INTERVIEW

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Tracks 1-18

Track 1 **Case discussion:** A 42-year-old man with previously untreated chronic lymphocytic leukemia (CLL) receives obinutuzumab and venetoclax on a clinical trial

Track 2 Viewpoint on efficacy and long-term outcomes with first-line fludarabine/cyclophosphamide/rituximab (FCR) versus bendamustine/rituximab (BR)

Track 3 Counseling younger patients with CLL about long-term treatment options

Track 4 Activity and tolerability of obinutuzumab/venetoclax in CLL

Track 5 Management of obinutuzumab-associated infusion reactions

Track 6 Incorporation of the newly FDA-approved agent venetoclax into the treatment algorithm for patients with CLL and 17p deletions

Track 7 Activity of obinutuzumab versus rituximab in CLL

Track 8 Activity of idelalisib in combination with rituximab for patients with CLL

Track 9 **Case discussion:** A 78-year-old woman with relapsed/refractory mantle-cell lymphoma (MCL) receives ibrutinib and palbociclib on a clinical trial

Track 10 Approach to choosing observation versus initiating treatment for patients with indolent MCL

Track 11 Incidence of extranodal disease in patients with MCL

Track 12 Therapeutic options for patients with relapsed/refractory MCL

Track 13 Lenalidomide and rituximab (R^2) as initial treatment for MCL

Track 14 ECOG-E1411: A Phase II trial of BR with or without bortezomib followed by consolidation rituximab with or without lenalidomide for elderly patients with previously untreated MCL

Track 15 Outcomes in patients with MCL and disease progression on ibrutinib

Track 16 Activity and tolerability of ibrutinib/palbociclib in relapsed/refractory MCL

Track 17 Role of rituximab maintenance therapy in MCL

Track 18 Updated results from the Phase II S1106 trial of R-hyper-CVAD versus BR followed by ASCT in MCL

Select Excerpts from the Interview

Tracks 4, 6

DR LOVE: Would you discuss what venetoclax is and how it works?

DR LEONARD: Venetoclax is an oral second-generation Bcl-2 inhibitor. Bcl-2 plays a significant role in chronic lymphocytic leukemia (CLL) cells and their ability to stay alive. Most of the data on venetoclax are as a single agent in relapsed disease, and the response rates have been high. The main challenge has been the associated tumor lysis syndrome, but it can be worked out by using the recommended dosing schedule. In

relapsed disease this is less of a concern because those patients have fewer options, but you need to watch out for it.

In terms of up-front regimens, patients are not excited about being admitted to the hospital for treatment. I believe the future holds combination regimens, such as venetoclax/obinutuzumab, as we're starting to see in other settings (Flinn 2015).

We will likely end up with regimens that are a sort of chemotherapy debulking followed by venetoclax or some overlap between the chemotherapy and venetoclax. Then the question will be, what does venetoclax add? For now, it does have value in refractory disease.

Editor's note: Subsequent to this interview, on April 11, 2016, venetoclax was approved for the treatment of CLL with 17p deletion in patients who have received at least 1 prior therapy.

Track 8

DR LOVE: What are your thoughts on the data reported at ASH evaluating idelalisib in CLL in the up-front and relapsed settings?

DR LEONARD: Idelalisib is a good drug for CLL if patients have contraindications to ibrutinib. There are also randomized data showing a benefit to combining it with bendamustine/rituximab (BR) (Zelenetz 2015; [4.1]), although later studies suggest the emergence of toxicities such as respiratory tract infections.

4.1

Study 115: A Phase III Trial of Idelalisib (IDELA) with Bendamustine/Rituximab (BR) in Relapsed/Refractory Chronic Lymphocytic Leukemia

Outcome	IDELA + BR (n = 207)		Placebo + BR (n = 209)	
Median progression-free survival*	23.1 months		11.1 months	
Median overall survival	Not reached		Not reached	
Overall response rate	68%		45%	
≥50% reduction in lymph nodes	96%		61%	
Select adverse events (n = 207, 209)	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	63%	60%	54%	46%
Pyrexia	42%	7%	30%	3%
Febrile neutropenia	22%	20%	7%	6%
Pneumonia	17%	11%	11%	6%
ALT elevation	15%	11%	1%	<1%

* $p = 2.8 \times 10^{-14}$

Zelenetz AD et al. *Proc ASH* 2015;**Abstract LBA-5**.

Tracks 13-14

DR LOVE: Where are we with the lenalidomide/rituximab (R^2) regimen in terms of ongoing trials and available data in patients with mantle-cell lymphoma (MCL)?

DR LEONARD: Lenalidomide is approved as a single agent for relapsed MCL, with an approximate 30% response rate (Goy 2013). Combining it with rituximab is an active approach. The question is, what about using it earlier in the course of the disease? We have reported data with up-front R^2 in a fairly balanced albeit small study for patients with MCL (Ruan 2015; [4.2]). Those patients are now out more than 3 years, and most of them are still in remission. Some are now in remission for 5 years.

