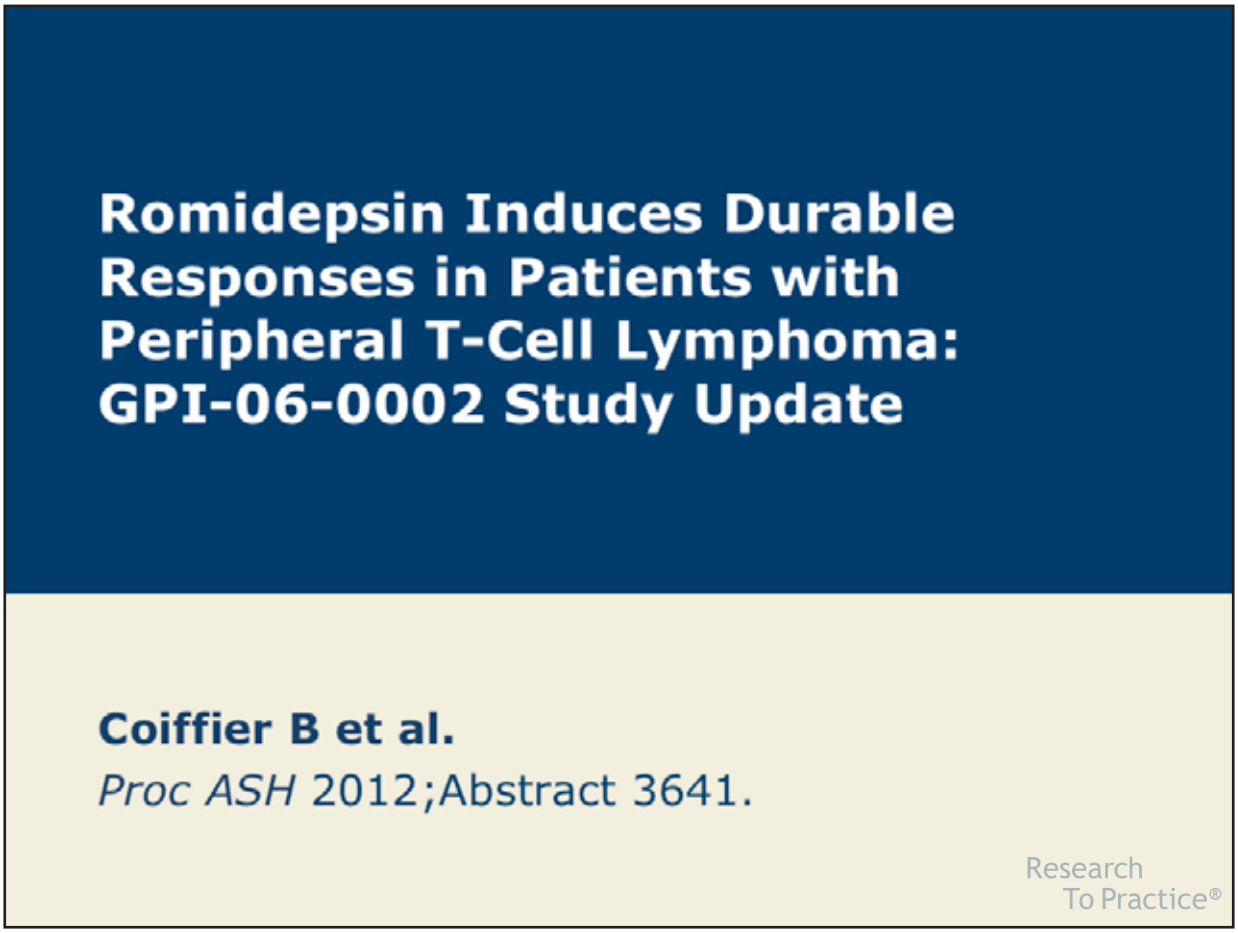
Updated Results of Phase II Study GPI-006-02 of Single-Agent Romidepsin in Relapsed/Refractory PTCL

Presentation discussed in this issue

Coiffier B et al. **Romidepsin induces durable responses in patients with peripheral T-cell lymphoma: GPI-06-0002 study update.** *Proc ASH* 2012;**Abstract 3641**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Steven M Horwitz, MD (3/14/13)

