



POST-ASH Issue 1, 2015

**Results of the Phase 3 AETHERA Trial of
Brentuximab Vedotin for Patients with
Hodgkin Lymphoma at Risk for Progression
After Autologous Stem Cell Transplant**

For more visit ResearchToPractice.com/5MJCASH2015

Research
To Practice®

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 Hematology (ASH) annual meeting, 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're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider 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 emerging data sets on the use of brentuximab vedotin and novel immune checkpoint inhibitors in the treatment of Hodgkin lymphoma (HL) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Assess the efficacy and safety of brentuximab vedotin in investigational settings, such as in combination with AVD for patients with newly diagnosed HL, as consolidation after autologous stem cell transplant or as first-line salvage therapy alone or in combination with bendamustine prior to stem cell transplant.
- Appraise recent clinical trial data on the use of immune checkpoint inhibition for patients with relapsed or refractory 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 1.75 *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/5MJCASH2015/1/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:

Stephen M Ansell, MD, PhD
Professor of Medicine
Division of Hematology
Mayo Clinic
Rochester, Minnesota

Research Funding: Bristol-Myers Squibb Company, Celldex Therapeutics.

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: Genentech BioOncology, Seattle Genetics;
Contracted Research: Genentech BioOncology, GlaxoSmithKline, Merck, 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: AbbVie Inc, Amgen Inc, Astellas, AstraZeneca Pharmaceuticals LP, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Boston Biomedical Pharma Inc, Bristol-Myers Squibb Company, Celgene Corporation, Clovis Oncology, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, Exelixis Inc, Foundation Medicine, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Janssen Biotech Inc, Jazz Pharmaceuticals Inc, Lilly, Medivation Inc, Merck, Myriad Genetic Laboratories Inc, Novartis Pharmaceuticals Corporation, Novocure, Onyx Pharmaceuticals, an Amgen subsidiary, Pharmacyclics Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

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 Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics and Takeda 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: February 2015

Expiration date: February 2016

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

Last fall, I received a set of slides submitted by Memorial Sloan Kettering's "tell it like it is" lymphoma maven Dr Craig Moskowitz for a presentation we'd asked him to give at our Year in Review regional CME meeting in Orlando, and it became instantly clear that the year's top story at ASH would be Hodgkin lymphoma (HL). What immediately grabbed my attention was a reference to 2 presentations that Craig would be giving at the upcoming Annual Meeting in San Francisco. The first focused on the initial results of the much anticipated Phase III randomized

AETHERA trial evaluating the antibody-drug conjugate brentuximab vedotin (BV) as maintenance treatment after autologous stem cell transplant (ASCT) for relapsed HL, while the second was one of a pair of very much *un*anticipated parallel presentations of Phase I studies of the anti-PD-1 monoclonal antibodies nivolumab and pembrolizumab, both of which are now approved by the FDA for metastatic melanoma.

Investigators who are about to present landmark clinical trials usually have embargoes up the wazoo, and while I couldn't squeeze many details out of Craig a month or so before ASH, there was no mistaking the enthusiasm in his voice as he told us what he could. Several weeks later when the abstracts became available it was evident why this often skeptical and conservative researcher was so genuinely excited: The 19-month jump in progression-free survival on the BV arm of AETHERA and the off-the-charts waterfall plots in the anti-PD-1 papers pretty much spoke for themselves.

After spending the last couple of months chatting with investigators (Craig among them) and general oncologists about what happened in San Francisco, we chose to profile HL on this first issue of our ASH review series, and it is interesting that the cancer that in many ways became the prototype for oncologic therapy for a generation has suddenly become the focal point of 2 of the most important innovations in the field. Unlike MOPP and its descendants, however, these newer modalities often lead to striking clinical outcomes not only in efficacy but also in tolerability. Here in a nutshell is what the justifiable fuss is all about.



Craig Moskowitz, MD

Maintenance BV after ASCT for relapsed/refractory HL

When I met with Dr Moskowitz not long after ASH he glowed about the previously mentioned AETHERA trial, noting that it was the first ever placebo-controlled, randomized study reported in HL. Over the last few years we have learned that CD30, a transmembrane glycoprotein receptor in the tumor necrosis factor receptor superfamily, is expressed on virtually all Reed-Sternberg cells in classical HL and at notably low levels in normal cells. Thus the anti-CD30 antibody-drug conjugate BV has proved to be among the most effective agents for the disease, and this study brings that into full focus.

