# 5 Minute JournalClub

***Key ASH Presentations***
Issue 2, 2012

# Efficacy and Safety of Brentuximab Vedotin with ABVD or AVD in Newly Diagnosed Advanced HL

For more visit ResearchToPractice.com/5MJCASH2012

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

- Consider the inclusion of brentuximab vedotin in the treatment algorithm for relapsed/refractory Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL).
- Assess the benefit and toxicity resulting from prolonged treatment with brentuximab vedotin in patients with relapsed/refractory HL or sALCL.
- Evaluate the efficacy and toxicity outcomes from studies with brentuximab vedotin in combination with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) or AVD as front-line therapy for advanced HL.

## 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 1.25 *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/5MJCASH2012/2/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:

Craig Moskowitz, MD
Clinical Director, Division of Hematologic Oncology
Attending Physician, Lymphoma and Adult BMT Services
Member, Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University
New York, New York

Advisory Committee: Cephalon Inc, Genentech BioOncology, Seattle Genetics; Paid Research: Cephalon Inc, Genentech BioOncology, Lilly USA LLC, Plexxikon Inc, Seattle Genetics.

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: Abbott Laboratories, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Bayer HealthCare Pharmaceuticals/Onyx Pharmaceuticals Inc, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Cephalon Inc, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Genentech BioOncology, Genomic Health Inc, ImClone Systems, a wholly owned subsidiary of Eli Lilly and Company, Incyte Corporation, Lilly USA LLC, Medivation Inc, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics and Teva Pharmaceuticals.

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 Allos Therapeutics, Celgene Corporation, Genentech BioOncology/Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

Last review date: January 2012
Expiration date: January 2013

5 MinuteJournalClub

Key ASH Presentations
Issue 2, 2012

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

Monoclonal antibodies are an important part of current oncology management, but limitations in efficacy have led to the development of a related class of antitumor agents — so-called immunoconjugates or antibody-drug conjugates (ADCs). These unique therapeutics have become the focus of a plethora of recent and ongoing clinical trials, and in August — following data sets presented at ASH 2010 — for the first time since 2000 when gemtuzumab ozogamicin was approved in AML, we saw the FDA give the green light to another ADC, namely brentuximab vedotin for the management of Hodgkin lymphoma (HL) and systemic anaplastic large cell lymphoma (sALCL). Like its sister agent in HER2-positive breast cancer, T-DM1, and other ADCs, B-vedotin has 3 components (**Figure 1**):

**Monoclonal Antibody**
B-vedotin includes a chimeric IgG1 monoclonal antibody, SGN-30, that targets CD30, an antigen that has limited expression in normal tissues and uniformly high expression in HL (specifically Reed-Sternberg cells), sALCL and select other cancers, including cutaneous and peripheral T-cell lymphomas, where responses were **recently reported**. The "naked" antibody has less antitumor effect than, for example, trastuzumab in HER2-positive breast cancer (in T-DM1).

**Cytotoxic Agent**
Because of the specificity of delivery, next-generation ADCs have included highly potent smaller cytotoxic agents, in this case the vinblastine-like MMAE that inhibits microtubule polymerization. Hence, its most important clinical toxicity is peripheral neuropathy.

**Linker**
Investigators get all wide-eyed and excited when they talk about linker molecules used to conjugate ADC components, I guess because of the spectacular technology. B-vedotin includes a dipeptide that is selectively cleaved by lysosomal enzymes after being rapidly internalized into cells. The result is the release of MMAE that causes apoptosis in CD30-positive tumor cells.

Currently, many ADCs are in development targeting a variety of cell types in both myeloid/hematopoietic cancers and carcinomas (**Figure 2**). In this issue of our series we provide slide sets based on presentations from last month's ASH meeting that bring into sharper focus why there is so much excitement about B-vedotin.

**1. Abstract 443. More on B-vedotin in sALCL**
Memorial's Dr Craig Moskowitz has extensive on- and off-trial experience with this ADC, and in his words, "It approaches a home run in sALCL. It's changed the lives of people with this disease." This ASH paper updates the impressive Phase II study first presented at ASH

2010 in patients with refractory disease, but the real hope is in the up-front setting, where exciting new trials are evaluating a novel "CHOP" in which B-vedotin replaces vincristine.

