



**POST-ASH** Issue 6, 2014

# **FDG-PET-Adapted Sequential Therapy with Brentuximab Vedotin and Augmented ICE Followed by ASCT for Relapsed/Refractory HL**

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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 targeted therapies for Hodgkin lymphoma 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

- Evaluate the benefits and risks of brentuximab vedotin after long-term follow-up of patients with relapsed or refractory Hodgkin lymphoma.
- Assess the efficacy and safety of brentuximab vedotin in investigational settings, such as for elderly and pediatric patients with Hodgkin lymphoma or as salvage therapy prior to stem cell transplant.
- Appraise recent clinical trial data on the use of panobinostat in combination with chemotherapy for relapsed or refractory Hodgkin lymphoma.
- Recall the clinical features, treatment, survival outcomes and prognosis of gray zone lymphoma.

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**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:

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Advisory Committee and Contracted Research: Celgene Corporation, Millennium: The Takeda Oncology Company, Seattle Genetics.

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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: March 2014

Expiration date: March 2015

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

One of the best ways to allow experienced clinical investigators to illustrate their perspectives on the translation of research to clinical care is to ask them to present and discuss patients from their practices, and this month in Miami and New York we will do just that by hosting daylong CME symposia structured around 32 cases managed by 10 invited researchers ([Join us! Click here](#)). In reviewing the first faculty slide set submitted for the Miami meeting by Dr Craig Moskowitz, I was immediately drawn to his selection of a case of a 72-year-old woman with classical Hodgkin lymphoma (cHL) who had significant comorbidities requiring a plethora of medications. The dilemma of this important cHL subset — which is estimated to comprise up to 35% of cHL patients — is that the natural history of the disease seems somewhat more aggressive, yet poor health and reduced baseline renal function often mean that even modified chemotherapy regimens may not be delivered at close to full doses.

Dr Moskowitz includes in his talk a slide illustrating the design of a single-arm Phase II trial in older patients evaluating the antibody-drug conjugate brentuximab vedotin (bv) followed by scaled back chemotherapy (AVD [doxorubicin/vinblastine/dacarbazine]) and then bv consolidation. This is not the first time we have heard about this intriguing study, as last summer at our lymphoma think tank Dr Andrew Evens presented an 87-year-old woman who had entered the trial but unfortunately had major problems with the chemotherapy during the first cycle, including sepsis and congestive heart failure.

