INTERVIEW

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Tracks 1-11

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the activity of lenalidomide-based therapy in patients with central nervous system (CNS) lymphoma?

DR FRIEDBERG: This disease has been a struggle to treat, but recent data from a study of R^2 followed by lenalidomide maintenance in primary CNS lymphoma demonstrated that lenalidomide crosses the blood-brain barrier. The responses were reasonably durable, and it was tolerated well in patients with significant refractory disease (Rubenstein 2016). Primary CNS lymphoma is a disease of older patients, many of whom may not tolerate standard induction treatment with high doses of methotrexate. In that scenario the favorable tolerability and efficacy in this study make lenalidomide appealing.

DR LOVE: Do you use lenalidomide for patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL)?

DR FRIEDBERG: Older, transplant-ineligible patients with disease progression on standard R-CHOP have incurable disease, and often oncologists use modifications of salvage regimens, such as modified ICE or high-dose cytarabine. I believe lenalidomide has been shown to be as active as that type of therapy, with less toxicity, and it's my "go-to" drug for relapsed DLBCL in transplant-ineligible patients when no clinical trial is available.

Tracks 2-3

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

DR FRIEDBERG: This was of interest to me because many years ago John Leonard, Julie Vose and I conducted a trial of bortezomib with BR. The response rate was high, particularly in FL and mantle cell lymphoma, with reasonable tolerability (Friedberg 2011).

The ECOG study was made up of 2 parts. Up front the investigators compared BR to BR with bortezomib, and the primary endpoint was complete response (CR). The second part evaluated lenalidomide as maintenance therapy. Neuropathy was more prevalent with bortezomib, but with schedule modification and subcutanous administration it was low grade. Most patients were able to receive all the prescribed doses, which is compelling.

The CR rate was higher for the patients who received bortezomib with BR than for those who received BR alone, although the benefit was incremental (Evens 2016). We don't generally see CR rates much higher than this, and it was higher than normal. Also, if patients experience a better response up front, it's more likely their PET scan will be negative and they'll maintain a longer response.

I'm not sure this constitutes a new standard, but it is important to follow because FL is a heterogeneous disease. Most patients fare well, but identifying those who do not necessitates a PET scan at the end of therapy and evaluation of the time to disease progression after first-line therapy. It will be interesting to see whether this CR rate translates to a change in the natural history of the disease. Future extensive correlative analyses should help define which patients will benefit.

DR LOVE: What do we know about obinutuzumab compared to rituximab up front for FL?

DR FRIEDBERG: Obinutuzumab is a novel CD20 antibody that's approved for chronic lymphocytic leukemia (CLL). Combined with chlorambucil, it was shown to be better than chlorambucil/rituximab in the CLL11 trial and was recently approved for relapsed FL based on a trial for patients with rituximab-refractory disease.

In addition, the large Phase III GALLIUM trial is evaluating obinutuzumab with standard chemotherapy followed by obinutuzumab alone versus rituximab with standard chemotherapy followed by rituximab alone. A recent press release announced that the trial has been stopped because of a positive result, and I believe we'll see the data at ASH. It will be important to understand the magnitude of benefit. Replacing rituximab with obinutuzumab would be a significant change.

Tracks 6-9

DR LOVE: Would you discuss the available data with Bruton tyrosine kinase (BTK) inhibitors beyond ibrutinib in CLL?

DR FRIEDBERG: It may be a challenge for other BTK inhibitors to demonstrate superiority compared to ibrutinib in CLL. If you treat even high-risk CLL with ibrutinib, the majority of patients experience a response. It's difficult to imagine the newer agents being better. I do see potential for patients with ibrutinib-refractory disease — can we overcome the resistance mechanism of the BTK binding site?

The other issue with ibrutinib is the risk of bleeding. Many of these patients are receiving anticoagulation medication for atrial fibrillation, and we are all nervous about administering ibrutinib in that case. If a drug clearly showed a lesser propensity for bleeding, it could become important.

Aside from ibrutinib, the BTK inhibitor furthest along in development is acalabrutinib. Data were published in *The New England Journal of Medicine* not long ago demonstrating its efficacy, and the early data also suggest a low risk of atrial fibrillation (Byrd 2016; [1.1]).

Many of us didn't appreciate the atrial fibrillation risk with ibrutinib until after it was approved and used more widely. Although we must be careful comparing acalabrutinib to ibrutinib on the basis of a narrow clinical trial rather than real-world experience, the risk of atrial fibrillation with ibrutinib is in the range of 5% to 10%. It's clearly a concern, but the majority of patients to whom I've administered ibrutinib have received it for a long time without that type of complication.

