INTERVIEW

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Tracks 1-17

Select Excerpts from the Interview

Tracks 1-2, 4

DR LOVE: Would you discuss your ongoing Phase II ECOG-E2408 trial of bendamustine/rituximab (BR) with or without bortezomib followed by rituximab with or without lenalidomide for high-risk follicular lymphoma (FL)?

DR EVENS: This is a 3-arm study with BR as the backbone for induction for 6 cycles followed by 2 years of rituximab maintenance (NCT01216683). Bortezomib is integrated as part of induction into 1 arm. Lenalidomide will be added to a third arm at 20 mg for a year as consolidation. The goal is to achieve high remission rates and long survival without a lot of side effects. Blood, bone marrow and tissue samples will be collected for correlative studies. Host genetics will be analyzed. We are trying to identify predictive markers to determine which patients will benefit from a specific therapy.

DR LOVE: Would you also discuss the Phase III LYM-3001 study of bortezomib/rituximab versus rituximab alone for relapsed/refractory FL?

DR EVENS: LYM-3001 was the largest randomized study ever conducted in FL, with more than 500 patients with relapsed FL randomly assigned to bortezomib/rituximab or rituximab alone. The results indicated an increase in progression-free survival of 1.8 months with bortezomib/rituximab versus rituximab (Coiffier 2011). That improvement, though statistically significant, was not clinically meaningful.

A retrospective follow-up study analyzed specific biomarkers to determine which patient subgroups might benefit from bortezomib/rituximab or rituximab alone. Patients who had a specific single-nucleotide polymorphism related to the proteasome level along with low expression of CD68, a marker associated with the number of tumor-infiltrating macrophages, had a significantly better PFS with the addition of bortezomib to rituximab, and a trend for an association with OS was observed (Coiffier 2013). We need such analysis in prospective studies to identify better predictive markers, and we'll evaluate these and other biomarkers in ECOG-E2408.

Track 7

DR LOVE: What is your take on the study presented at ASH 2013 comparing consolidation therapy with a single dose of ^{90}Y-ibritumomab tiuxetan to rituximab maintenance for patients with newly diagnosed FL?

DR EVENS: This randomized Phase II trial evaluated 2 years of rituximab maintenance or a single dose of ^{90}Y-ibritumomab tiuxetan consolidation in patients with newly diagnosed FL responding to R-CHOP. I thought any differences would be insignificant, so it was interesting that PFS analysis favored the rituximab arm (Lopez-Guillermo 2013; [3.1]). These data are not mature and will need further follow-up.

3.1

Phase II Study Comparing Consolidation Therapy with a Single Dose of ^{90}Y-Ibritumomab Tiuxetan to Rituximab Maintenance for Patients with Newly Diagnosed Follicular Lymphoma Responding to R-CHOP

Efficacy	Rituximab maintenance (n = 62)	^{90}Y-ibritumomab tiuxetan (n = 64)
Three-year progression-free survival	77%	63%
	Hazard ratio = 0.517, p = 0.044	

- No significant differences in overall survival or time to next treatment were observed between arms. The safety profile was reasonable with no unexpected toxicities in either arm.

Lopez-Guillermo A et al. *Proc ASH* 2013;**Abstract 369**.

I'm not sure these results will be practice changing. I believe the standard is still 2 years of rituximab maintenance. However, I might consider administering ^{90}Y-ibritumomab tiuxetan consolidation in certain situations — for example, for a patient who is planning to be out of town for a significant period.

Tracks 12-13, 15

DR LOVE: Would you discuss the Phase II study of single-agent brentuximab vedotin as front-line therapy for Hodgkin lymphoma (HL) in patients older than age 60 (Yasenchak 2013)?

DR EVENS: This is an interesting study. HL is a more virulent disease in older patients. This Phase II study reported a respectable response rate with single-agent brentuximab vedotin without chemotherapy. The critical question is whether the response will be durable. Will relapses occur because of the lack of an alkylating or chemotherapeutic agent? We will need to see those data. Even so, this would be an attractive treatment strategy for older patients who cannot tolerate chemotherapy.

DR LOVE: Your group presented a poster at ASH 2013 on pancreatitis as a serious adverse event in patients who are receiving brentuximab vedotin (Gandhi 2013). Would you discuss that data set?

DR EVENS: This study was initiated after an elderly woman, who was on an ongoing study of brentuximab vedotin for previously untreated HL, developed pancreatitis 9 days after the second dose of brentuximab vedotin and died a week later. She had no risk factors. An autopsy showed that she had no evidence of disease and both the tumor and pancreas were necrotic. High-resolution immunohistochemistry showed CD30 on her exocrine pancreatic cells. This is one of the few normal tissues that expresses CD30. We reached out to lymphoma specialists at other centers and were able to put together a total of 9 cases. Pancreatitis is a rare adverse event, but I believe it is real. It is on the label so practitioners are aware that pancreatitis should be considered in the differential diagnosis for a patient who presents with abdominal pain.