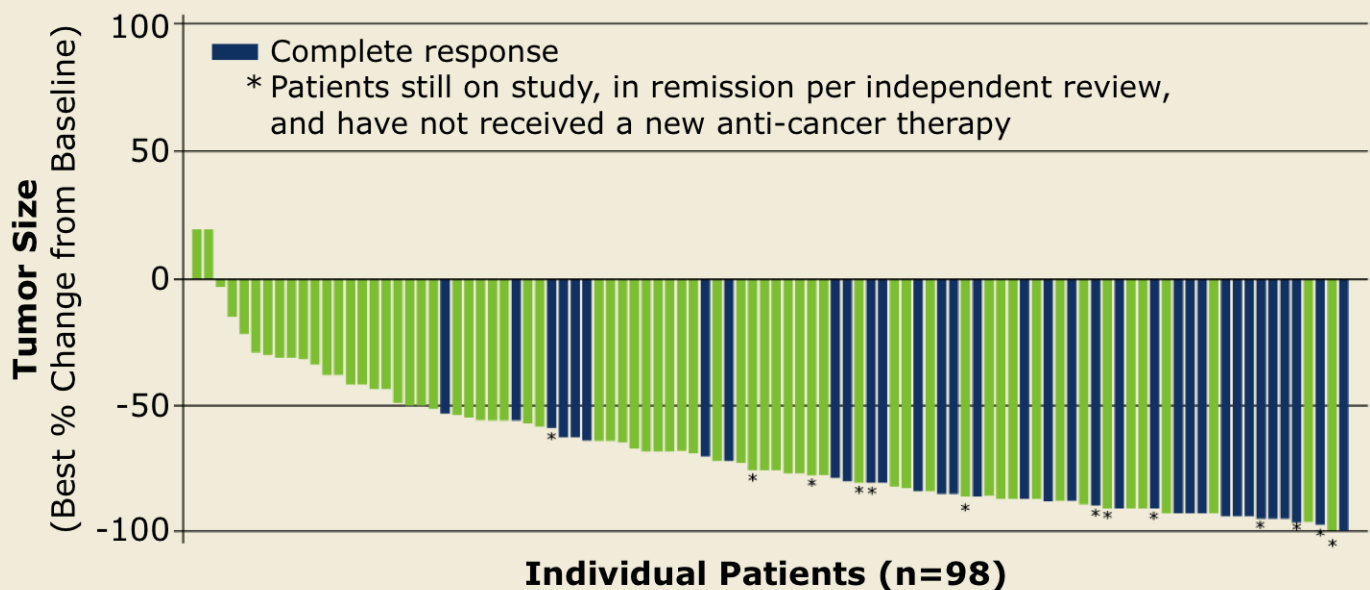
For precisely this reason many clinicians have for some time expressed great interest in taking things even further and eliminating chemotherapy altogether for the “frail elderly” population, and at ASH we got a first glimpse that this in fact may be quite possible. Specifically, preliminary data were presented from 11 of the projected 50 patients aged 60 and older enrolled on [an ongoing Phase II study](#) of bv up front. The results were impressive, as 7 patients achieved a complete response (CR) and 2 had a partial response. Among these, the 2 that got my attention were a 92-year-old woman with Stage IV disease and PS 1 and an 88-year-old man with Stage II disease and PS 2, both of whom had CRs. It is worth noting that the durability of these responses in this very early data set has not yet been established, and it could be, as is being tested in the trial discussed at the think tank, that integration of some form of chemotherapy will be optimal.

The challenge of the frail elderly patient permeates all corners of oncology, and oncologists frequently inquire about the potential up front role of agents like T-DM1 in HER2-positive breast cancer or ibrutinib in CLL and mantle-cell lymphoma as less toxic alternatives when even “gentle” forms of chemotherapy like paclitaxel and bendamustine pose a significant risk. I will be curious to find out in Miami what happened with Dr Moskowitz’s 72-year-old patient and to hear his thoughts and those of the other faculty members on how this compelling issue plays out in their practices as well as their perspectives on new HL data sets presented in New Orleans, including those profiled below:

- **More follow-up of bv in relapsed/refractory (RR) HL**

The **3-year update** from the pivotal Phase II study revealed a median overall survival of 40.5 months with 14 of the 76 patients who had objective responses still in remission, suggesting that a fraction of these patients may be cured. Perhaps even more impressive, the waterfall plot (see below) illustrates that all but 2 of the 98 patients experienced decreases in tumor size, and 34 patients (35%) achieved CR.

## Responses in a Phase II Trial of Brentuximab Vedotin in Relapsed/Refractory Hodgkin Lymphoma



- Patients received a median of 9 cycles (range, 1–16) of B-vedotin
- Those who achieved an objective response received more cycles of therapy

With permission from Gopal AK et al. *Proc ASH* 2013;Abstract 4382.

On the flip side of the coin, while bv is generally better tolerated than conventional chemotherapy, toxicities are a reality, and almost half of the patients in this study experienced some form of neuropathy (only 9% being Grade 3 or 4). In a related matter, an interesting ASH poster described **8 cases of pancreatitis** in patients receiving bv, including 2 who died of that complication. Although this rare but

concerning side effect has been reported with other tubulin drugs, it is of interest that CD30 is present on normal pancreatic cells, but it is not clear if this is of clinical significance with regard to this phenomenon. Regardless, many investigators caution that a baseline serum amylase and lipase should be obtained and that abdominal discomfort be investigated thoroughly.

In New Orleans we were also treated to [a fascinating report](#) from Memorial Sloan-Kettering on the use of bv prior to autotransplant. This Phase II study demonstrated that in 11 of 42 patients (26%), bv resulted in FDG PET-negative scans, allowing patients to proceed to transplant without more chemotherapy. This appealing strategy seems likely to be considered for nonprotocol therapy in the future. Finally, [a Phase I/II study](#) reported encouraging response and tolerability findings using bv in 16 pediatric patients with HL.

