5 Minute JournalClub

Key ASH Presentations
Issue 4, 2011

Brentuximab in Relapsed/Refractory Hodgkin Lymphoma

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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 from a plethora of ongoing clinical trials 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 and other cancer clinicians in the formulation of optimal clinical management strategies for hematologic cancer.

LEARNING OBJECTIVE

- Describe the mechanism of action, activity and safety of brentuximab vedotin in the setting of relapsed or refractory Hodgkin lymphoma.

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Consulting Agreements: Allos Therapeutics, Celgene Corporation, Millennium, The Takeda Oncology Company; Paid Research: Allos Therapeutics, Genzyme Corporation.

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This program is supported by educational grants from Allos Therapeutics, Celgene Corporation, Millennium, The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc and Seattle Genetics.

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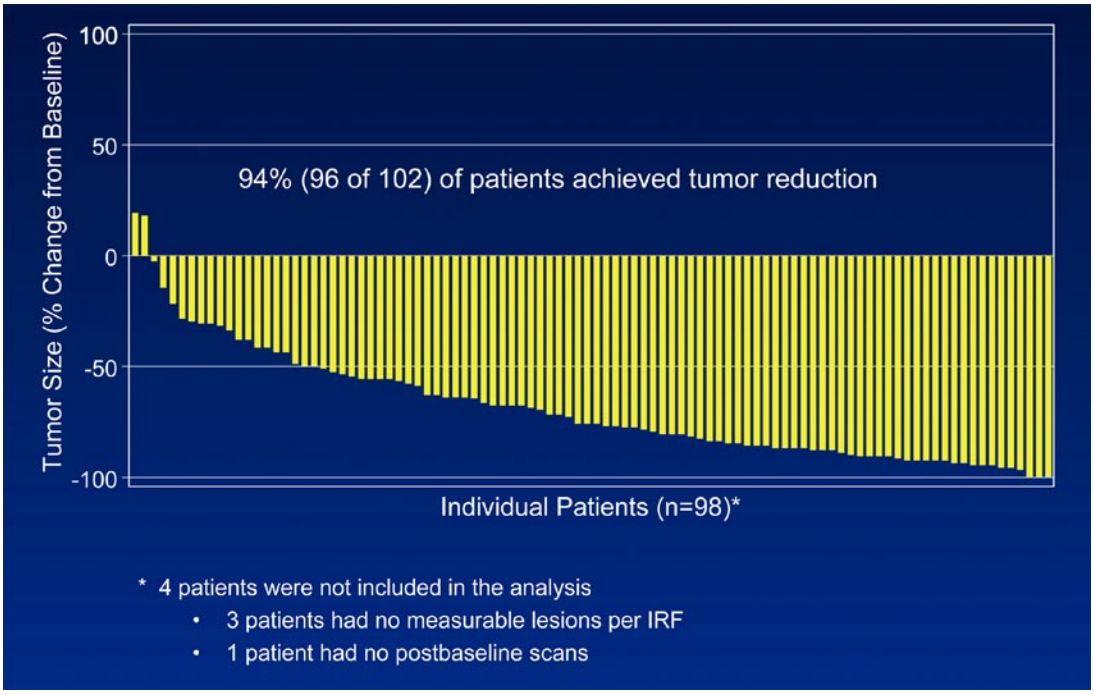
Click here for papers on Hodgkin lymphoma.

When one queries lymphoma investigators about the key data sets from the December ASH meeting, at the top of almost every list is a stunning **report** in which 102 patients with Hodgkin lymphoma (HL) and disease progression after a median of 3.5 prior chemotherapy treatments and an autologous stem cell transplant were treated with brentuximab vedotin. "B vedotin" is an immune conjugate, with an antibody against CD30 hooked to an antitubulin agent (monomethyl auristatin E) that is similar to vinblastine.

Like the trastuzumab/maytansine conjugate T-DM1 in breast cancer, B vedotin is thought to deliver the cytotoxic to or into the tumor cell, but the exact mechanism of antitumor effect has yet to be defined. Of great interest, unlike its breast cancer cousin, the naked antibody in B vedotin is not active in heavily pretreated HL.

In this pivotal Phase II, single-arm trial, more than 90 percent of patients had tumor responses (check out the waterfall plot), with 34 percent complete and 40 percent partial remissions. The agent was well tolerated with apparently reversible peripheral neuropathy identified as the only important toxicity. It should come as no surprise that this fascinating agent is quickly tracking through the FDA and being incorporated into ongoing and emerging clinical trials, including as consolidation after transplant and up front with ABVD.



Three other ASH presentations on HL are also profiled in our slide sets:

1. The long-awaited **Phase III ECOG/Intergroup trial** in locally extensive or bulky advanced HL randomizing between ABVD and Stanford V.

