



POST-ASH Issue 6, 2014

**Gray Zone Lymphoma: A
Retrospective Multicenter Analysis
of Clinical Characteristics, Treatment,
Outcomes and Prognosis**

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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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This activity is supported by educational grants from Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Seattle Genetics and Spectrum Pharmaceuticals Inc.

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.

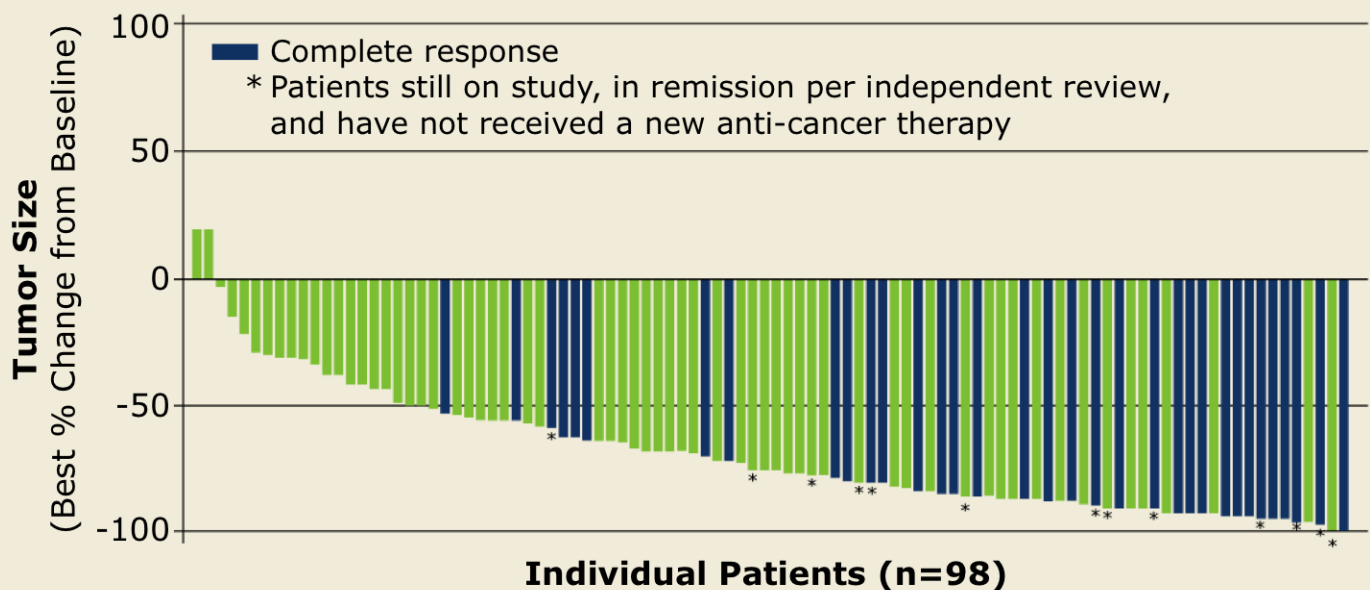
For precisely this reason many clinicians have for some time expressed great interest in taking things even further and eliminating chemotherapy altogether for the “frail elderly” population, and at ASH we got a first glimpse that this in fact may be quite possible. Specifically, preliminary data were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

Research To Practice

Miami, Florida

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Gray Zone Lymphoma: A Retrospective Multicenter Analysis of Clinical Characteristics, Treatment, Outcomes and Prognosis

Presentation discussed in this issue

Evens AM et al. **Gray zone lymphoma (GZL) with features intermediate between classical Hodgkin lymphoma (cHL) and diffuse large B-cell lymphoma (DLBCL): A large retrospective multicenter analysis of clinical characteristics, treatment, outcomes and prognosis in the current era.** *Proc ASH 2013*; **Abstract 847.**

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

Gray Zone Lymphoma (GZL) with Features Intermediate between Classical Hodgkin Lymphoma (cHL) and Diffuse Large B-Cell Lymphoma (DLBCL): A Large Retrospective Multicenter Analysis of Clinical Characteristics, Treatment, Outcomes, and Prognosis in the Current Era

Evens AM et al.

Proc ASH 2013; Abstract 847.

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Background

- GZL is recognized by the WHO as a category of B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and cHL.
- GZL is uncommon and is reported to present primarily with mediastinal involvement, with very few nonmediastinal presentations reported.
- Treatment of GZL is challenging due to disease heterogeneity, lack of data regarding prognostication and no standard guidelines for management (*Curr Hematol Malig Rep* 2012;7:241).
- **Study objective:** To conduct a large retrospective multicenter analysis of clinical characteristics, treatment, outcomes and prognosis of patients with GZL.

Evens AM et al. *Proc ASH* 2013;Abstract 847.

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Study Design

- Multicenter retrospective analysis of patients with newly diagnosed GZL treated from 2003 to 2012 at 18 North American academic centers
- Inclusion criteria included availability of clinical information and a minimum follow-up of 12 months for nonrelapsing patients
- 96 patients analyzed (100 patients identified, 4 excluded for inadequate follow-up)
- Diagnosis established by institutional expert pathology review
- Patient characteristics, treatment and outcome were examined, and prognostic factors associated with survival on univariate and multivariate Cox regression analyses were determined

Evens AM et al. *Proc ASH* 2013;Abstract 847.