- **Phase I study of panobinostat combined with ICE (ifosfamide/carboplatin/etoposide) in RR cHL**

The subject of novel agents in HL was addressed at ASH in [a brilliant review lecture by Dr Anas Younes](#). In addition to other monoclonal antibodies and antibody-drug conjugates, he highlighted histone deacetylase inhibitors and agents targeting the PI3 kinase pathways as ones to look out for. In that regard, in New Orleans we saw [data from a Phase I study](#) evaluating panobinostat combined with ICE. The regimen resulted in CR in 15 of 21 (71%) patients, and all were able to have stem cells harvested successfully, with 17 responding patients going on to autotransplant without additional treatment except mobilization chemotherapy. Toxicity was considered “acceptable” and included fatigue, GI complaints and myelosuppression, but of course Phase III testing will be needed to determine the potential additional benefit of this regimen.

- **Gray zone lymphoma case series**

Dr Evens and colleagues [reported a retrospective analysis](#) of 96 patients diagnosed with this difficult-to-classify B-cell lymphoma that commonly has features intermediate between primary mediastinal diffuse large B-cell lymphoma (DLBCL) and cHL. This important paper identified a subset of these patients who present without mediastinal involvement and have distinct characteristics. Patients in this series received various forms of chemotherapy and, in most cases, rituximab, and overall the outcomes seem less favorable than with either DLBCL or cHL. At a median follow-up of 25 months, 2-year progression-free survival is 41% and overall survival is 84%, suggesting that much more research is needed to optimize the care of these patients.

- **Reduced-intensity conditioning for allotransplant for RR HL in the “bv era”**

Allotransplant is thought to have the potential to eradicate HL via a graft-versus-host effect, and [this retrospective report](#) of 27 patients suggested better outcomes among patients who had received prior bv. The findings, while preliminary, appear to have renewed interest in allotransplant for HL.

Next, on the final issue of our ASH review series, we visit perhaps the most exciting corner of the field — chimeric antigen receptor T-cell therapy, as discussed by an investigator in the middle of it all, Dr David Porter.

Neil Love, MD

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Miami, Florida

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# **FDG-PET-Adapted Sequential Therapy with Brentuximab Vedotin and Augmented ICE Followed by ASCT for Relapsed/Refractory HL**

## **Presentation discussed in this issue**

Moskowitz A et al. **FDG-PET adapted sequential therapy with brentuximab vedotin and augmented ICE followed by autologous cell transplant for relapsed and refractory Hodgkin lymphoma.** *Proc ASH 2013*; **Abstract 2099**.

**Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Craig Moskowitz, MD (7/17/13)**

## **FDG-PET Adapted Sequential Therapy with Brentuximab Vedotin and Augmented ICE Followed by Autologous Stem Cell Transplant for Relapsed and Refractory Hodgkin Lymphoma**

**Moskowitz A et al.**

*Proc ASH 2013*; Abstract 2099.

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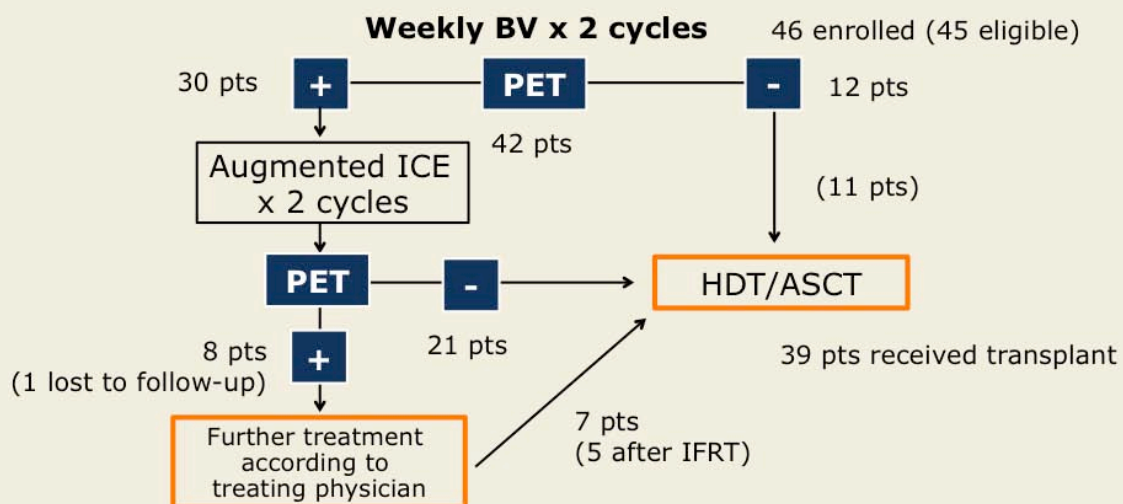
# Background