Many were disappointed to see that there was no major efficacy difference between the two arms, and in the US, ABVD remains the standard. In this trial, only patients with bulky mediastinal disease received radiation therapy with ABVD as opposed to essentially a multimodality approach with Stanford V.

2. **A German study** evaluating PET scanning in patients with advanced-stage HL and a residual mass on CAT scan greater than 2.5 cm after BEACOPP.

Ninety-two percent of patients with negative PETs were disease-free at three years without radiation therapy. Whether this can be extrapolated to ABVD is being debated.

3. **An Italian study** of interim PET scanning after two cycles of ABVD in patients with both early and advanced disease.

Patients with PET positivity did poorly and should be considered for immediate referral to a tertiary center for clinical trial consideration.

It is worth remembering that while most of the 8,000 patients diagnosed with HL annually in the US are cured, approximately 1,500 (mostly those presenting with advanced disease) are not. Fortunately, for the first time maybe ever there are a number of promising agents in development, including B vedotin, lenalidomide, panobinostat and everolimus, offering new hope that some of these mostly younger patients can be salvaged.

Next up on ASH *5-Minute Journal Club*: Another major paper on B vedotin — this time in anaplastic large cell lymphoma — and other new data in T-cell lymphomas.

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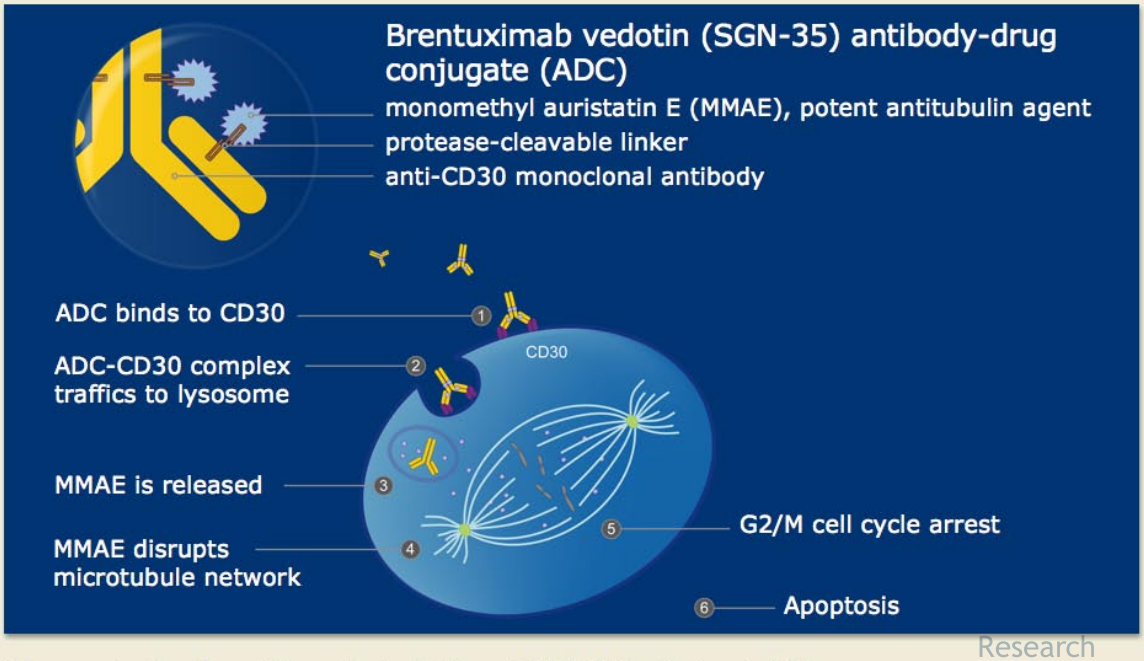
Brentuximab in Relapsed/Refractory Hodgkin Lymphoma

Presentation discussed in this issue

Chen R et al. **Results of a pivotal phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma.** *Proc ASH* 2010;**Abstract 283**.

Slides from a presentation at ASH 2010 and transcribed comments from a recent interview with Steven M Horwitz, MD (12/29/10)

Brentuximab Vedotin Mechanism of Action



With permission from Chen R et al. *Proc ASH* 2010;Abstract 283.

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Study Schema

Accrual = 102 (Closed)

Eligibility
Relapsed or refractory CD30+ Hodgkin lymphoma (HL) Post autologous stem cell transplant (ASCT)

→ Brentuximab vedotin
1.8 mg/kg
IV over 30 minutes
q 3 weeks
x up to 16 cycles

Primary Objective
Overall objective response rate (CR + PR) by independent review facility (IRF)

Secondary Objectives
Assess duration of response and progression-free survival (PFS)
Assess overall survival
Assess safety and tolerability

Chen R et al. *Proc ASH* 2010;Abstract 283.

