5 Minute JournalClub

POST-ASH Issue 4, 2013

Phase II Study of Combination Bortezomib and Panobinostat in Relapsed/Refractory PTCL or NK/T-Cell Lymphoma

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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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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
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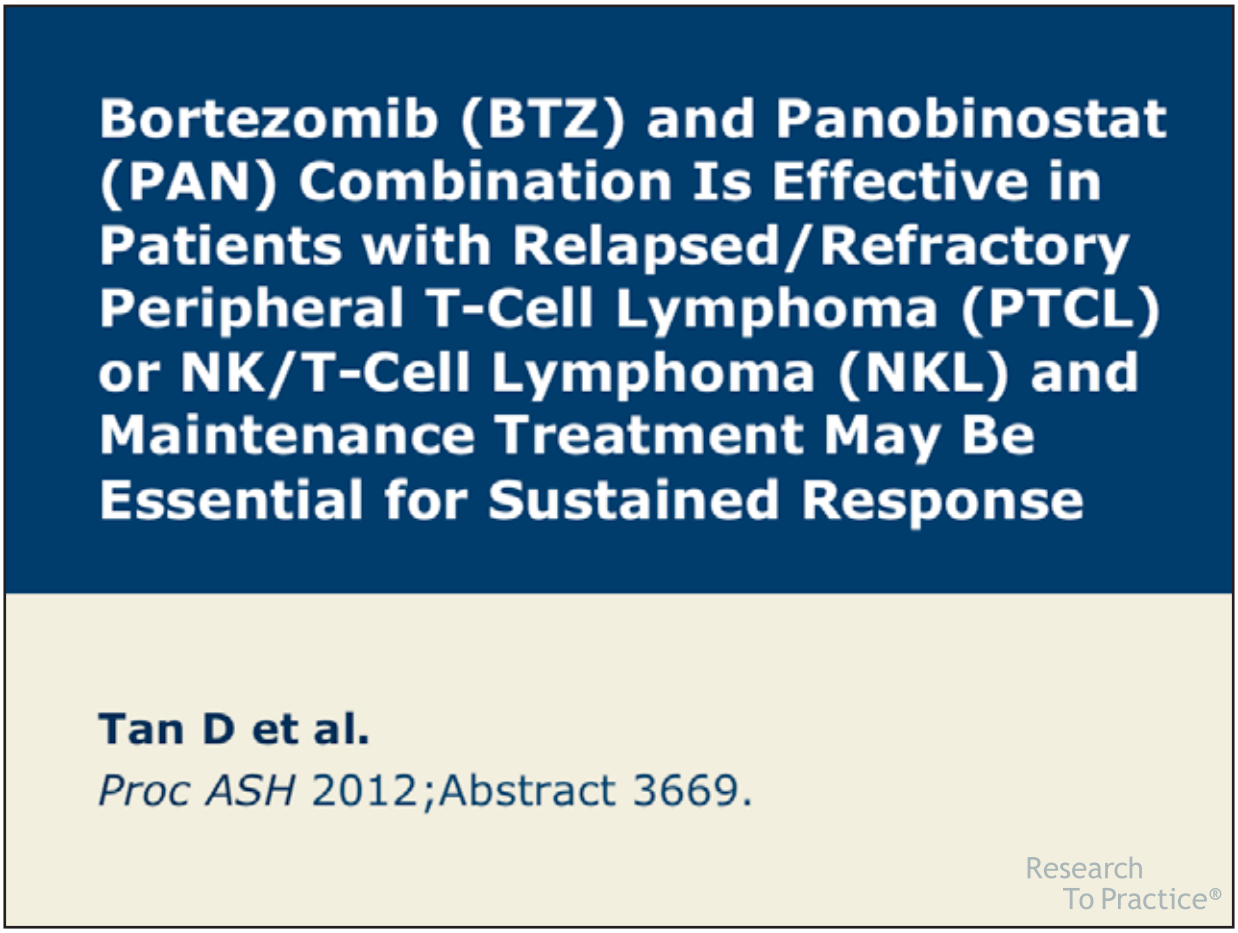
Phase II Study of Combination Bortezomib and Panobinostat in Relapsed/Refractory PTCL or NK/T-Cell Lymphoma

Presentation discussed in this issue

Tan D et al. **Bortezomib (BTZ) and panobinostat (PAN) combination is effective in patients with relapsed/refractory peripheral T-cell lymphoma (PTCL) or NK/T-cell lymphoma (NKL) and maintenance treatment may be essential for sustained response.** *Proc ASH* 2012;**Abstract 3669**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Brad S Kahl, MD (1/17/13)