- Pretransplant  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) normalization is the strongest predictor of outcome after autologous stem cell transplant (ASCT) for patients with relapsed or refractory Hodgkin lymphoma (HL) (*Blood* 2010;116:4934).
- Brentuximab vedotin (BV) has demonstrated high efficacy in patients for whom ASCT has failed.
- **Study objective:** To determine whether BV can replace ICE (ifosfamide/carboplatin/ etoposide) salvage therapy, increase the rate of PET normalization and enhance referral to ASCT among patients with HL after the failure of front-line therapy.

Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.

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## Phase II Trial Design



HDT = high-dose therapy; IFRT = involved-field radiation therapy

- Disease status before ASCT:
  - Deauville 2, 34 patients (2 after IFRT)
  - Partial response after IFRT, 3 patients
  - Deauville 3, 2 patients

Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.

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## Patient Characteristics

Characteristic	N = 42
Median age (range)	31 years (13-65)
Initial disease stage	
I	2%
II	48%
III	21%
IV	29%
Stage at enrollment	
II	45%
III	14%
IV	40%
Relapse after initial Tx: >1 year/≤1 year	17%/33%
Primary refractory disease	50%
Extranodal disease	43%
Presence of B symptoms	31%

Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.

## Transplant Characteristics

Stem cell collection	Median (range), million/kg
BV alone	6.28 (2.96-13.29)
BV → augmented ICE	9.41 (4.56-31.43)

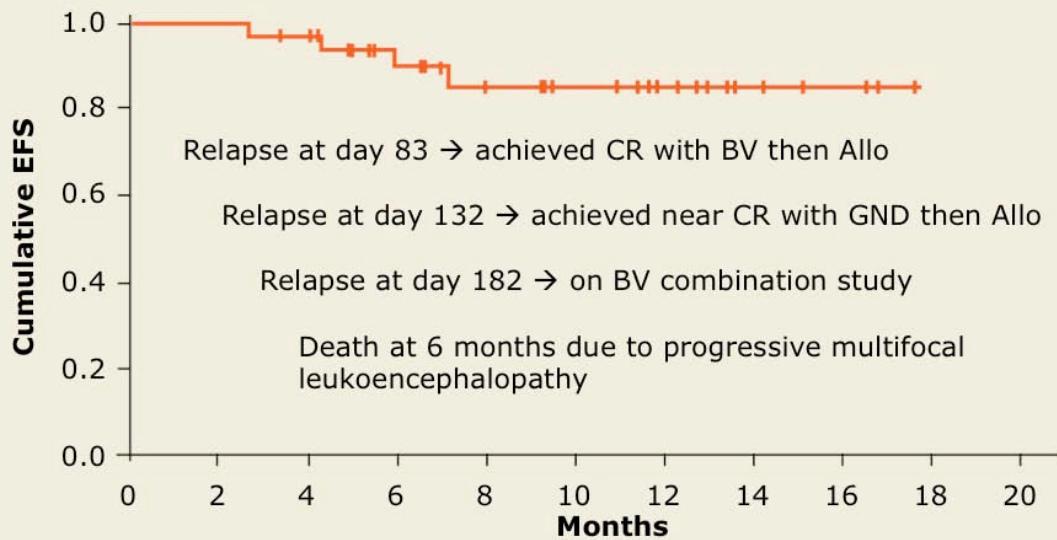
Conditioning regimen	N = 39
Hyperfractionated IFRT → CBV or BEAM	3
Hyperfractionated IFRT → TLI/CV	7
IFRT → CBV or BEAM	5
CBV or BEAM	24

C = cyclophosphamide; B = carmustine; V = etoposide; BEAM = carmustine/etoposide/cytarabine/melphalan; TLI = total lymphoid irradiation

Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.