Patients on the trial were randomly assigned to receive 16 cycles of maintenance BV or placebo every 3 weeks, and one of the most striking outcomes was that the risk of relapse at 2 years was reduced from 55% to 35%. From Craig's perspective this is likely to translate into improved cure rates because relapse after 24 to 30 months is uncommon. The bottom line is pretty much an instant change in standard of care.

BV up front in newly diagnosed HL

As many as 25% of patients with advanced-stage HL are not cured by chemotherapy regimens such as ABVD, and many others experience long-term toxicities, particularly bleomycin-induced pulmonary damage. For these reasons there has been great interest in evaluating alternative up-front regimens, and at ASH we saw more encouraging follow-up from a **Phase I trial** that initially combined BV with ABVD but then removed the bleomycin because of unacceptable pulmonary toxicity. The findings include a 3-year failure-free survival of 92% and seem compelling enough to lead any eligible patient with newly diagnosed, advanced-stage HL to consider entering the Phase III ECHELON-1 trial comparing ABVD to AVD-BV.

More on BV

Other key ASH BV data sets included a **Phase II trial** investigating the use of up to 4 cycles of the drug prior to ASCT in 36 patients with relapsed disease. This study demonstrated a 36% complete response rate and a 33% partial response rate, and 52% of the patients were able to proceed to transplant without additional chemotherapy.

In another **Phase II study** also evaluating patients at first relapse prior to ASCT, bendamustine was added to BV, producing outstanding efficacy outcomes, with 83% complete and 13% partial responses among 48 evaluable patients. Investigators initially observed a high rate of infusion reactions with the combination, but this problem was reportedly solved with more intensive premedication regimens.

Anti-PD-1 antibodies in HL

The biologic story here is fascinating. It has long been known that HL tumor masses are occupied mainly by inflammatory cells with only rare cancer (Reed-Sternberg)

cells. Analyses have shown that classical HL frequently harbors amplification of genetic material at the 9p24.1 locus and that these genes lead to overexpression of the PD-L1 and PD-L2 ligands. The Epstein-Barr virus — signs of which are observed in about half of patients with classical HL — is also thought to cause overexpression of PD-L1 and PD-L2, and for these and perhaps other reasons, these ligands are almost uniformly expressed on the surface of Reed-Sternberg cells. This had led to the rational hypothesis that classical HL is a tumor with a genetically determined vulnerability to PD-1 blockade.

At ASH we saw confirmation of this theory as the very busy Dr Moskowitz unveiled results from the **Phase IB study (KEYNOTE-013)** of pembrolizumab. Among the 31 patients with relapsed or refractory HL, all demonstrated PD-L1 expression on tumors and 66% achieved objective responses. Craig noted that as has been observed with solid tumors, responses often occur early, usually in the first 12 weeks. Although more follow-up is needed, it is intriguing that to this point almost 70% of patients remain on treatment.

The other major ASH anti-PD-1 HL paper came from a **Phase I trial** evaluating nivolumab for a variety of hematologic cancers. The HL cohort included 23 patients, and objective responses were observed in 87%. Analysis of pretreatment tumor specimens from 10 individuals demonstrated increased expression of both PD-L1 and PD-L2, and all 10 tumors had a genetic abnormality at 9p24.1. Note that the FDA recently bestowed breakthrough therapy designation on nivolumab in HL, although as in other tumors, including melanoma, investigators at this point can't really distinguish major differences in efficacy or tolerability of the 2 anti-PD-1 antibodies.

A related ASH data set from the same study included findings from patients with B-cell and T-cell lymphomas in addition to patients with multiple myeloma. The results were mixed: More than a third of patients with follicular and diffuse large B-cell lymphoma experienced objective responses, and the decision has been made to continue investigation of nivolumab in these diseases, either alone or combined with other therapies, including anti-CTLA4 antibodies such as ipilimumab. Fewer responses (17%) were observed in 23 patients with T-cell lymphoma and none were reported in 27 patients with multiple myeloma or 2 patients with primary mediastinal B-cell lymphoma, and for this reason this agent will not be further evaluated in these tumors.

As in prior trials of anti-PD-1 antibodies in other cancers, both nivolumab and pembrolizumab were generally well tolerated in patients with HL, with few Grade 3 or 4 adverse events. However, the spectrum of autoimmune complications with these and other checkpoint inhibitors is specific and quite different from the side effects seen with traditional anticancer systemic therapies, such as cytotoxic and targeted treatment. In this regard Dr Moskowitz noted that while autoimmune toxicities like pneumonitis and thyroid or adrenal dysfunction are uncommon, oncologists must be vigilant in identifying and managing such complications. Similarly, during a recent interview for our audio series, lung cancer investigator Dr Julie Brahmer noted that she tells patients that "anything that ends in an 'itis'" might be observed.