Background

- Relapsed/refractory PTCL and NKL have a poor prognosis after conventional chemotherapy, and there is currently no effective treatment available.
- Panobinostat (PAN), a pan-deacetylase inhibitor, targets multiple oncogenic pathways, whereas bortezomib (BTZ) exerts pleotropic antitumor effects, leading to cell apoptosis.
- Inhibition of histone deacetylase (HDAC) 6 by PAN abrogates BTZ-induced protective aggresome formation and accentuates BTZ-induced endoplasmic reticulum stress, leading to further apoptosis.
- *In vitro* and *in vivo* studies have demonstrated potent synergistic cytotoxicity of the combination (*Leuk Res* 2012;36 (6):e128).
- **Objective:** Evaluate the efficacy and safety of BTZ and PAN in relapsed/refractory PTCL or NKL.

Tan D et al. *Proc ASH* 2012;Abstract 3669.

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Phase II Study Eligibility and Endpoints

- Eligibility (n = 20 patients enrolled)
  - Histologically confirmed PTCL-NOS, angioimmunoblastic T-cell lymphoma (AITL), extranodal NK/T-cell lymphoma nasal type, enteropathy-type T-cell lymphoma, hepatosplenic T-cell lymphoma, ALCL (ALK-1 negative), or patients with ALK 1-expressing ALCL who have relapsed after ASCT or are ineligible to undergo an ASCT
  - Progressive disease following at least one systemic therapy or refractory to at least one prior systemic therapy
  - ANC ≥1,000 x 10^9 cells/L
- **Primary endpoint:** Objective response rate
- **Secondary endpoints:** Include time to response, PFS, OS, safety, tolerability

Tan D et al. *Proc ASH* 2012;Abstract 3669.

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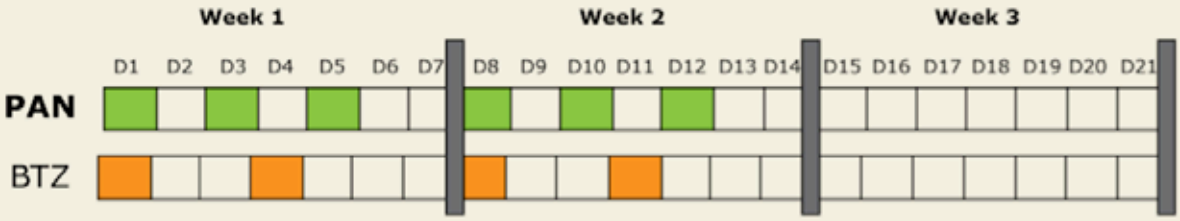
Phase II Study Design

- **Dosing schedule**
  PAN (20 mg, PO), thrice weekly + BTZ (IV 1.3 mg/m^2) twice weekly, both for 2 of 3 weeks, up to 6 cycles or until unacceptable toxicity or disease progression.



- **Statistics:** Gehan's 2-stage optimum design: Aiming for a response rate of ≥25%, 11 patients recruited in stage 1 and 14 in stage 2 if ≥1 responses are observed at stage 1.
- Assessment of response and progression evaluated after every 2 cycles of treatment.

Tan D et al. *Proc ASH* 2012;Abstract 3669.

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Response to Combination of BTZ and PAN in Stage 1

Response, n (%)	(n = 11)
ORR	6 (54%)
CR	2 (18%)
PR	4 (36%)
Stable disease	2 (18%)
Progressive disease	3 (27%)

- Among patients who responded or had stable disease, the median PFS was 6 months and disease progression occurred at a median of 2.5 months after stopping therapy.
- Three patients successfully underwent subsequent allogeneic SCT.
- Six patients demonstrated a decrease in tumor size of >50% from baseline.

Tan D et al. *Proc ASH* 2012;Abstract 3669.

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Select Treatment-Emergent Adverse Events

Adverse event	All grades	Grade 3/4
Hematologic		
Thrombocytopenia	64%	55%
Neutropenia	45%	36%
Nonhematologic		
Diarrhea	45%	18%
Vomiting	36%	9%
Rash	27%	0
Fever	64%	27%
Peripheral neuropathy	45%	18%

Tan D et al. *Proc ASH* 2012;Abstract 3669.