**2. Abstracts 664 and 3091. B-vedotin and reduced-intensity allogeneic stem cell transplant (allo-SCT) in relapsed/refractory HL**

These 2 reports detail the courses of a total of 33 patients who received B-vedotin prior to allo-SCT. This strategy had no adverse impact on engraftment, GVHD or survival and provided sufficient disease control for patients to successfully proceed to allo-SCT. Investigators like Dr Moskowitz are currently using B-vedotin extensively as a bridge to transplant, although the appropriate number of doses to deliver is controversial.

**3. Abstract 3711. Prolonged treatment with B-vedotin**

This retrospective analysis evaluated a subset of 15 patients with HL and sALCL who received B-vedotin until disease progression or unacceptable toxicity. Treatment ranged from 17 to 29 cycles and was well tolerated and not limited by the major side effect, peripheral neuropathy, which was usually reversible and Grade 2 or lower.

**4. Abstract 955. Front-line treatment with B-vedotin and either ABVD or AVD in newly diagnosed advanced-stage HL**

This Phase I trial from MD Anderson demonstrated excellent responses among 44 patients (97% FDG-PET negativity after 2 treatment cycles). However, concerning adverse effects were seen in the ABVD/B-vedotin arm — specifically a 40% incidence of bleomycin-like pulmonary toxicity that was not observed with AVD/B-vedotin — and the concomitant use of bleomycin and B-vedotin is now contraindicated. A Phase III trial will assess front-line AVD/B-vedotin compared to ABVD.

Up next, having just returned from the GI Cancers Symposium in San Francisco we flip back to solid tumors and some interesting new developments (finally) in colorectal cancer, including perspectives on 2 promising systemic agents: aflibercept and regorafenib.

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 1.25 *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 Allos Therapeutics, Celgene Corporation, Genentech BioOncology/Biogen Idec, Incyte Corporation, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

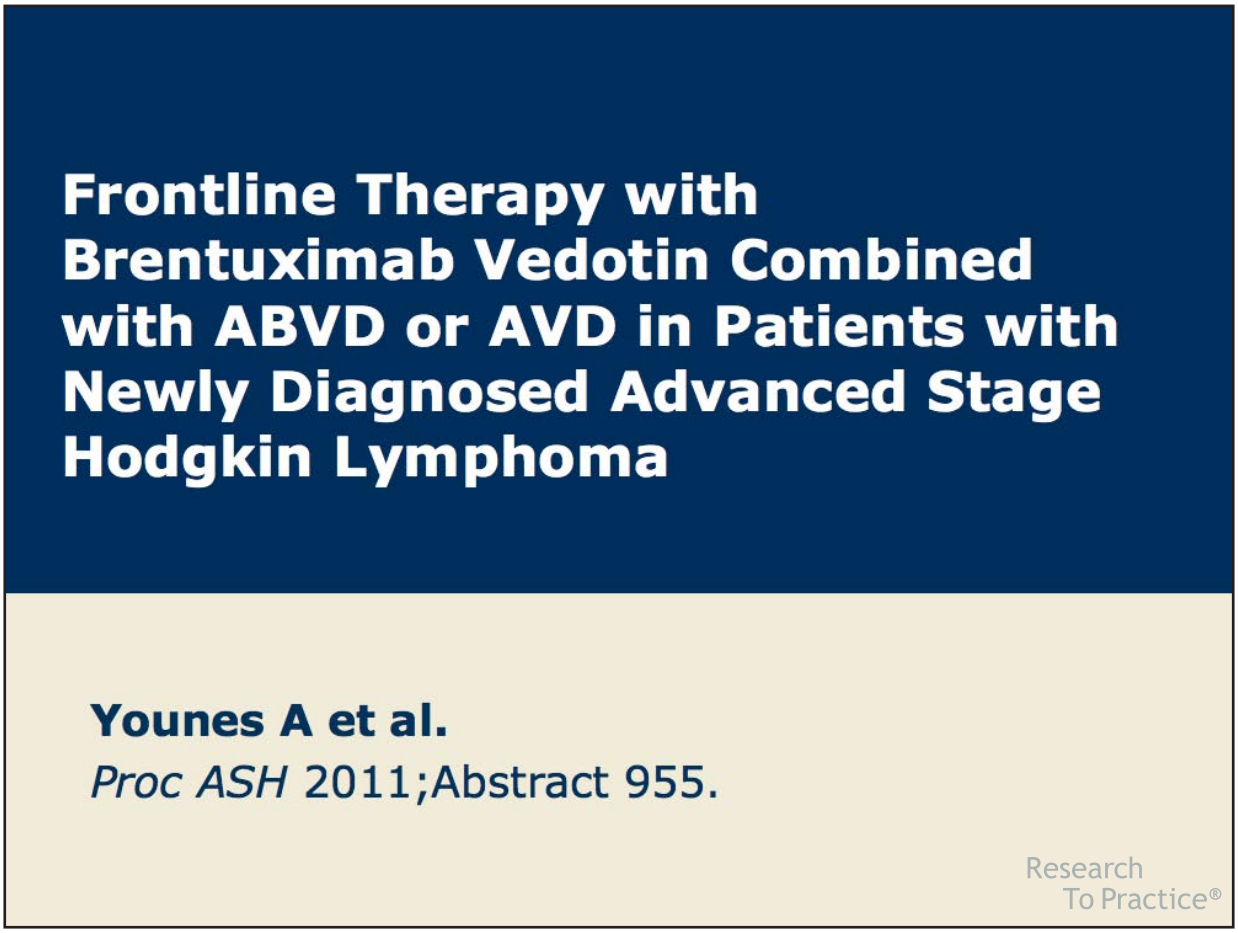
Research To Practice
One Biscayne Tower
2 South Biscayne Boulevard, Suite 3600
Miami, FL 33131