BV has been around long enough for oncologists to have integrated it into their practices relatively effectively, but while checkpoint inhibitors have been used for a while in melanoma, it seems entirely possible that as early as this summer anti-PD-1 agents could be approved and used widely in non-small cell lung cancer. This development will transform the practice of oncology perhaps more than any other event in the history of the field as chemotherapy infusion rooms become, to a great extent, immunotherapy centers. Even more, this revolution will likely not be limited to melanoma and lung cancer because it seems plausible that many other, less common diseases, including HL but also bladder cancer and renal cell carcinoma, will soon incorporate checkpoint inhibitors into standard treatment algorithms and offer patients running out of options a novel approach that appears to be unique and very promising. Next on this series we chat about multiple myeloma and a major new Phase III study (ASPIRE) that exemplifies how far we have come with this difficult disease.

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 1.75 *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 Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics and Takeda Oncology.

Results of the Phase 3 AETHERA Trial of Brentuximab Vedotin for Patients with Hodgkin Lymphoma at Risk for Progression After Autologous Stem Cell Transplant

Presentation discussed in this issue

Moskowitz CH et al. **The AETHERA trial: Results of a randomized, double-blind, placebo-controlled Phase 3 study of brentuximab vedotin in the treatment of patients at risk of Hodgkin lymphoma progression following autologous stem cell transplant.** *Proc ASH 2014*; **Abstract 673**.

Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Craig Moskowitz, MD (1/6/15)

The AETHERA Trial: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Brentuximab Vedotin in the Treatment of Patients at Risk of Hodgkin Lymphoma Progression Following Autologous Stem Cell Transplant

Moskowitz CH et al.

Proc ASH 2014; Abstract 673.

Research
To Practice®

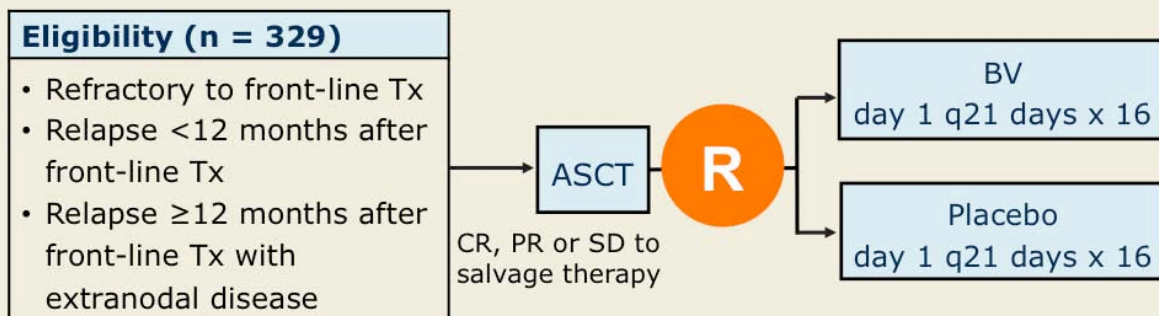
Background

- Autologous stem cell transplant (ASCT) can achieve cure in approximately 50% of patients with relapsed or refractory Hodgkin lymphoma (HL).
- Over the past 20 years, no improvement has been shown in efficacy outcomes from randomized trials of ASCT regimens for aggressive lymphomas.
- Brentuximab vedotin (BV) is a CD30-directed therapy that has shown efficacy in patients with HL who experienced relapse or had refractory disease after prior ASCT (*J Clin Oncol* 2012;30:2183).
- **Study objective:** To assess whether BV consolidation could prevent disease progression after ASCT in patients at risk for relapse or disease progression.

Moskowitz CH et al. *Proc ASH* 2014;Abstract 673.

