# 5 Minute JournalClub

**POST-ASH** Issue 4, 2013

# Front-Line Therapy with Brentuximab Vedotin Combined with ABVD or AVD for Advanced HL

For more visit ResearchToPractice.com/5MJCASH2013

Research To Practice®

## 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.

## ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

## CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

## HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2013/4/CME.

## CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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

5 MinuteJournalClub

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

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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

# Front-Line Therapy with Brentuximab Vedotin Combined with ABVD or AVD for Advanced HL

## Presentation discussed in this issue

Ansell SM et al. **Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma.** *Proc ASH* 2012;**Abstract 798**.

## Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Bruce D Cheson, MD (1/14/13)

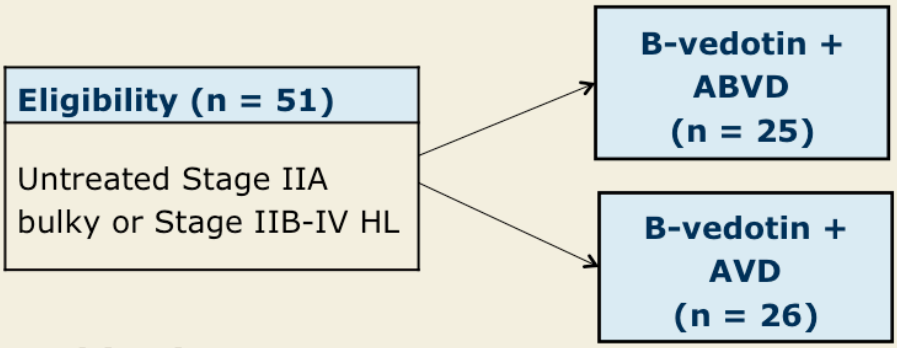
# Background

- A Phase II trial of brentuximab vedotin (b-vedotin) in relapsed or refractory Hodgkin lymphoma (HL) showed an objective response rate of 75% (CR, 34%) after autologous stem cell transplant (*JCO* 2012;30:2183).
- Front-line therapy for HL with ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) generally yields a 70% to 80% CR rate. However, bleomycin-induced pulmonary toxicity occurs in 10% to 25% of patients.
- **Study objective:** To evaluate the safety and efficacy of b-vedotin with ABVD or AVD (ABVD without bleomycin) in the front-line treatment of newly diagnosed, advanced HL.

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Research To Practice®

# Phase I Dose-Escalation Study Design

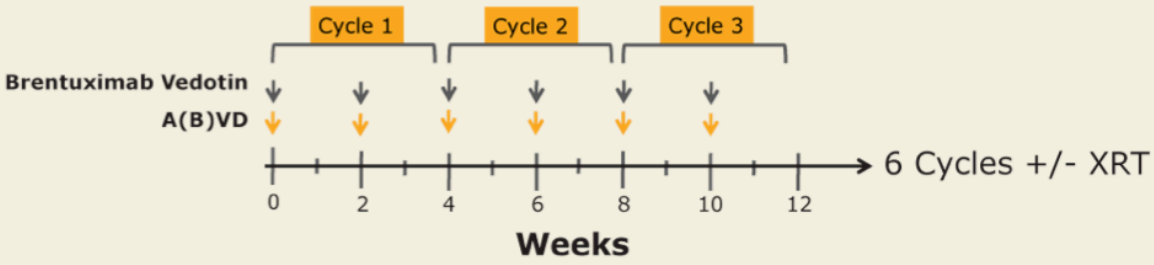



- **Key objectives:**
  - Safety of b-vedotin in combination with ABVD or AVD
  - Maximum tolerated dose (MTD) of b-vedotin in combination with ABVD or AVD
  - Antitumor activity of b-vedotin in combination with ABVD or AVD

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Research To Practice®

# Dose Schedule and Dose Cohorts




- 28-day cycles (up to 6 cycles) with dosing on days 1, 15
- Dose cohorts:
  - ABVD + b-vedotin (n = 25): Cohorts 1-3 (0.6-1.2 mg/kg)
  - AVD + b-vedotin (n = 26): Cohort 4 and an expansion cohort (both 1.2 mg/kg)