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## Event-Free Survival (EFS)



Median follow-up from transplant: 10 months

- CR = complete response; Allo = allogeneic stem cell transplant; GND = gemcitabine/vinorelbine/doxorubicin

With permission from Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.

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## Select Salvage-Related Adverse Events (AEs) (N = 42)

BV-related AEs	Grade 1	Grade 2	Grade 3
Neuropathy	40%	14%	0%
Rash	55%	14%	2%

Augmented ICE-related serious AEs	Grade 3 or 4
Febrile neutropenia	43%
Vomiting	2%
Bone pain	2%
Sepsis	2%
Anemia	2%
Thrombocytopenia	2%
Anorectal infection	2%

Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.



## Transplant-Related Morbidity (N = 39)

Early	No. of patients	Status
Pneumonitis	3	Resolved
Neuropathy (Grade 3)	1	Ongoing
Acute kidney injury	1	Resolved
Late	No. of patients	Status
Pneumonitis	1	Resolved
Esophagitis	1	Underwent dilatation
Chronic renal failure	1	Ongoing
PML	1	Death

PML = progressive multifocal leukoencephalopathy

Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.

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## Author Conclusions

- PET-adapted sequential salvage therapy with BV with or without augmented ICE:
  - Produces high rates of PET normalization
    - 79% Deauville 2, 83% Deauville 2 or 3
  - Facilitates referral to ASCT for virtually all patients
    - 93% of evaluable patients have undergone transplant
  - Is associated with manageable toxicity and adequate stem cell collection
- With short (median 10 months) follow-up, 92% of patients who underwent transplant are progression free.
- This treatment strategy is a reasonable approach for transplant-eligible patients with relapsed/refractory HL and provides a platform for testing novel BV combinations.

Moskowitz A et al. *Proc ASH* 2013;Abstract 2099.

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### **Investigator Commentary: FDG-PET-Adapted Sequential Treatment with BV and Augmented ICE → ASCT in Relapsed/Refractory HL**

BV is the best drug I've ever seen in HL, and I would say that most experts would agree. Currently, single-agent BV is not approved for patients after first relapse. In this study, we administered BV on a weekly basis as opposed to the label dose, which is every 3 weeks. Patients received weekly BV on a 3 weeks on, 1 week off schedule for 2 cycles, followed by a repeat PET scan. This is novel because if the PET scans were negative, patients did not receive any salvage chemotherapy. Stem cells were collected from the patients before they underwent transplant. This study attempts to reduce treatment prior to stem cell transplant (SCT). Preliminary data that we presented at Lugano showed that the sequential treatment was remarkable — about 80% of patients were in remission at the time of transplant (*Proc ICML 2013*; Abstract 141).

There are a variety of reasons for this approach. I'm convinced that salvage chemotherapy causes infertility and many other problems that we observe. Changing the management of advanced HL with a novel drug is unique. Although the cost of BV is an issue, if BV has the capacity to markedly improve clinical outcome, cost will no longer be an issue.

**(Continued)**

The sequential treatment has been remarkable, with little toxicity other than the typical rash. It's unusual for the peripheral neuropathy associated with BV to be more intense than Grade 1, and in my experience it is usually reversible. Also, BV is associated with PML, which has been observed with almost all antibody-based treatments. I am not convinced that PML is causally related because the patients who develop PML have usually received a considerable amount of previous treatment. However, if patients experienced PML in the early-stage setting, that would pose a major problem for BV. Some recent evidence suggests that BV induces pancreatitis, a toxicity reported with other microtubule inhibitors.

In my practice I use BV according to its label. I administer BV to patients who are transplant ineligible and in cases of post-transplant failure.

***Interview with Craig Moskowitz, MD, July 17, 2013***