5 Minute JournalClub

POST-ASH Issue 1, 2015

Brentuximab Vedotin in Combination with Bendamustine for Patients with Relapsed/Refractory Hodgkin Lymphoma After Front-Line Therapy

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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.

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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

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POST-ASH Issue 1, 2015

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

Craig Moskowitz, MD

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.

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.

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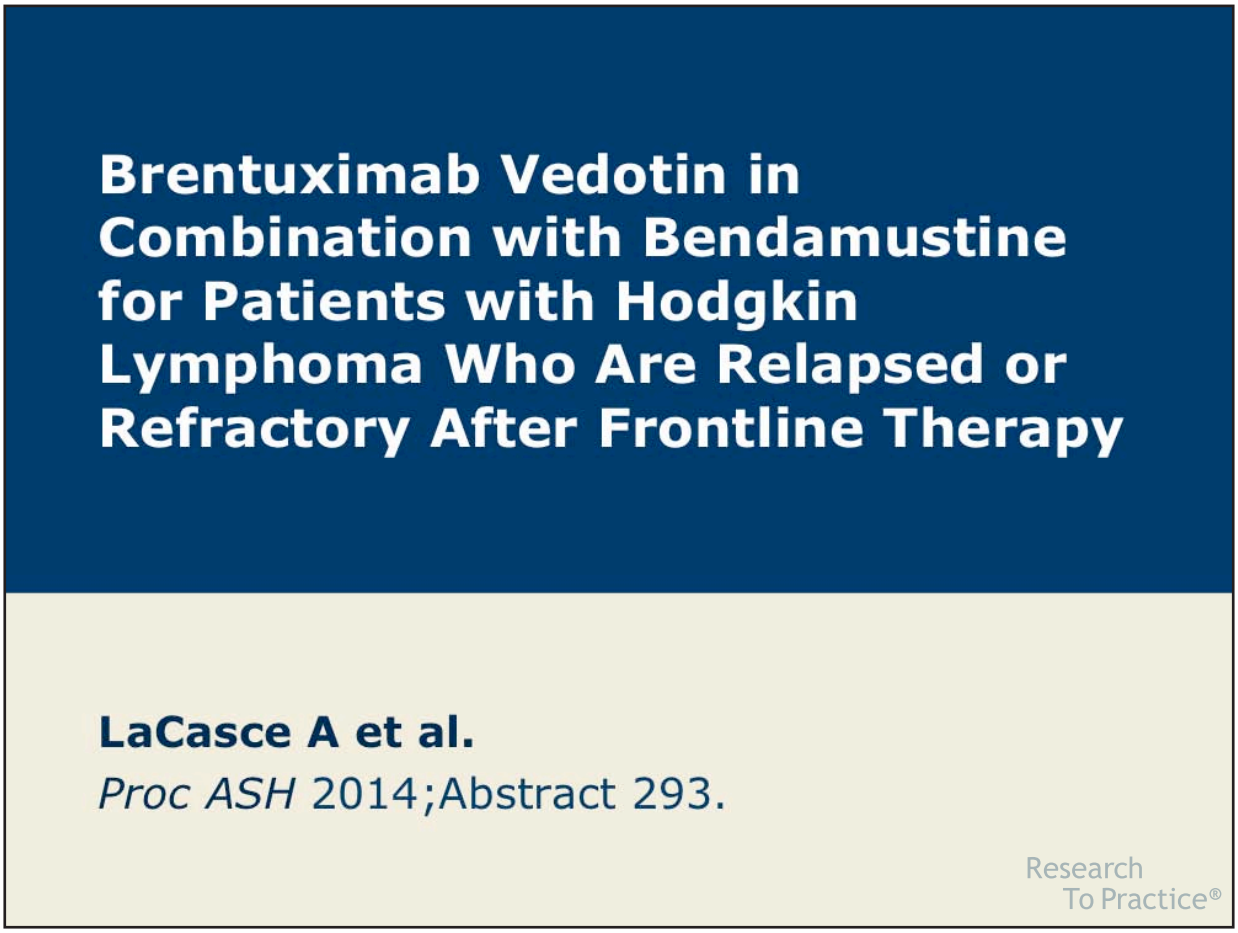
Brentuximab Vedotin in Combination with Bendamustine for Patients with Relapsed/Refractory Hodgkin Lymphoma After Front-Line Therapy

Presentation discussed in this issue

LaCasce A et al. **Brentuximab vedotin in combination with bendamustine for patients with Hodgkin lymphoma who are relapsed or refractory after frontline therapy.** *Proc ASH* 2014;**Abstract 293**.