DR LOVE: What are your thoughts on the ongoing Phase II study of brentuximab vedotin for patients with relapsed/refractory CD30-positive NHL (Bartlett 2013)?

DR EVENS: This was one of the most important presentations at ASH 2013. The study demonstrated a good response rate with single-agent brentuximab vedotin for patients with relapsed/refractory diffuse large B-cell lymphoma, which is difficult to treat.

Response to brentuximab vedotin was irrespective of the intensity of CD30 levels, a theme that is also emerging in other studies. This could result in part from off-target effects. In addition, currently available staining techniques may not be highly sensitive and CD30 expression is probably higher than we can detect. We would not want to exclude patients from therapy because our technology cannot detect a certain marker. Hence, ongoing studies are evaluating the efficacy of brentuximab vedotin in B-cell lymphomas regardless of CD30 expression (eg, NCT01925612).

Track 17

DR LOVE: Would you comment on the results of the Phase III CLL11 trial comparing obinutuzumab/chlorambucil to rituximab/chlorambucil for patients with CLL and coexisting conditions?

DR EVENS: The study demonstrated an impressive benefit for obinutuzumab/chlorambucil compared to rituximab/chlorambucil in terms of PFS (Goede 2014; [3.2]). I believe the superiority of obinutuzumab compared to rituximab may be because of the way it binds to CD20, resulting in less complement-related cell death, increased direct cell killing and greater antibody-dependent cellular cytotoxicity. Obinutuzumab was recently approved for untreated CLL in combination with chlorambucil. I believe in the future it will be used in the front-line setting in combination with chemotherapy. ■

3.2

Final Stage II Results of the Phase III CLL11 Trial of Obinutuzumab/Chlorambucil (O-Clb) versus Rituximab/Chlorambucil (R-Clb) for Patients with Chronic Lymphocytic Leukemia and Comorbidities

Efficacy	O-Clb	R-Clb
Overall response rate (ORR) (n = 333, 329)	78.4%	65.1%
Complete response	20.7%	7.0%
Partial response	57.7%	58.1%
Median progression-free survival (PFS) (n = 333, 330)	26.7 mo	15.2 mo
Death rates (n = 333, 330)	8%	12%
Select Grade ≥3 adverse events	O-Clb (n = 241)	R-Clb (n = 225)
Infusion-related reaction	21%	4%
Neutropenia	35%	27%
Anemia	5%	4%
Thrombocytopenia	11%	4%
Infection	11%	13%

ORR: O-Clb versus R-Clb, $p < 0.001$; PFS: O-Clb versus R-Clb: hazard ratio (HR) = 0.39, $p < 0.001$

Death rates: O-Clb versus R-Clb: HR = 0.66, $p = 0.08$

Goede V et al. *New Engl J Med* 2014;370(12):1101-10.

SELECT PUBLICATIONS

Bartlett NL et al. **A Phase 2 study of brentuximab vedotin in patients with relapsed or refractory CD30-positive non-Hodgkin lymphomas: Interim results in patients with DLBCL and other B-cell lymphomas.** *Proc ASH* 2013;**Abstract 848**.

Coiffier B et al. **Prespecified candidate biomarkers identify follicular lymphoma patients who achieved longer progression-free survival with bortezomib-rituximab versus rituximab.** *Clin Cancer Res* 2013;19(9):2551-61.

Coiffier B et al. **Bortezomib plus rituximab versus rituximab alone in patients with relapsed, rituximab-naive or rituximab-sensitive, follicular lymphoma: A randomised phase 3 trial.** *Lancet Oncol* 2011;12(8):773-84.

Gandhi M et al. **Pancreatitis in patients treated with brentuximab vedotin: A previously unrecognized serious adverse event.** *Proc ASH* 2013;**Abstract 4380**.

Goede V et al. **Head-to-head comparison of obinutuzumab (GA101) plus chlorambucil (Clb) versus rituximab plus Clb in patients with chronic lymphocytic leukemia (CLL) and co-existing medical conditions (comorbidities): Final stage 2 results of the CLL11 trial.** *Proc ASH* 2013;**Abstract 6**.

Yasenchak C et al. **A Phase 2 study of single-agent brentuximab vedotin for front-line therapy of Hodgkin lymphoma in patients age 60 years and above: Interim results.** *Proc ASH* 2013;**Abstract 4389**.