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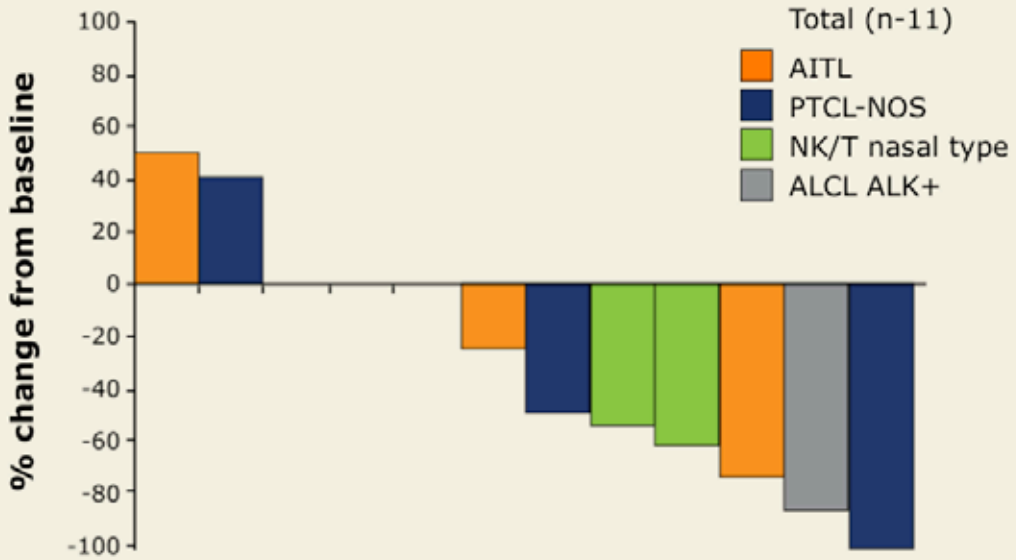
Maximal Tumor Change from Baseline



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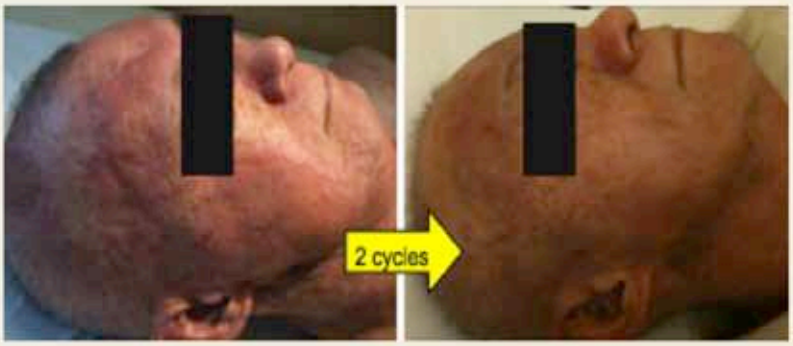
Patient with PTCL-NOS Refractory to CHOP



Anecdotal case of response to 2 cycles of BTZ+PAN in a patient with PTCL-NOS refractory to CHOP.

With permission from Tan D et al. *Proc ASH* 2012;Abstract 3669.

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Author Conclusions

- The study regimen shows activity across T/NK-cell lymphoma subtypes.
- ORR of 54% greatly exceeds the predefined threshold of 25%, allowing, together with early tolerability data, continuation of study enrollment into stage 2.
- The early progression of the disease after stopping therapy suggests that the novel combination provides a tonic suppression of tumor proliferation and that continual treatment will be beneficial for patients without the option of sequential treatment like stem cell transplantation.
- An extension phase for maintenance treatment will be incorporated into stage 2 of the study to allow patients to optimally benefit from the combination.
- Ongoing correlative studies are designed to determine if the study regimen is more active in diseases with upregulation of NF-kappa B or transcription factors/coregulators known to be modified by acetylation.

Tan D et al. *Proc ASH* 2012;Abstract 3669.

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Investigator Commentary: BTZ and PAN Are Effective for Relapsed/Refractory PTCL or NKL, and Maintenance Treatment May Be Essential for Sustained Response

This study investigated the efficacy of a combination of BTZ and PAN in patients with relapsed/refractory peripheral T-cell lymphoma or NK T-cell lymphoma. Many preclinical data suggest that proteasome inhibition with HDAC inhibition is a good combination in vitro and would be a good combination in patients.

This was a small study with only 11 patients. The overall response rate was impressive at 54%. However, the responses tended to be relatively brief. On average, within 2.5 months of stopping the treatment, patients experienced recurrence. The authors speculated that perhaps a long-term maintenance strategy might be important to help keep these patients in remission once they have responded.

Interview with Brad S Kahl, MD, January 17, 2013

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