5 Minute JournalClub

POST-ASH Issue 6, 2014

Ongoing Phase II Study of Brentuximab Vedotin in Relapsed/Refractory HL: 3-Year Follow-Up and Characterization of Long-Term Remissions

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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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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

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POST-ASH Issue 6, 2014

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.

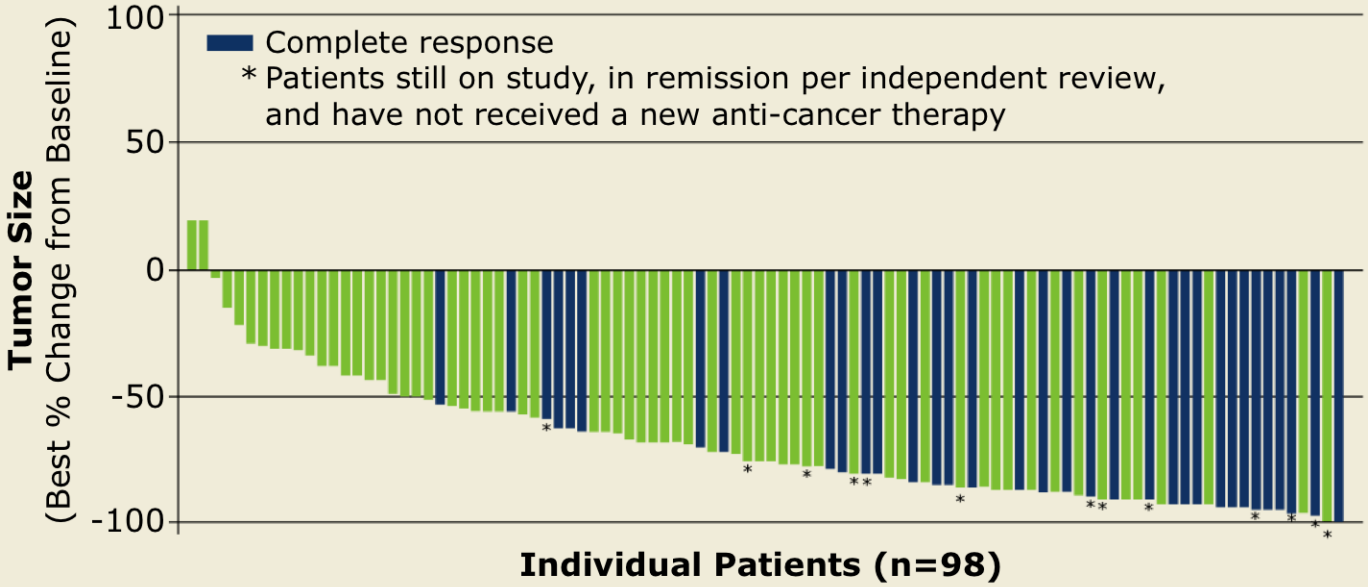
For precisely this reason many clinicians have for some time expressed great interest in taking things even further and eliminating chemotherapy altogether for the "frail elderly" population, and at ASH we got a first glimpse that this in fact may be quite possible. Specifically, preliminary data were 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.