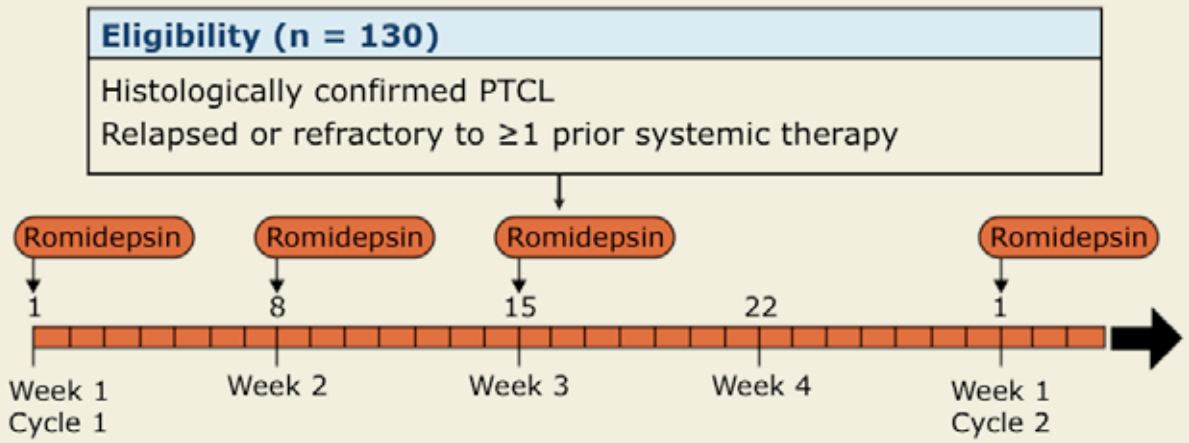


Background

- Romidepsin is a histone deacetylase (HDAC) inhibitor that is FDA approved for the treatment of peripheral T-cell lymphoma (PTCL) after failure of 1 or more prior therapy.
- Preliminary analysis of the single-arm Phase II GPI-06-0002 study demonstrated clinical benefit and tolerability of romidepsin in patients with relapsed or refractory PTCL (*Blood* 2010;116:114).
- **Study objective:** To present updated efficacy analysis of romidepsin from the GPI-06-0002 study and characterize patients who achieved long-term responses of 12 months or longer after a median follow-up of 22.3 months.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

Phase II GPI-06-0002 Trial Design



- Romidepsin: 14 mg/m^2 (IV) for 4 h on days 1, 8 and 15 of a 28-day cycle x 6 cycles; treatment could be extended for responding patients
- **Primary endpoint:** Confirmed/unconfirmed complete response (CR/CRu) by independent review committee (IRC)

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

Demographics and Baseline Characteristics

Characteristic	n = 130
Median number of prior systemic therapies (range)	2 (1-8)
Patients with PTCL refractory to last line of therapy	38%
Patients with Stage III or IV PTCL	70%
Patients with bone marrow involvement	28%
PTCL subtype (%)	
PTCL-NOS*	53%
Angioimmunoblastic T-cell lymphoma*	21%
ALK-1-negative anaplastic large cell lymphoma*	16%

*Most common PTCL subtypes

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

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Best Response

Response, n (%)	n = 130
Overall response rate (ORR)	33 (25%)
CR/CRu	19 (15%)
CR	14 (11%)
CRu	5 (4%)
Partial response (PR)	14 (11%)
Stable disease (SD)	33 (25%)
Progressive disease/not evaluable	64 (49%)

- Median time to response was 1.8 months.
- Median duration of response (DoR) was 28 months.
- Median duration of CR/CRu has not been reached (range, <1-48+ months).
  - Patient with DoR <1 month discontinued to receive stem cell transplant.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

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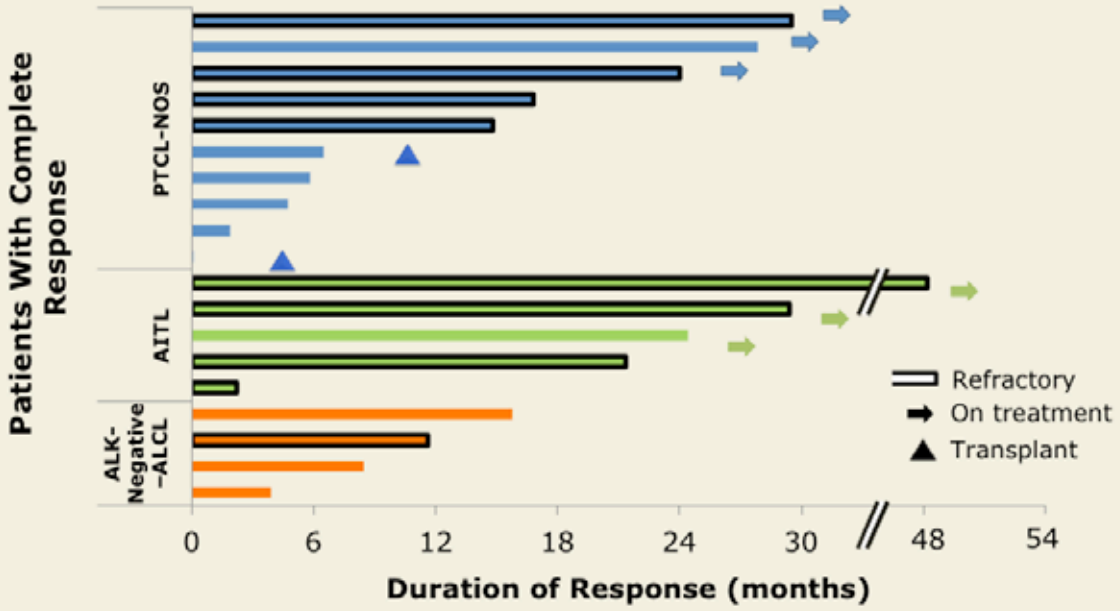
DoR for Patients with CR/CRu