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



Background

- Salvage chemotherapy with or without autologous stem cell transplant (ASCT) is the standard of care for patients with relapsed/refractory Hodgkin lymphoma (HL) after front-line therapy.
- Patients who achieve complete remission on salvage chemotherapy regimens prior to ASCT have improved outcomes, although the regimens are associated with significant toxicities.
- Brentuximab vedotin (B-vedotin)[1] and bendamustine[2] are highly active with manageable safety profiles as single agents for patients with HL who experience relapse after ASCT ([1] *JCO* 2012;30:2183-9; [2] *JCO* 2013;31:456-60).
- **Study objective**: Evaluate the safety and efficacy of B-vedotin in combination with bendamustine in patients with HL in first relapse.

LaCasce A et al. *Proc ASH* 2014;Abstract 293.

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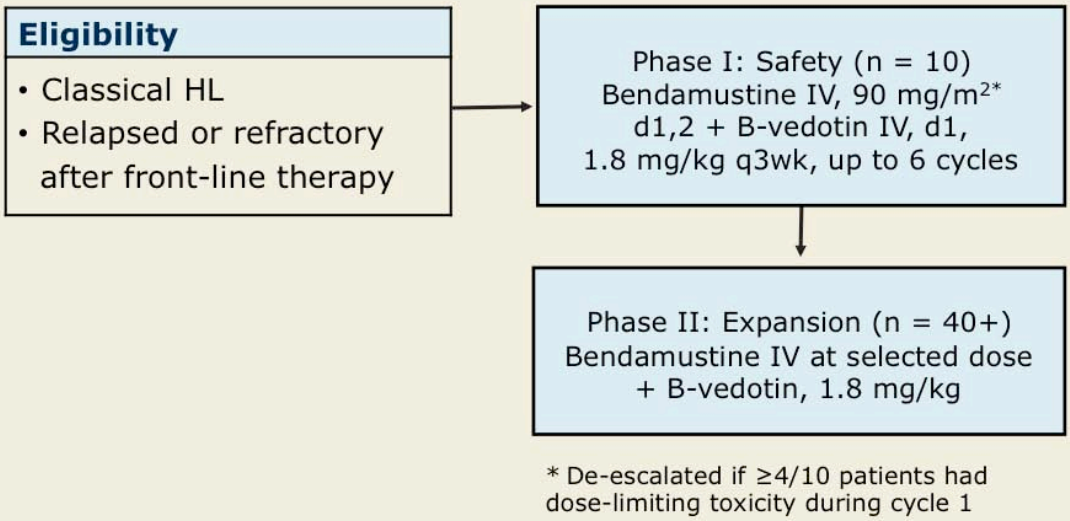
Phase I/II Study Design



* De-escalated if ≥4/10 patients had dose-limiting toxicity during cycle 1

- ASCT any time after cycle 2
- Post-transplant, B-vedotin monotherapy, up to 16 total doses

LaCasce A et al. *Proc ASH* 2014;Abstract 293.

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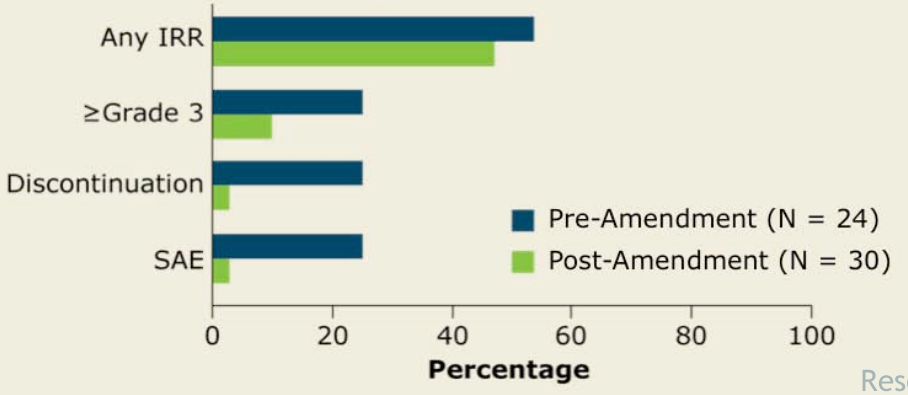
Adverse Events