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Research To Practice®

# Response

| Response at end of front-line therapy | ABVD + b-vedotin (n = 22) | AVD + b-vedotin (n = 25) |
|---|---|---|
| Complete remission | 95% | 96% |
| Progressive disease | 0% | 4% |
| Not evaluable due to AEs* | 5% | 0% |

* Patient had a Grade 5 pulmonary adverse event (AE) prior to end of front-line therapy

- Cycle 2 FDG-PET results evaluated by central review for 48 patients
  - ABVD cohorts: 100% (22/22) negative
  - AVD cohorts: 92% (24/26) negative
- Prognostic value of interim PET in these regimens not established

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Research To Practice®

# Select Adverse Events

| Grade ≥3 AEs* | ABVD + b-vedotin (n = 25) | AVD + b-vedotin (n = 26) |
|---|---|---|
| Neutropenia | 80% | 77% |
| Anemia | 20% | 12% |
| Febrile neutropenia | 20% | 8% |
| Pulmonary toxicity | 24% | 0% |
| Dyspnea | 12% | 4% |
| Pulmonary embolism | 12% | 0% |
| Leukopenia | 4% | 4% |

* Occurring in >1 patient overall, regardless of relationship

- Peripheral neuropathy (PN), mostly Grade 1/2, occurred in 72% of pts in the ABVD + b-vedotin arm and 77% of pts in the AVD + b-vedotin arm and was managed with dose modifications.
- One pt had Grade 3 PN, but no Grade 4/5 events were reported.
- Overall 6/51 pts discontinued b-vedotin in treatment cycle 5 or 6, due to PN.

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Research To Practice®

# Pulmonary Toxicity

| | ABVD + b-vedotin (n = 25) | AVD + b-vedotin (n = 26) |
|---|---|---|
| Any event | 44% | 0% |
| Pulmonary toxicity | 36% | 0% |
| Interstitial lung disease | 4% | 0% |
| Pneumonitis | 4% | 0% |

- Events generally occurred during cycles 3-4
- Events resolved in 9/11 (82%) of patients
- 8/11 patients with events discontinued bleomycin and were able to complete treatment with AVD + b-vedotin
- Deaths associated with pulmonary toxicity, n = 2

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Research To Practice®

# Author Conclusions

- Concomitant administration of b-vedotin and bleomycin is contraindicated due to pulmonary toxicity.
- The recommended regimen is 1.2 mg/kg b-vedotin every 2 weeks combined with AVD.
- AVD combined with b-vedotin appears to be well tolerated with manageable AEs.
- A complete remission rate of 96% was observed at the end of front-line therapy with b-vedotin combined with AVD.
- A Phase III study to assess treatment with b-vedotin in combination with AVD as compared to ABVD alone in treatment-naïve patients is ongoing (NCT01712490).

Ansell SM et al. *Proc ASH* 2012;Abstract 798.

Research To Practice®

**Investigator Commentary: Front-Line Therapy with Brentuximab Vedotin Combined with ABVD or AVD for Advanced HL**

This study showed that the addition of b-vedotin to ABVD resulted in pulmonary toxicity, interstitial lung disease and pneumonitis in 44% of patients. However, this did not occur when b-vedotin was combined with AVD. A previous study by the CALGB had warned that the combination of GVD (gemcitabine, vinorelbine and doxorubicin) with SGN-30, the antibody backbone of b-vedotin, in patients with relapsed HL results in serious pulmonary toxicity (*Ann Oncol* 2010;21:2246).

Peripheral neuropathy was also observed in more than 70% of patients in both arms of this study. Although neuropathy can be a problem, it can be managed with dose modifications and is partially reversible in the majority of patients.

The current study showed spectacular response rates. It forms the basis for a pivotal Phase III trial for patients with untreated HL. This important trial has the potential to change how we care for these patients. I believe that b-vedotin-based regimens have a bright future, but the treatment will have to be fine-tuned and associated with less toxicity for it to make a major impact on HL in the front-line setting.

***Interview with Bruce D Cheson, MD, January 14, 2013***

Research To Practice®