With permission from Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

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Characteristics of Patients Who Achieved CR/CRu with Romidepsin

Of the 19 patients who achieved CR/CRu,

- Thirteen (68%) had not experienced disease progression by IRC at a median follow-up of 25.8 months.
- Two patients who achieved CR/CRu discontinued treatment to receive stem cell transplant.
- Ten patients were long-time responders (≥12 months).
- Six patients with responses of 2 years or more continued to receive romidepsin therapy.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

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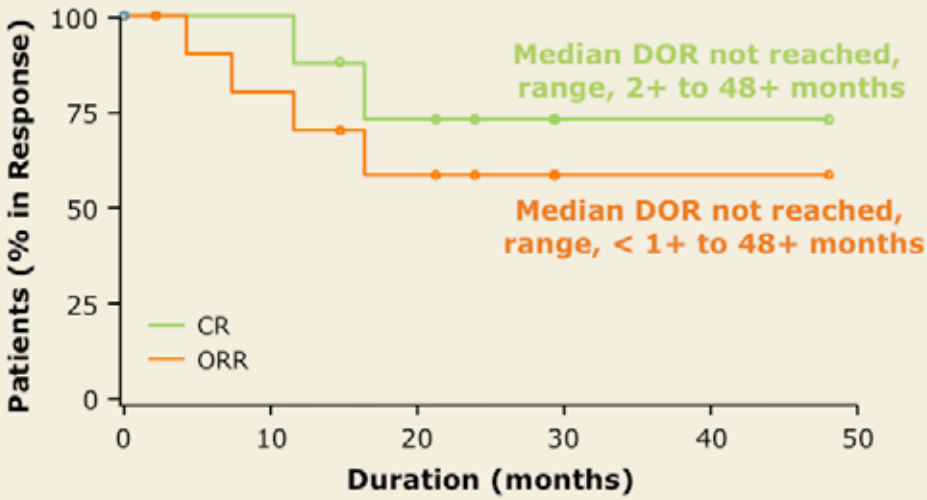
DoR for Patients with PTCL Refractory to Last Prior Therapy (n = 49)



- Median DoR has not been reached for all patients who achieved a response
  - Patients who achieved response (n = 14)
  - Patients who achieved CR/CRu (n = 9)

With permission from Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

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Author Conclusions

- Single-agent romidepsin induced durable responses in patients with heavily pretreated relapsed or refractory PTCL:
  - Median time to objective response was 1.8 mo.
  - Median DoR was 28 mo, with responses ongoing at 48 mo.
  - Median DoR for patients with CR/CRu has not been reached.
  - Long-lasting responses were observed in the 3 major PTCL subtypes and in patients with PTCL refractory to the last prior therapy.
- More than 50% of patients who achieved CR/CRu experienced long-term responses (≥12 months) to romidepsin.
  - CR was achieved in patients with typically poor prognoses.
  - None of the examined patient and disease characteristics predicted failure to achieve long-term remission.
  - CR/CRu was associated with prolonged survival.
- Extended dosing of romidepsin can be tolerated.

Coiffier B et al. *Proc ASH* 2012;Abstract 3641.

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Investigator Commentary: GPI-06-0002 — Romidepsin Induces Durable Responses in Patients with PTCL

This presentation is an update of the registration or pivotal trial of romidepsin that led to its approval for PTCL. With a longer follow-up period, the overall response rate remains about the same with 25% of patients responding. A significant proportion of the responders (a minority of the entire group of patients who received treatment) experienced durable or maintained responses to therapy. The median duration of response for all responders was 28 months, and that curve is largely upheld by the complete responders (19/33 responders), for whom the median duration of response was not reached.

This presentation highlights the point that of the minority of patients who respond, many can achieve disease control beyond 1 year. In this data set a handful of patients are now at 2 to 3 years and up to 4 years with maintained responses on therapy. We know from participation in the trial that some of the patients with particularly long-term responses had their schedule reduced after a time and received less frequent dosing than 3 out of every 4 weeks.

Interview with Steven M Horwitz, MD, March 20, 2013

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