Another interesting approach is being evaluated on the Phase II ECOG-E1411 study for elderly patients with untreated MCL (NCT01415752). On this study everyone is receiving BR and then some patients receive bortezomib in addition to the BR. All patients receive maintenance therapy, either rituximab alone or R^2.

BR followed by rituximab is a good regimen for MCL. I believe the PFS will be somewhere between 4 and 5 years. If you add bortezomib and lenalidomide to the maintenance therapy, you might yield durable remissions.

4.2

Results from a Phase II Trial of Lenalidomide and Rituximab as Initial Treatment for Mantle-Cell Lymphoma

Efficacy	**Intent-to-treat population** (n = 38)
Overall response rate	87%
Complete response	61%
Median progression-free survival	Not reached
2-year progression-free survival	85%
Select adverse events	Grade ≥3
Neutropenia	50%
Thrombocytopenia	13%
Rash	29%
Tumor flare	11%

Median follow-up = 30 months

Ruan J et al. *N Engl J Med* 2015;373(19):1835-44.

Track 16

DR LOVE: Would you discuss the activity and tolerability of ibrutinib/palbociclib in relapsed/refractory MCL?

DR LEONARD: Palbociclib is an oral cell-cycle inhibitor targeting cyclin-dependent kinase 4/6 (CDK4/6) that is already approved for patients with metastatic breast cancer. In MCL, the cell cycle is important because of the associated cyclin D1 expression. A drug that can target CDK4/6 makes sense.

In a Phase I study conducted a couple of years ago, we demonstrated that palbociclib had single-agent activity in relapsed MCL. We know that ibrutinib yields approximately a 70% response rate and about a 1-year PFS for patients with relapsed/refractory MCL (Wang 2013). The question is, can we improve the response rate and durability by adding palbociclib? An ongoing study is evaluating the combination, and we are seeing more CRs than you'd expect with ibrutinib alone. Slightly more cytopenias are observed when palbociclib is added, but they're manageable.

Track 18

DR LOVE: Would you discuss the background of the Phase II SWOG-S1106 trial evaluating R-hyper-CVAD versus BR, followed by ASCT, in MCL and the data reported at ASH (Chen 2015; [4.3])?

DR LEONARD: The idea of this trial was to compare BR to R-hyper-CVAD followed by autotransplant as initial therapy for MCL, particularly in younger patients. One of the endpoints was mobilization of stem cells. The initial bias was that BR is an older person's regimen — not that effective — and R-hyper-CVAD is a younger person's regimen. Various studies of pretransplant R-hyper-CVAD produced good results and excellent curves, so that was the assumed winner. We were all surprised by the rates of mobilization failure with R-hyper-CVAD on this trial, which suggest that in the real world mobilization is a problem. Hyper-CVAD is known to be profoundly myelosuppressive. Cytopenias and even MDS can result.

BR produced high rates of minimal residual disease (MRD) negativity, and MRD negativity correlates with better outcomes. I believe our next generation of trials will focus on how to take the most patients to MRD negativity, including through the use of combination regimens with novel agents. ■

4.3

SWOG-S1106: Updated Results of a Phase II Trial of Bendamustine/Rituximab (BR) versus R-Hyper-CVAD (RH) Followed by Autologous Stem Cell Transplant for Patients with Mantle-Cell Lymphoma

Efficacy	BR (n = 35)	RH (n = 17)
2-year progression-free survival (PFS)	81%	82%
2-year overall survival	87%	88%
Overall response rate	83%	94%
Complete response rate	40%	35%
Minimal residual disease (MRD) assessment		
Samples collected (n)	10	2
MRD-positive at baseline (n)*	9	2
Achieved MRD negativity before ASCT (n)	8	2
2-year PFS if MRD-negative after induction, n (%)	11 (100%)	Not reported

* Additional patient MRD-negative at baseline remained negative after induction.

This study was closed prematurely based on predetermined criteria of stem cell mobilization failures on the RH arm (53 of planned 160 patients were accrued).

Chen R et al. *Proc ASH* 2015;**Abstract 518**.

SELECT PUBLICATIONS

Flinn IW et al. **Safety and efficacy of a combination of venetoclax (GDC-0199/ABT-199) and obinutuzumab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia — Results from a Phase 1b study (GP28331).** *Proc ASH* 2015;**Abstract 494**.

Goy A et al. **Single-agent lenalidomide in patients with mantle-cell lymphoma who relapsed or progressed after or were refractory to bortezomib: Phase II MCL-001 (EMERGE) study.** *J Clin Oncol* 2013;31(29):3688-95.

Wang ML et al. **Targeting BTK with ibrutinib in relapsed or refractory mantle-cell lymphoma.** *N Engl J Med* 2013;369(6):507-16.