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Clinical Characteristics at Diagnosis

Characteristic	(n = 96)
Median age (range)	39 y (19-86)
ECOG PS 0-1	89%
Male:female ratio	1.5:1
Stage III/IV	52%
Bulky disease (>10 cm)	23%
Mediastinal involvement	45%

- Other characteristics: Bone marrow involvement 13%, nonmarrow EN disease 48%, IPI 3-5: 23%, IPS 4-7: 13%

Evens AM et al. *Proc ASH* 2013;Abstract 847.

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Mediastinal versus Nonmediastinal GZL

Characteristic	Mediastinal (n = 43)	Nonmediastinal (n = 53)	p-value
Age, years (range)	37 (19-72)	50 (20-86)	0.0001
Male-female ratio	1.3	1.9	0.09
Bulk (>10 cm)	42%	8%	<0.0001
>1 EN site*	11%	33%	0.02
Stage III/IV	14%	83%	<0.0001
IPI 3-5	5%	32%	0.0001
IPS 4-7	2%	21%	0.004

* Most common nonmarrow sites: Mediastinal — lung n = 8; Nonmediastinal — bone n = 10, lung n = 9, liver n = 4

Evens AM et al. *Proc ASH* 2013;Abstract 847.

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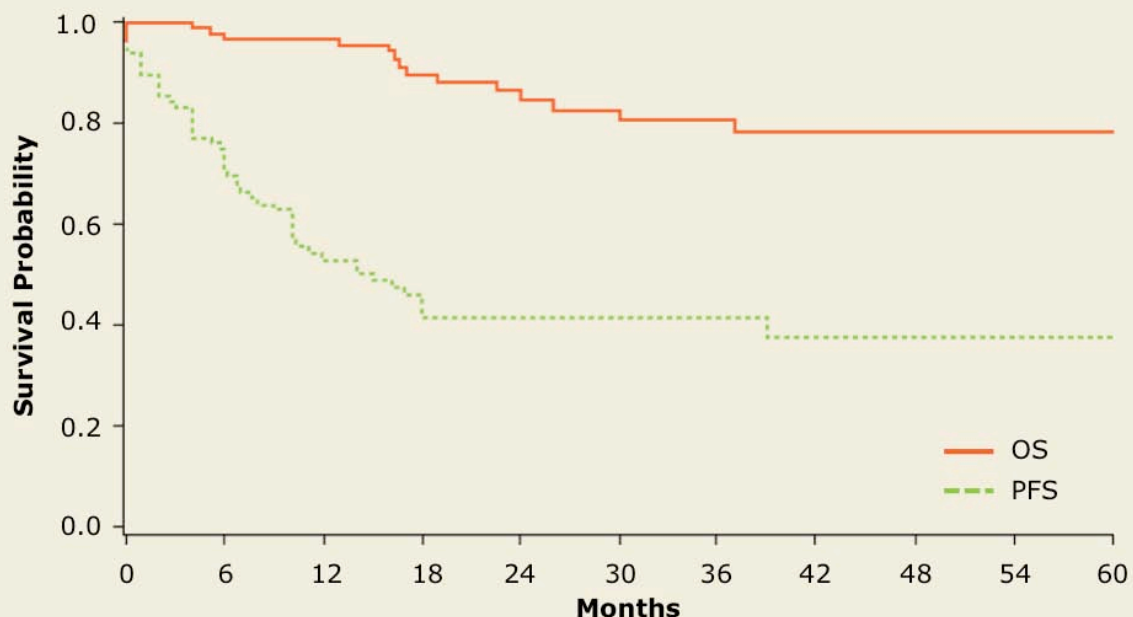
Treatment and Outcome

- First-line chemotherapy received: CHOP 58%, ABVD 26%, EPOCH 10%, BEACOPP or hyperCVAD 5%, other 1%
- Patients receiving rituximab as part of first-line therapy: 69%
- Patients receiving consolidative radiation therapy: 31%
- Overall response rate (ORR) to first-line therapy: 70% (58% complete remission [CR])
 - Mediastinal 67% (58% CR) versus nonmediastinal 71% (58% CR)
- ORR by front-line therapy: R-CHOP 71%, R-EPOCH 90%, ABVD 50%
- 2-year progression-free survival (PFS): Rituximab: yes 49% versus no 27%, $p = 0.10$
- 4-year PFS, Stage I/II: yes 52%, no 32%, $p = 0.02$
- 4-year overall survival (OS), Stage I/II: yes 97%, no 71%, $p = 0.003$

Evens AM et al. *Proc ASH* 2013;Abstract 847.