Research
To Practice®

Phase III AETHERA Study Design



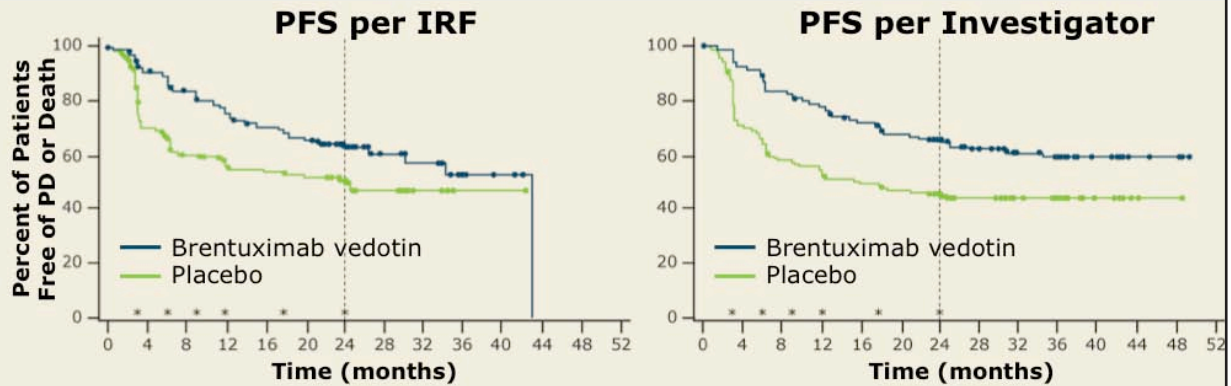
Patients who experienced disease progression on the placebo arm could subsequently receive BV on another trial.

- **Primary endpoints:** Progression-free survival per independent review
- **Secondary endpoints:** Overall survival, safety, tolerability

Moskowitz CH et al. *Proc ASH* 2014;Abstract 673.

Research
To Practice®

Progression-Free Survival

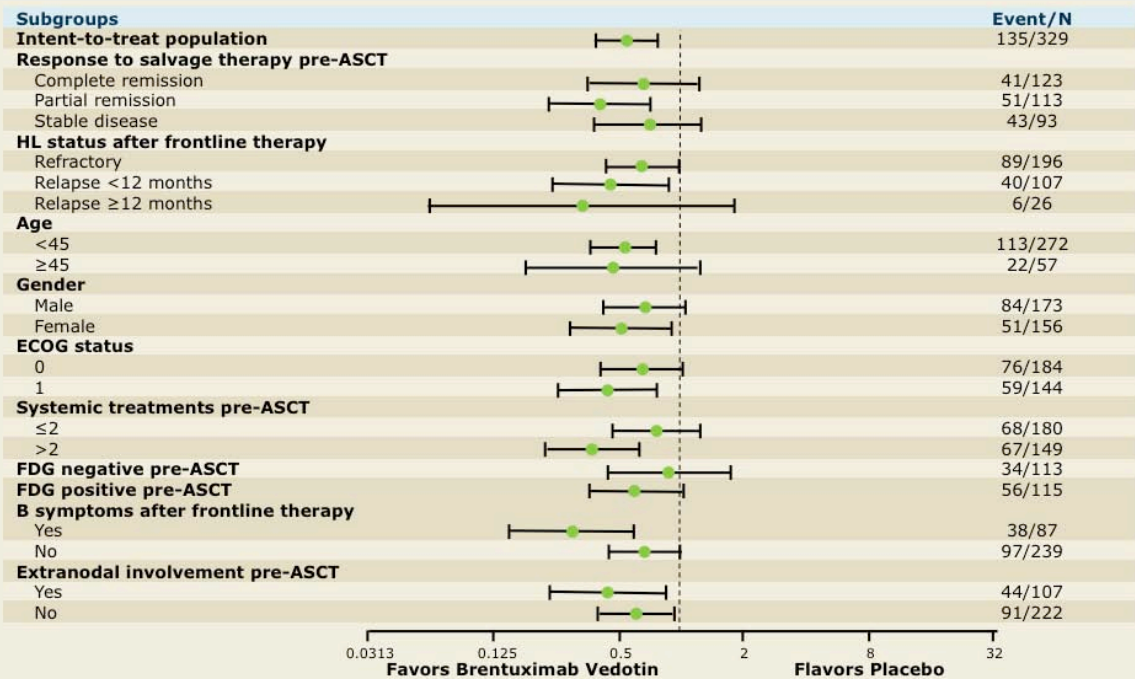


* Regularly scheduled CT scans; BV (n = 165), placebo (n = 164)

PFS Response	Per IRF		Per investigator	
	BV	Placebo	BV	Placebo
Median PFS	43 mo	24 mo	—	16 mo
2-y PFS rate	63%	51%	65%	45%
Hazard ratio	0.57 ($p = 0.001$)		0.5	