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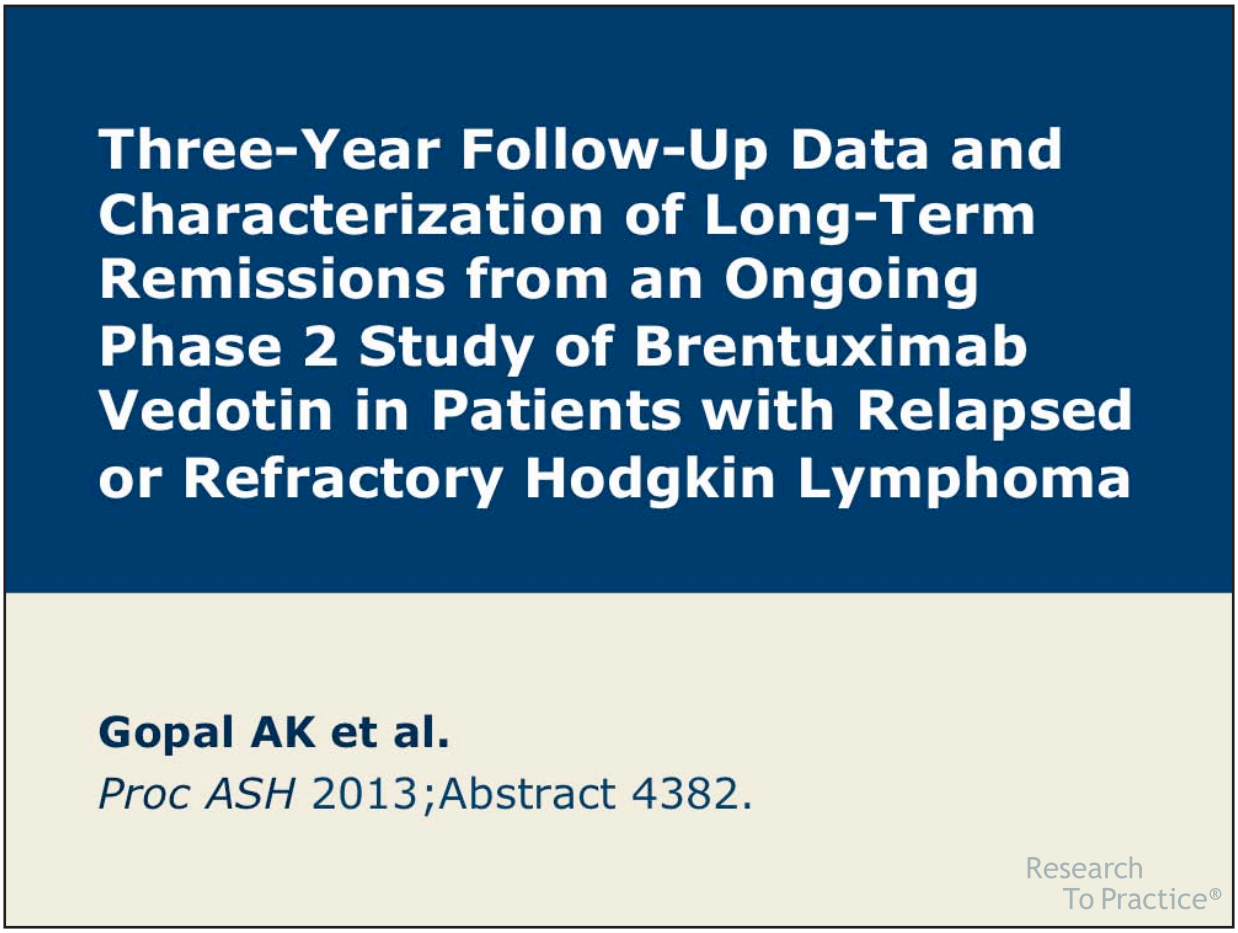
Ongoing Phase II Study of Brentuximab Vedotin in Relapsed/ Refractory HL: 3-Year Follow-Up and Characterization of Long-Term Remissions

Presentation discussed in this issue

Gopal AK et al. **Three-year follow-up data and characterization of long-term remissions from an ongoing Phase 2 study of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma.** *Proc ASH* 2013;**Abstract 4382**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with Christopher Flowers, MD, MS (2/24/14)



Background

- The standard treatment for patients with relapsed or refractory Hodgkin lymphoma (HL) is salvage chemotherapy followed by autologous stem cell transplant (auto-SCT).
- However, approximately 50% of patients experience relapse of HL after auto-SCT, and this population represents a pronounced unmet need.
- A pivotal Phase II study demonstrated an overall response rate of 75% with complete remission (CR) in 34% of patients with relapsed/refractory HL treated with brentuximab vedotin (B-vedotin) after auto-SCT (*JCO* 2012;30:2183-9).
- **Study objective:** To present 3-year follow-up data from this Phase II study on the efficacy and safety of B-vedotin for relapsed or refractory HL.

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

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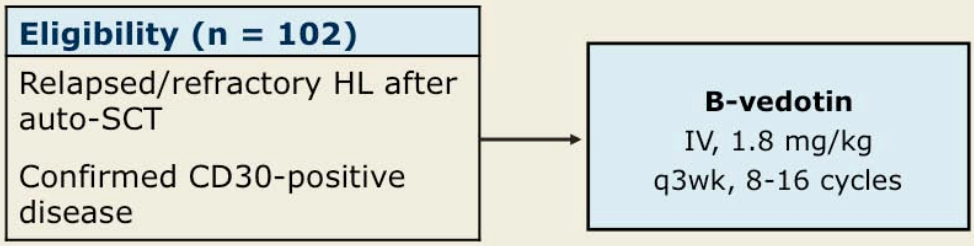
Ongoing Phase II Study Design

NCT00848926



Primary endpoint: Objective response rate per independent review facility

Secondary endpoints include: CR rate, progression-free survival (PFS), overall survival and safety.