# Efficacy and Safety of Brentuximab Vedotin with ABVD or AVD in Newly Diagnosed Advanced HL

## Presentation discussed in this issue

Younes A et al. **Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma.** *Proc ASH* 2011;**Abstract 955**.

## Slides from a presentation at ASH 2011 and transcribed comments from a recent interview with Craig Moskowitz, MD (1/11/12)



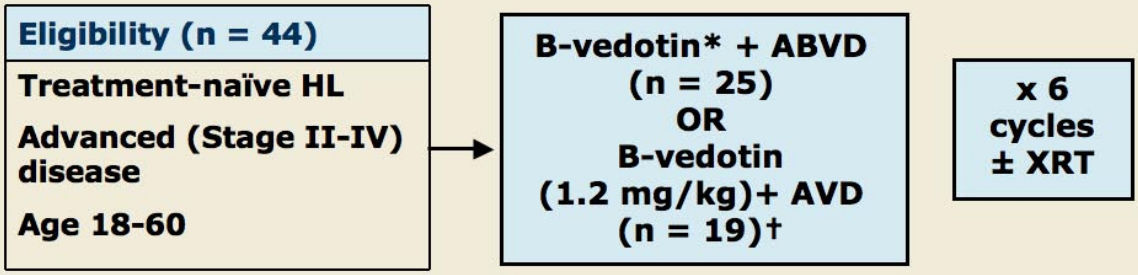
# Background

- Hodgkin lymphoma (HL) is characterized by the presence of CD30+ Hodgkin Reed-Sternberg cells.
- Brentuximab vedotin (B-vedotin), a novel anti-CD30 antibody-drug conjugate, selectively induces apoptosis of CD30+ cells.
- A previous Phase II study reported a 75% overall response rate and 34% durable complete remission rate for patients with treatment-refractory HL treated with single-agent B-vedotin (*Proc ASCO* 2011;Abstract 8031).
- **Current Study Aim:** To evaluate the efficacy and safety of brentuximab vedotin in combination with doxorubicin/bleomycin/vinblastine/dacarbazine (ABVD) or AVD in patients with newly diagnosed, advanced HL.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

# Phase I Study Design




* Dose expansion cohorts:

Cohort 1 (n = 6): 0.6 mg/kg
Cohort 2 (n = 13): 0.9 mg/kg
Cohort 3 (n = 6): 1.2 mg/kg

† Thirteen patients in this cohort are still receiving treatment.

