INTERVIEW

## Jeff Sharman, MD

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### Tracks 1-11

Track 1 **Case discussion:** A 57-year-old woman who presented in 2011 with Stage IIIA follicular lymphoma (FL) with high tumor burden, refused chemoimmunotherapy, received lenalidomide/rituximab ($R^2$) and remains in complete remission (CR) after 4 years

Track 2 Synergy of the $R^2$ regimen

Track 3 Efficacy and side-effect profile of idelalisib for relapsed FL or chronic lymphocytic leukemia (CLL)

Track 4 **Case discussion:** A 55-year-old man with previously treated CLL with 17p deletion receives idelalisib/ofatumumab on a clinical trial

Track 5 Integrating the B-cell receptor signaling inhibitors idelalisib and ibrutinib into the treatment algorithm for CLL with and without adverse cytogenetics

Track 6 **Case discussion:** An 89-year-old woman with CLL and multiple comorbidities who responds to single-agent obinutuzumab

Track 7 Management of obinutuzumab-associated infusion reactions

Track 8 Similarities and differences between rituximab and obinutuzumab

Track 9 Rates of minimal residual disease (MRD) with obinutuzumab/chlorambucil versus rituximab/chlorambucil on the pivotal Phase III CLL11 trial

Track 10 Clinical experience with obinutuzumab monotherapy in CLL

Track 11 Brentuximab vedotin in CD30-positive lymphomas

## Select Excerpts from the Interview

### Track 3

**DR LOVE:** Recently, the FDA granted accelerated approval to idelalisib for the treatment of relapsed follicular lymphoma (FL) or small lymphocytic lymphoma (SLL) for patients who have received at least 2 prior systemic therapies. What is your clinical experience with idelalisib, and how does it fit into your practice?

**DR SHARMAN:** I generally administer idelalisib prior to ibrutinib for patients with relapsed FL. Idelalisib was approved based on a trial for patients with indolent non-Hodgkin lymphoma refractory to both rituximab and alkylating agents (Gopal 2014). These patients received single-agent idelalisib at 150 mg BID.

In the study that led to the labeled indication for idelalisib in chronic lymphocytic leukemia (CLL), patients did not have disease that was rituximab refractory and received idelalisib with rituximab or rituximab with placebo (Furman 2014). Hence, in CLL I use idelalisib in combination with rituximab, and in FL or SLL I administer it as a single agent.

The most significant toxicity issues are elevated transaminases, diarrhea and colitis. Elevated transaminases tend to occur quite early, almost exclusively within the first 3 months. Patients who are receiving idelalisib need to have their liver function tests monitored every other week during this time. The likelihood of a transaminase elevation goes down quite a bit after that 3-month period, and you can then check once monthly at that point. Once the patient recovers from elevated transaminases, it usually does not recur.

Diarrhea and colitis tend to occur later in the course of therapy, with a median time frame closer to 6 months. When diarrhea occurs, it's more of an inflammatory phenomenon than typical pill-based diarrhea. The label information suggests management with dose interruption or discontinuation. Diarrhea can be significant and lead to hospitalizations.

So as long as you know how to use the drug, what to look for and when to look for it, I've found it to be quite easy to use. Once the patient recovers from elevated transaminases, diarrhea or colitis, it is possible to reinitiate therapy depending on what the other options are, how severe the side effects were and how well the patient is performing at that point.

## Tracks 7-10

**DR LOVE:** Would you describe the differences between rituximab and obinutuzumab?

**DR SHARMAN:** The key clinical difference between the 2 agents is that obinutuzumab has been demonstrated to be superior to rituximab in CLL, and no other anti-CD20 antibody can make that claim. Importantly, obinutuzumab was approved in combination with chlorambucil for patients with untreated CLL on the basis of the German Phase III CLL11 trial that included arms comparing it to rituximab/chlorambucil and chlorambucil alone (Goede 2014; [1.1]).

**DR LOVE:** Would you discuss some of the key findings of the CLL11 trial?

**DR SHARMAN:** Patients on the CLL11 trial had previously untreated CLL with comorbidities, and overall, obinutuzumab/chlorambucil improved efficacy in this population that might be considered inappropriate for cytotoxic chemotherapy. The study also evaluated MRD negativity. MRD in the bone marrow is more difficult to achieve than it is in the blood. Essentially, MRD negativity was not achieved with chlorambucil alone but was achieved to a small degree in the bone marrow with rituximab/chlorambucil, and with obinutuzumab/chlorambucil approximately 20% of patients were MRD-negative.

**DR LOVE:** How do you administer obinutuzumab, and what are the toxic effects associated with its use?

**DR SHARMAN:** I administer obinutuzumab as monotherapy, not in combination with chlorambucil. I recognize this is an off-label use, but I believe that chlorambucil adds relatively little to the overall efficacy and there are practical challenges with its use. Unfortunately, the CLL11 study did not include obinutuzumab with or without chlorambucil, which would have teased out the effect of chlorambucil.

Most patients who receive obinutuzumab experience considerable infusion-related reactions (IRRs) in the first cycle. The first 1,000-mg dose of obinutuzumab can be administered intravenously at a split dose of 100 mg on day 1 and 900 mg on day 2.

**1.1**

**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 (all patients) | 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% |
| **Minimal residual disease (MRD) negativity** | **O-Clb** | **R-Clb** |
| Bone marrow (BM) (n = 133, 114) | 19.5% | 2.6% |
| Peripheral blood (PB) (n = 231, 243) | 37.7% | 3.3% |
| **Select Grade ≥3 adverse events** | **O-Clb (n = 241)** | **R-Clb (n = 225)** |
| Infusion-related reactions | 21% | 4% |
| Neutropenia | 35% | 27% |
| Anemia | 5% | 4% |
| Thrombocytopenia | 11% | 4% |
| Infections | 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, $p = 0.08$

MRD negativity (BM or PB): O-Clb versus R-Clb, $p < 0.001$

Negative test results for MRD in blood after O-Clb therapy were associated with a favorable disease course during follow-up.

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

I've administered obinutuzumab to approximately 50 patients, and it appears that the kinetics of the IRRs are different from those with rituximab, with "obinutuzumab being more like lightning and rituximab like thunder." Obinutuzumab causes early and significant IRRs, which, once settled down, don't reoccur. On the other hand, with rituximab, every time you increase the dose, patients experience more IRRs.

With obinutuzumab IRRs are generally experienced during the administration of the first 25 mg, so it's imperative to discontinue the infusion as soon as a reaction is observed. Early interruption after administering 5 mg to 10 mg of the agent seems to offset some of the acuity of the infusion, although I can't say that I have strong data to support this. We have become quite comfortable with obinutuzumab at our institution since we started working with it in our own clinical trial and gained familiarity with IRRs and how to manage them. ■

## SELECT PUBLICATIONS


Furman RR et al. **Idelalisib and rituximab in relapsed chronic lymphocytic leukemia.** *N Engl J Med* 2014;370(11):997-1007.

Goede V et al. **Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions.** *N Engl J Med* 2014;370(12):1101-10.

Gopal AK et al. **PI3Kδ inhibition by idelalisib in patients with relapsed indolent lymphoma.** *N Engl J Med* 2014;370(11):1008-18.