- No dose-limiting toxicity in cycle 1
- Main toxicities were infusion-related reactions (IRRs) — dyspnea (15%), chills (13%) and flushing (13%); hypotension requiring vasopressor support also observed
- Delayed hypersensitivity reactions (n = 14, mostly rash) also noted
- Protocol amended to require premedication with corticosteroids and antihistamines
- Premedication decreased severity of IRRs



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Response

Best response	n = 48
Objective response rate	46 (96%)
Complete remission	40 (83%)
Partial remission	6 (13%)
Stable disease	1 (2%)

- Majority of complete remissions (34/40) achieved at Cycle 2 restage
- Stem cell mobilization and collection (n = 33)
  - Median CD34+ cell yield (cells/kg): 4.0 x 10^6 (range 1.7-11.8) in a median of 2 apheresis sessions (range 1-5)
  - Median time to platelet and neutrophil engraftment <2 weeks

LaCasce A et al. *Proc ASH* 2014;Abstract 293.

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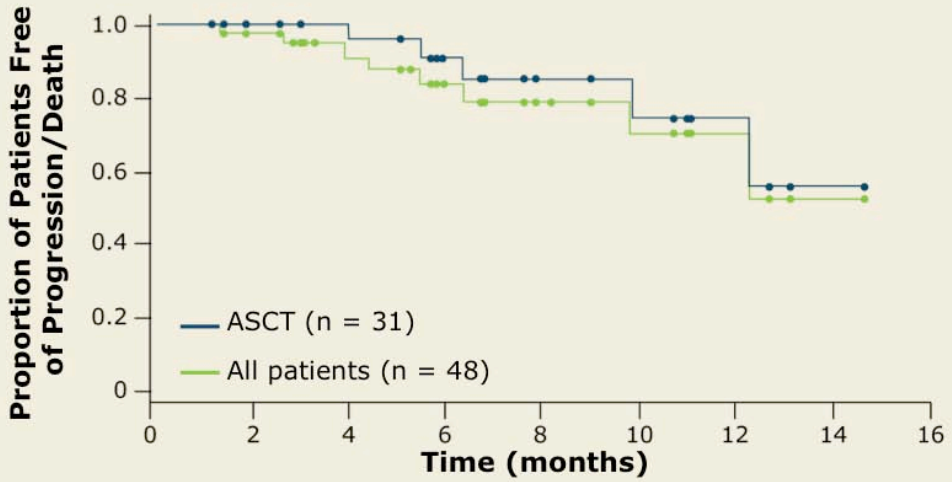
Progression-Free Survival (PFS)



- Median PFS not reached
  - 4 progressions and 1 death subsequent to ASCT (8 events overall)
- Medians are not yet estimable for response duration

With permission from LaCasce A et al. *Proc ASH* 2014;Abstract 293.

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Author Conclusions

- B-vedotin in combination with bendamustine:
  - Induced a response rate (83% complete response rate, 96% overall response rate) that compares favorably to historical data.
  - Has a manageable safety profile with premedication for IRRs.
  - Has had no adverse impact on stem cell mobilization or engraftment.
- This combination represents a promising salvage regimen for patients with HL who have relapsed/refractory disease after front-line therapy.
- Response durability continues to be assessed.

LaCasce A et al. *Proc ASH* 2014;Abstract 293.

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Investigator Commentary: B-Vedotin and Bendamustine for Relapsed/Refractory HL

Back in 2013 we published results of a Phase II evaluation of single-agent bendamustine in relapsed/refractory HL. This study by LaCasce and colleagues is an interesting one that investigated the combination of bendamustine and B-vedotin for relapsed/refractory disease.

The results of this study demonstrated a high overall response rate and complete remission rate with the combination of bendamustine and B-vedotin. Many patients who achieved a complete response after the first staging went to transplant. The number of stem cells collected was modest and lower than normal. I like the treatment, but I was not impressed by the PFS curves. At a short follow-up, the curves look fairly similar to the curves we observed in the AETHERA trial (ASH 2014;Abstract 673) investigating B-vedotin for patients at risk of relapse or disease progression after ASCT.

The combination of bendamustine and B-vedotin caused a high frequency of IRRs. Though unusual, IRRs are known to occur with bendamustine, and they may also occur with B-vedotin. However, after the protocol was amended to include corticosteroid premedication the side effects with the combination were much more manageable.

Interview with Craig Moskowitz, MD, January 6, 2015