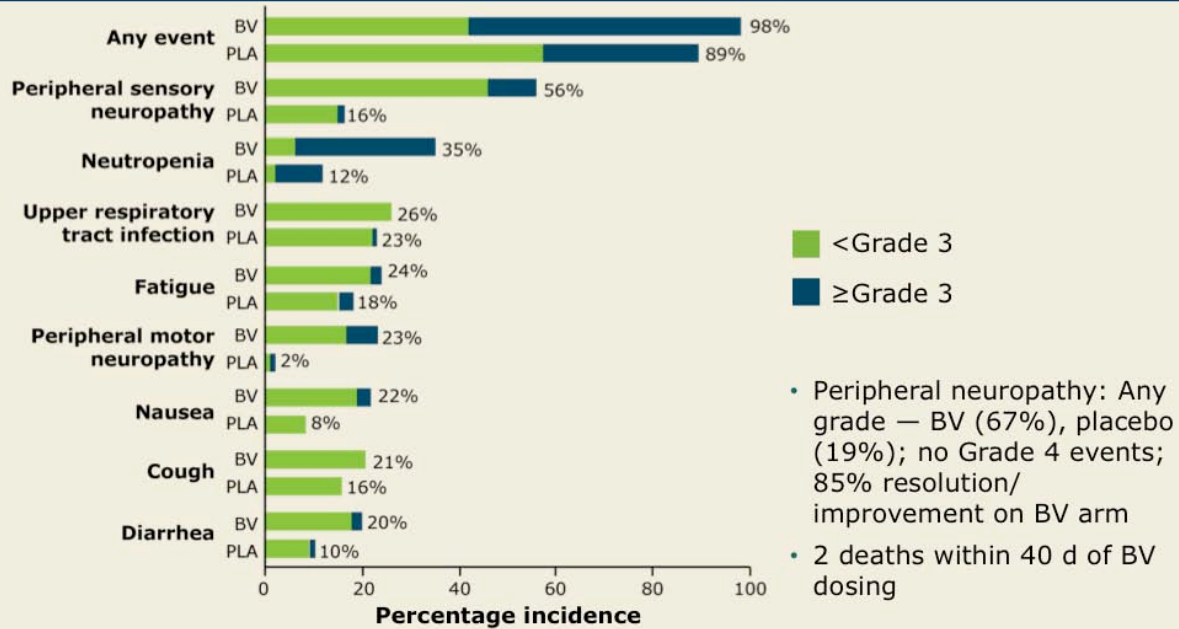
With permission from Moskowitz CH et al. *Proc ASH 2014*;Abstract 673.

Subgroup Analysis of PFS per IRF



With permission from Moskowitz CH et al. *Proc ASH 2014*;Abstract 673.

Adverse Events*



* Treatment-emergent AEs regardless of relationship to Tx; incidence $\geq 20\%$ on BV arm
 With permission from Moskowitz CH et al. *Proc ASH 2014*;Abstract 673.

Author Conclusions

- Early consolidation after ASCT with BV demonstrated improved PFS per IRF in patients with HL and risk factors for relapse or disease progression (HR = 0.57, $p = 0.001$).
 - PFS benefit was sustained
 - Consistent benefit observed across subgroups
- Interim analysis of overall survival did not show a significant difference between treatment arms.
- Consolidation therapy was generally well tolerated.
 - Peripheral sensory neuropathy and neutropenia were common, manageable with dose reductions/delays
- BV consolidation therapy is an important therapeutic option for patients with HL who are undergoing ASCT to reduce the risk of relapse or disease progression.

Moskowitz CH et al. *Proc ASH 2014*;Abstract 673.

Research
To Practice®

Investigator Commentary: Phase III AETHERA Trial of BV in Patients at Risk of HL Progression After ASCT

This is the only placebo-controlled randomized study that has been conducted in HL. It is also the only positive trial in the HL transplant setting.

The primary endpoint of this study was PFS at 2 years. The PFS rate was 65% for patients who received BV versus 45% for those on the placebo arm by investigator analysis. In my opinion these patients who are progression free in both arms are cured because it is rare for patients to relapse 24 to 30 months after ASCT.

When the study was designed in 2009, the median survival of patients whose disease had progressed after ASCT was 26 months. In the current era with agents like BV and panobinostat, median survival is closer to 48 months. To determine if there is an overall survival benefit it will take 3 or 4 more years. I do believe that once the study has been peer reviewed there will be a window when BV therapy in this setting will become the standard.

In terms of side effects with BV, sensory and sometimes motor neuropathy was a problem. However, severe, long-term neuropathy was not common. Peripheral neuropathy was managed with dose reductions, and if there was continued toxicity, treatment was stopped.

Interview with Craig Moskowitz, MD, January 6, 2015