DR LOVE: How would you incorporate the newly FDA-approved Bcl-2 inhibitor venetoclax into the clinical treatment algorithm for patients with CLL?

DR FRIEDBERG: Venetoclax is approved for patients with 17p-deleted CLL that has already been treated with ibrutinib. The efficacy is outstanding, and some investigators believe it may be superior to ibrutinib in this subset of patients (Stilgenbauer 2015; [1.2]). Whether it becomes more widely used remains to be seen — the risk of tumor lysis syndrome makes it cumbersome because sometimes admission to the hospital is required.

DR LOVE: How do you approach choice of first-line therapy for CLL in your practice (Cramer 2016)?

1.1

ACE-CL-001 Trial: A Novel Bruton Tyrosine Kinase Inhibitor, Acalabrutinib, for Chronic Lymphocytic Leukemia

	Overall response rate	Partial response (PR) rate	PR with lymphocytosis
All evaluable patients (n = 60)	95%	85%	10%
Del(17p13.1) (n = 18)	100%	89%	11%
Prior idelalisib (n = 4)	100%	75%	25%

- Most common Grade 1 and 2 adverse events: Headache, diarrhea, weight gain
- No cases of major bleeding or atrial fibrillation at 14.3 months follow-up

Byrd JC et al. *N Engl J Med* 2016;374(4):323-32.

DR FRIEDBERG: For younger patients who I believe are capable of receiving it, fludarabine/cyclophosphamide/rituximab (FCR) remains a standard. But for older or frailer patients for whom I'm worried about toxicity — and that's the majority of these patients because CLL is a disease of older people — I consider ibrutinib rather than BR as front-line therapy.

DR LOVE: People are also discussing the use of FCR as a way to launch patients into an unmaintained remission that might last for years, but isn't that also a possibility with BR and even obinutuzumab/chlorambucil?

DR FRIEDBERG: The durability of response with obinutuzumab/chlorambucil is much shorter than that reported with FCR. A subset of patients who receive BR fare well — in a randomized trial comparing BR to FCR the progression-free survival (PFS) rates were good on both arms, although it appeared that FCR won out, albeit with more toxicity, especially among patients aged 60 to 62 years (Eichhorst 2014). For younger patients I believe the current consensus based on randomized trials is that if you want to use a chemoimmunotherapy platform to achieve a prolonged PFS, the FCR regimen does that. ■

1.2

Venetoclax Monotherapy for Relapsed/Refractory Chronic Lymphocytic Leukemia with Del(17p)

Response (assessed by independent review committee)	n = 107
Overall response rate	79.4%
Complete response (CR) or CR with incomplete bone marrow recovery	7.5%
Nodular partial remission/partial remission	72%
Survival rate (12 months)	
Progression-free survival	72%
Overall survival	86.7%

- Risk of tumor lysis syndrome (TLS) effectively mitigated with no clinical TLS
- Incidences of neutropenia (43%) and infection Grade ≥3 (205) similar to those with front-line chemotherapy

Stilgenbauer S et al. *Proc ASH* 2015;**Abstract LBA-6**.

SELECT PUBLICATIONS

Cramer P et al. **Advances in first-line treatment of chronic lymphocytic leukemia: Current recommendations on management and first-line treatment by the German CLL Study Group (GCLLSG).** *Eur J Haematol* 2016;96(1):9-18.

Eichhorst B et al. **Frontline chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) shows superior efficacy in comparison to bendamustine (B) and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Final analysis of an international, randomized study of the German CLL Study Group (GCLLSG) (CLL10 Study).** *Proc ASH* 2014;**Abstract 19**.

Evens AM et al. **Effect of bortezomib on complete remission (CR) rate when added to bendamustine-rituximab (BR) in previously untreated high-risk (HR) follicular lymphoma (FL): A randomized phase II trial of the ECOG-ACRIN Cancer Research Group (E2408).** *Proc ASCO* 2016;**Abstract 7507**.

Friedberg JW et al. **The combination of bendamustine, bortezomib, and rituximab for patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma.** *Blood* 2011;117(10):2807-12.

Rubenstein JL et al. **Phase I investigation of lenalidomide plus rituximab and outcomes of lenalidomide maintenance in recurrent CNS lymphoma.** *Proc ASCO* 2016;**Abstract 7502**.