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

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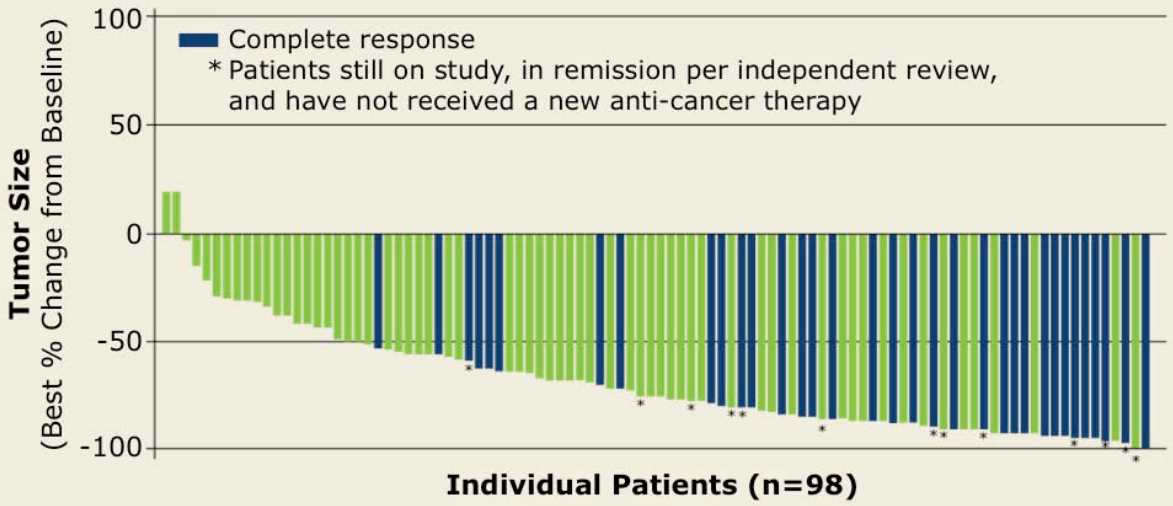
Response by Central Independent Review



- Patients received a median of 9 cycles (range, 1–16) of B-vedotin
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With permission from Gopal AK et al. *Proc ASH* 2013;Abstract 4382.

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Survival Outcomes

- The median overall survival was 40.5 months.
- The estimated 3-year survival rate was 54%.
- At a median of 32.7 months since first dose of B-vedotin, 51 of 102 patients (50%) were alive at the time of last follow-up.
- The median PFS by central independent review was 5.6 months.
  - 76 patients achieved CR/partial response: median PFS = 9 months
  - 26 patients experienced stable/progressive disease: median PFS = 2.8 months

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

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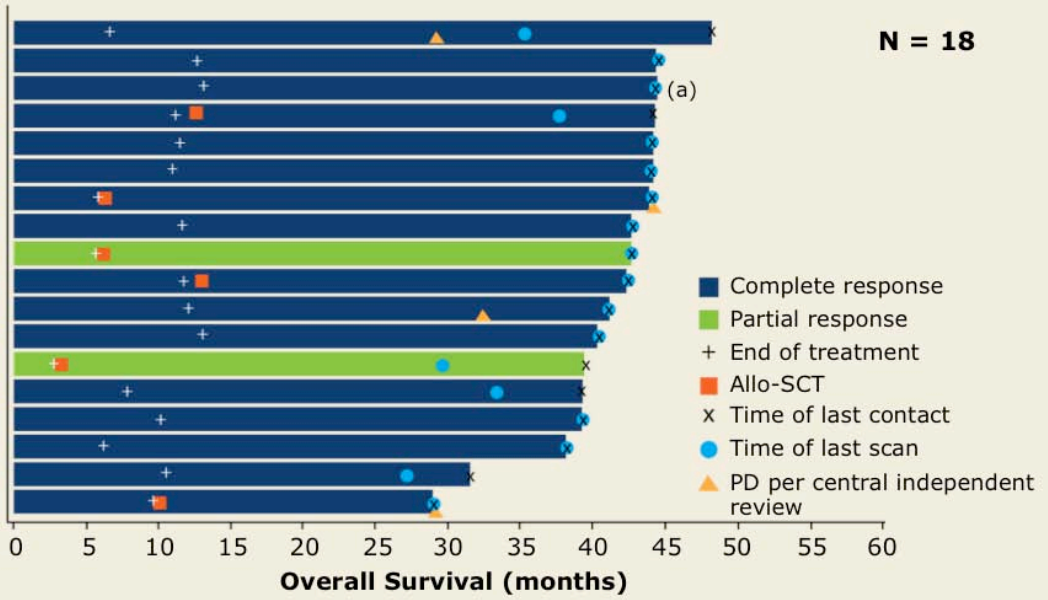
Characterization of Long-Term Remissions by Central Independent Review