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Survival: All Patients

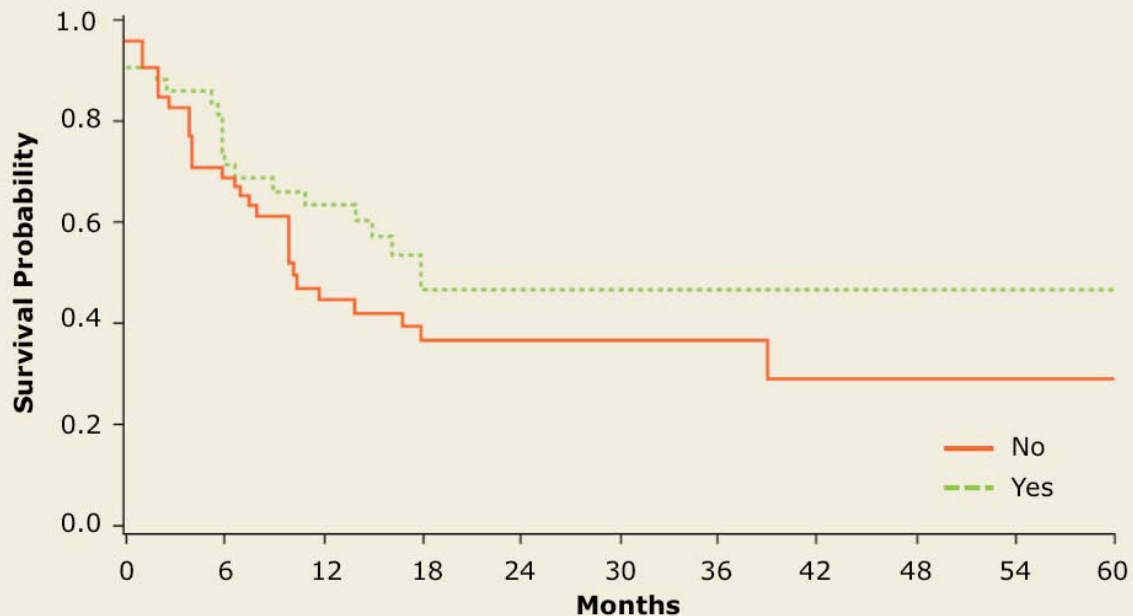


2-year PFS 41%, OS 84% (median follow-up 25 months)

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PFS Subset Analyses: Mediastinal versus Nonmediastinal



2-year PFS mediastinal: Yes 47% versus No 37%, $p = 0.27$

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Prognosis – Univariate Analysis

Characteristics (at diagnosis)	PFS		OS	
	HR	p -value	HR	p -value
Stage (III/IV vs I/II)	1.91	0.03	11.85	0.02
Stage (IV vs I-III)	2.76	0.0004	7.05	0.004
Prognostic scores	HR	p -value	HR	p -value
IPI (3-5 vs 0-2)	2.50	0.006	3.89	0.03
IPS (3-7 vs 0-2)	1.91	0.06	4.77	0.06

- Other prognostic factors evaluated for PFS: performance status (2-4 vs 0-1), HR 3.44, $p = 0.001$; hemoglobin <10.5 g/dL, HR 2.13, $p = 0.02$; elevated LDH, HR 2.03, $p = 0.025$
- Other prognostic factors evaluated for OS: hypoalbuminemia, HR 3.14, $p = 0.08$; B symptoms (yes vs no), HR 7.8, $p = 0.05$

Evens AM et al. *Proc ASH 2013*;Abstract 847.

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Prognosis – Multivariate Analysis

- On multivariate regression analysis for PFS, elevated LDH predicted poorer outcome (HR 2.01, $p = 0.05$).
- Factors significant for inferior OS:
 - Presence of B symptoms (HR 17.41, $p = 0.02$)
 - Hypoalbuminemia (HR 8.09, $p = 0.02$)
 - Stage IV versus I-III disease (HR 21.39, $p = 0.003$)

Evens AM et al. *Proc ASH* 2013;Abstract 847.

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Author Conclusions

- GZL is an important entity to recognize.
- Nonmediastinal GZL has distinct characteristics (age, bulk, EN, stage).
- PFS (all patients) appeared inferior to that expected in cHL and DLBCL, though OS was good.
- B symptoms, albumin and stage are critical prognostic factors for OS.
- Continued analysis is warranted (eg, pathology and salvage therapy).

Evens AM et al. *Proc ASH* 2013;Abstract 847.

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Investigator Commentary: GZL with Features between cHL and DLBCL – Retrospective Analysis

This study was conducted to understand the characteristics, treatment, outcomes and prognosis of patients with GZL, which is a challenging subset of lymphomas to manage. GZL are B-cell lymphomas that are not clearly classifiable as one subtype or another. They are commonly thought to have features intermediate between HL and primary mediastinal DLBCL and typically present in the mediastinum.

A key feature of this study was that a new group of GZL was identified that did not have mediastinal involvement, which was about half of the patients with GZL. A wide array of first-line chemotherapy regimens were administered to these patients. A trend toward a benefit for rituximab was seen, but a fair amount of heterogeneity among the patient characteristics and the types of regimens was also present. Hence, it's difficult to conclude that one approach was superior to the others. The 2-year PFS of 41% and OS of 84% suggest that the outcome can be quite varied and may differ from that with both DLBCL and HL. This is a patient population for whom we need to conduct additional studies and identify specific therapies.

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

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