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Patient Characteristics

Characteristic	
Age (median)	31 years
Number of prior chemotherapy regimens (median)	3.5
Primary refractory disease*	71%
Refractory to most recent salvage therapy (excluding transplant)	42%

* Failure to achieve a complete response or progression within 3 months of completing front-line therapy

Chen R et al. *Proc ASH* 2010;Abstract 283.

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Efficacy Outcomes (n = 102)

Response	IRF	Investigator
Overall response rate (ORR)	75%	72%
Complete remission	34%	33%
Partial remission	40%	38%

Secondary endpoints	IRF	Investigator
Progression-free survival	25.1 weeks	39.1 weeks
Median duration of ORR	29 weeks	47 weeks
Median duration of CR	Not reached	Not reached
Overall survival (OS)	Not reached	Not reached
Estimated 12-month OS	88%	

Chen R et al. *Proc ASH* 2010;Abstract 283.

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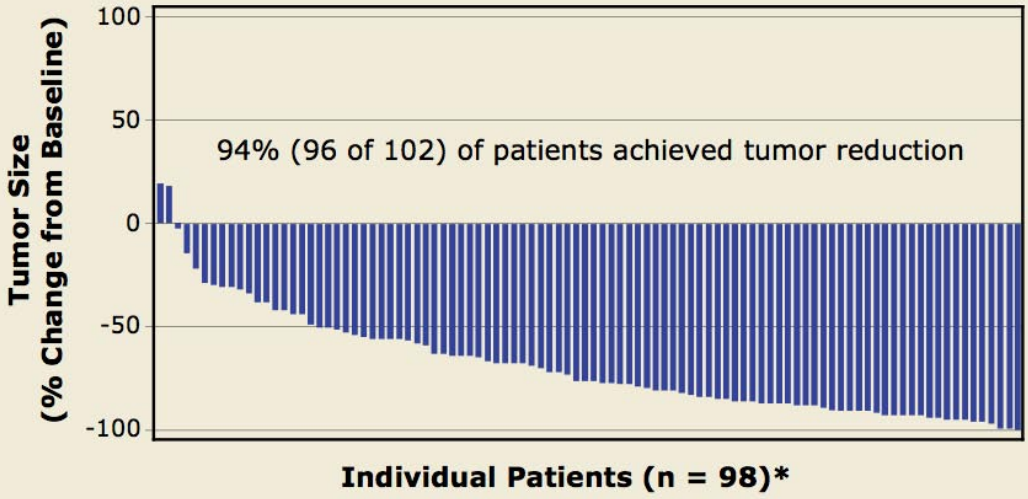
Maximum Tumor Reduction per IRF



* 4 patients were not included in the analysis
- 3 patients had no measurable lesions per IRF
- 1 patient had no postbaseline scans

With permission from Chen R et al. *Proc ASH* 2010;Abstract 283.

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Select Safety Events

Treatment-Related Adverse Events (AE)	All Grades*	Grade 3 or 4*
Peripheral sensory neuropathy	47%	8%†
Fatigue	46%	Not reported
Nausea	42%	Not reported
Diarrhea	36%	Not reported
Neutropenia	22%	20%

* All Grade AEs occurring in ≥20% of patients and Grade 3/4 AEs occurring in ≥5% of patients

† Grade 3 only

Chen R et al. *Proc ASH* 2010;Abstract 283.

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Author Conclusions

- Brentuximab vedotin is associated with encouraging activity in patients with heavily pretreated, relapsed/refractory HL.
  - ORR = 75% (median duration of response of 29 weeks by IRF)
  - CR = 34% (median duration not reached)
  - Patients achieving tumor reduction = 94%
  - Estimated 12-month OS = 88%
- Brentuximab vedotin treatment is associated with a manageable adverse-events profile.
  - Peripheral neuropathy largely reversible
- Brentuximab vedotin enables selective delivery of a potent cytotoxic agent to patients with relapsed/refractory HL.
- Ongoing Phase III AETHERA Trial is comparing brentuximab vedotin versus placebo in patients with residual Hodgkin lymphoma after ASCT (NCT01100502).

Chen R et al. *Proc ASH* 2010;Abstract 283; www.clinicaltrials.gov, January 2011.

Investigator comment on brentuximab for patients with relapsed/refractory Hodgkin lymphoma

I believe in terms of the new drugs, brentuximab caused the most excitement at ASH because these are high response rates in a study that was well done. These data are compelling, and I believe there is a good chance that the drug will be approved for relapsed/refractory Hodgkin lymphoma. I also think there will be an expanded access or compassionate use program while approval is pending.

There is also interest in moving this drug into earlier lines or even up front for poor-risk Hodgkin lymphoma. The main issue with combining it with the current up-front regimens is neuropathy, as vinca alkaloids, which are universally used up front, are also neuropathic. Hematologic toxicity, I believe, is less likely to be a problem. There could be many ways to potentially add this drug and help people with Hodgkin lymphoma.

Interview with Steven M Horwitz, MD, December 29, 2010

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