Characteristic	Still in remission and on study (N = 14)	With objective response but no longer in remission* (N= 62)	Non-responders (N = 26)
Demographics and baseline disease characteristics			
Median age (range)	26.5 (15-54)	32.0 (18-77)	35.0 (18-70)
Median number prior therapies (range)	2.5 (2-7)	3.0 (1-13)	4.0 (2-8)
Median time (mo) from auto-SCT to relapse (range)	7.8 (2-33)	7.3 (1-131)	5.2 (0-41)
Median PFS (wk) from last prior therapy	25.1	27.7	21.1
Exposure and safety information			
Median number of cycles (range)	13.5 (4-16)	9.5 (3-16)	7.0 (1-16)
Patients with Grade ≥3 AEs, n (%)	9 (64)	32 (52)	15 (58)
Patients with AE of peripheral neuropathy, n (%)	9 (64)	36 (58)	11 (42)

* Includes patients still on study for survival follow-up who have experienced disease progression or initiation of new therapy and patients who have discontinued study treatment for reasons including death, loss to follow-up, withdrawal of consent and physician decision

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

Long-Term Remissions by Investigator Review



[a] Allo-SCT information unknown

• 18 patients who remain in remission are being followed on study

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Select Adverse Events (≥20%)

Adverse event	All grades	Grade 3/4
Peripheral sensory neuropathy	47%	9%
Fatigue	46%	2%
Nausea	42%	—
Upper respiratory tract infection	37%	—
Diarrhea	36%	1%
Pyrexia	29%	2%
Neutropenia	22%	20%

Other Grade 3/4 events in ≥5% of patients: thrombocytopenia (8%) and anemia (6%)

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

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Author Conclusions

- After a median observation time of approximately 3 years from the first dose of B-vedotin, 50% of patients with relapsed or refractory HL were alive at the time of last follow-up.
  - Median overall survival was 40.5 months.
- Eighteen patients remain in remission per investigator review, and 14 of these patients remain in remission per central independent review.
  - This provides an early suggestion that a fraction of these patients may be cured.
- A randomized Phase III study is being conducted to evaluate B-vedotin in combination with AVD versus ABVD (doxorubicin, bleomycin, vinblastine and dacarbazine) for front-line treatment of advanced classical HL (NCT01712490).

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

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Investigator Commentary: Ongoing Phase II Study of B-Vedotin in Relapsed/Refractory HL — 3-Year Follow-Up and Characterization of Long-Term Remissions

This was a 3-year follow-up study of the pivotal trial of B-vedotin in patients with relapsed/refractory HL after an auto-SCT. The study reported a high overall response rate of 75%. Half of the patients were alive with a median overall survival of 40.5 months. This suggests that for patients who experience a response to B-vedotin after failure of auto-SCT, the responses are durable.

The standard approach for patients with relapsed/refractory HL is salvage chemotherapy followed by stem cell transplant. B-vedotin is usually administered after auto-SCT and is a good option for these patients.

In terms of the side effects of B-vedotin, neurologic toxicity is one that all physicians should be aware of. Pneumonitis is of particular concern for patients with HL because they may have received other agents like bleomycin that can cause overlapping toxicity. B-vedotin has also been associated with pancreatitis, and dermatologic problems may occur occasionally.

Interview with Christopher Flowers, MD, MS, February 24, 2014