XRT = radiation therapy

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

# Baseline Patient Characteristics

| Characteristic | (n = 44) |
|---|---|
| Age (median) | 32.5 years |
| Male | 75% |
| **ECOG performance status*** | |
| 0 | 45% |
| 1 | 52% |
| IPS score ≥4 | 23% |
| **Stage** | |
| IIA bulky | 5% |
| IIB | 16% |
| IIIA | 18% |
| IIIB | 16% |
| IV | 45% |

* One patient in the AVD cohort is missing baseline ECOG performance status.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

# Response Results After Completion of Therapy with B-Vedotin + ABVD

| Response | ABVD cohorts (n) |
|---|---|
| Complete response | 15 |
| Partial response | 0 |
| Stable disease | 0 |
| Progressive disease | 0 |
| Not evaluable | 5 |

- Fifteen of the 25 patients in the ABVD cohorts have completed front-line therapy on study and have response results.
- Five patients withdrew prior to completion of 6 cycles of front-line therapy due to adverse events (peripheral sensory neuropathy, dyspnea or hyponatremia) and did not have an end-of-treatment response on study.
- End-of-treatment response results are not yet available for the AVD cohorts.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

# Cycle 2 FDG-PET Results

| | Total N (%) |
|---|---|
| PET negative | 36 (97%) |
| PET positive | 1 (3%) |

- Cycle 2 FDG-PET results were completed for 37 patients:
  - FDG-PET interpretation for cycle 2 performed by a central review per Deauville criteria with uptake above liver background considered positive
- Of these 37 patients, 36 had a negative interim PET scan:
  - B-vedotin with ABVD cohorts: 22 of 22 negative (100%)
  - B-vedotin with AVD cohorts: 14 of 15 negative (93%)
- Prognostic value of interim PET in these regimens is not yet established.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

# Most Common Adverse Events

| Adverse event | Any grade* (n = 44) |
|---|---|
| Neutropenia | 77% |
| Nausea | 66% |
| Peripheral sensory neuropathy | 48% |
| Fatigue | 43% |
| Vomiting | 43% |
| Constipation | 36% |
| Alopecia | 32% |
| Pyrexia | 32% |
| Cough | 30% |
| Insomnia | 30% |
| Decreased appetite | 25% |

* Events occurring in ≥25% of patients

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

# Grade 3 or 4 Adverse Events

| Adverse event | Grade 3 or 4* (n = 44) |
|---|---|
| Neutropenia | 77% |
| Anemia | 14% |
| Febrile neutropenia | 11% |
| Pulmonary toxicity† | 11% |
| Dyspnea | 9% |
| Syncope | 9% |
| Pulmonary embolism | 7% |
| Leukopenia | 5% |

* Events occurring in ≥5% of patients

† Forty percent of patients in the ABVD cohort experienced pulmonary toxicity; none observed in the AVD cohort. Toxicity resembling that of bleomycin alone led to its discontinuation in 10 patients. Seven of these 10 patients continued treatment with AVD and B-vedotin.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

# Author Conclusions

- Preliminary results suggest that AVD combined with B-vedotin is generally well tolerated with manageable adverse events.
- Combination of bleomycin and B-vedotin is not recommended:
  - Increased incidence of pulmonary adverse events relative to historical observations of ABVD
  - No pulmonary toxicity events observed in the AVD cohort at current analysis
- No dose-limiting toxicity was observed in any cohort at the maximum planned dose of 1.2 mg/kg (data not shown).
- To date, all patients in the ABVD cohorts who completed front-line therapy on study achieved complete remission.
- A Phase III study is planned to assess front-line treatment with B-vedotin in combination with AVD as compared to ABVD alone.

Younes A et al. *Proc ASH* 2011;Abstract 955.

Research To Practice®

## Investigator Commentary: Front-Line Therapy with B-Vedotin and ABVD or AVD in Newly Diagnosed Advanced Hodgkin Lymphoma

In this study, interim PET scanning was performed after 2 cycles of therapy and all the patients whose PET results were negative have fared well. Unfortunately, the protocol had to be amended because of a 40% incidence of pulmonary toxicity of B-vedotin with ABVD. Patients were switched from the ABVD to the AVD regimen. Going forward, B-vedotin will have to be administered with AVD.

We know that B-vedotin alone doesn't cause pulmonary toxicity. Bleomycin does cause pulmonary toxicity but not a 40% rate. So the combination of B-vedotin and bleomycin was toxic. We already know that B-vedotin can't be combined with gemcitabine. We do not know how patients with Hodgkin lymphoma will fare with B-vedotin and radiation therapy. I believe those will have to be administered sequentially and will be tolerated.

We're performing a study in which we administer B-vedotin weekly at 1.2 mg with a 3 weeks on, 1 week off protocol. We administer chemotherapy sequentially with B-vedotin, not concomitantly. Patients who experience a response go on to transplant without any salvage chemotherapy.

***Interview with Craig Moskowitz, MD, January 11, 2012***