INTERVIEW

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Tracks 1-11

Select Excerpts from the Interview

Track 1

DR LOVE: Would you comment on the results of the Phase III CLL10 trial comparing fludarabine, cyclophosphamide and rituximab (FCR) to BR for patients with previously untreated advanced chronic lymphocytic leukemia (CLL)?

DR LACASCE: FCR resulted in a somewhat longer progression-free survival compared to BR in this study. In addition, there were more complete remissions with FCR (Eichhorst 2013; [3.1]). We know an alkylator is important for patients whose disease carries a deletion 11q, so that would be another setting in which we would prefer FCR. BR is a good option for older patients, but I believe it is inferior to FCR.

Track 2

DR LOVE: Can you talk about obinutuzumab, which was recently approved by the FDA in combination with chlorambucil for previously untreated CLL?

DR LACASCE: Obinutuzumab is a good option in CLL, for which rituximab doesn't seem to be as active as it is in other subtypes of non-Hodgkin lymphoma (NHL). Significant infusional toxicities do seem to be associated with obinutuzumab (Goede 2014; [3.2]). They must be carefully monitored, particularly when starting the drug for a patient with a high white blood cell count.

I've seen patients with severe reactions because not as much published experience is available with this agent. This is something that people need to be aware of and perhaps premedicate patients more than they might expect, even with rituximab. It appears that

3.1

CLL10: Interim Analysis of a Phase III Trial of Fludarabine, Cyclophosphamide and Rituximab (FCR) versus Bendamustine and Rituximab (BR) for Physically Fit Patients with Previously Untreated Advanced Chronic Lymphocytic Leukemia

Efficacy	FCR (n = 282)	BR (n = 279)	Hazard ratio	*p*-value
Two-year progression-free survival rate	85.0%	78.2%	1.385	0.041
Overall response rate (n = 274, 273)	97.8%	97.8%	—	1.0
Complete response rate (n = 274, 273)	47.4%	38.1%	—	0.031
Select Grade 3-5 adverse events (AEs)	**FCR**	**BR**	***p*-value**	
Severe hematologic AEs	90.0%	66.9%	<0.001	
Severe neutropenia	81.7%	56.8%	<0.001	
Severe infections	39.0%	25.4%	0.001	
Treatment-related death	3.9%	2.1%	Not reported	

Eichhorst B et al. *Proc ASH* 2013;**Abstract 526**.

3.2

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

Efficacy	O-Clb	R-Clb
Overall response rate (n = 333, 329) Complete response Partial response	78.4% 20.7% 57.7%	65.1% 7.0% 58.1%
Median progression-free survival (n = 333, 330)	26.7 mo	15.2 mo
Death rates (n = 333, 330)	8%	12%
Select Grade ≥3 adverse events	**O-Clb (n = 336)**	**R-Clb (n = 321)**
Infusion-related reaction	20%	4%
Neutropenia	33%	28%
Anemia	4%	4%
Thrombocytopenia	10%	3%
Infection	12%	14%

Overall response rate, O-Clb versus R-Clb: $p < 0.001$; progression-free survival, 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. *N Engl J Med* 2014;370(12):1101-10.

if the patient experiences a significant infusion reaction with the first dose, it does not seem to recur on subsequent doses, as we sometimes see with rituximab. But that first one can be quite severe.

DR LOVE: What is your approach for administering obinutuzumab to a patient with a high white blood cell count?

DR LACASCE: In the CLL11 study the dose was divided, so the patients received a small proportion on day 1 and the balance on day 2. But even in a patient with a particularly high white blood cell count, no substantial decrease will become apparent in 1 day, so I would delay longer if the patient experienced a severe reaction to the first infusion. Then I'd probably premedicate for several days with dexamethasone and diphenhydramine and add H1 and H2 blockers before administration of the next cycles.

Track 3

DR LOVE: How are you using ibrutinib in your practice now that its approval has been expanded to CLL (Byrd 2014; [3.3])?

DR LACASCE: Ibrutinib is a great agent with minimal toxicity. I have administered ibrutinib to a number of patients since it was approved and have been extremely impressed with the rapidity with which people respond and feel better.

You can observe their white count go up and kind of peak and then start to slowly come down as their hematocrit and platelets improve. Patients tolerate it well and are receiving it for a long period of time, even if they have persistent lymphocytosis.

3.3

RESONATE: Results of a Phase III Trial of Ibrutinib versus Ofatumumab for Previously Treated Chronic Lymphoid Leukemia

Efficacy	Ibrutinib (n = 195)	Ofatumumab (n = 196)	Hazard ratio	*p*-value
Median progression-free survival*	Not reached	8.1 mo	0.22	<0.001
Median overall survival	Not reached	Not reached	0.43	0.005
One-year overall survival	90%	81%		
Overall response rate	42.6%	4.1%	—	<0.001
	Ibrutinib (n = 195)		**Ofatumumab** (n = 191)	
Select adverse events	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	48%	4%	18%	2%
Fatigue	28%	2%	30%	2%
Nausea	26%	2%	18%	0%
Pyrexia	24%	2%	15%	1%
Cough	19%	0%	23%	1%
Infusion-related reaction	0%	0%	28%	3%

* Median follow-up = 9.4 months

Byrd JC et al; RESONATE Investigators. *N Engl J Med* 2014;371(3):213-23.

The one aspect that has been a little challenging is in patients who are receiving anticoagulation therapy. There is an increased risk of bleeding, and all of the studies excluded patients who were receiving warfarin. So we worry about that a little. But in general, the toxicity has been quite minimal.

Track 6

DR LOVE: Would you discuss the mechanisms of action, efficacy and tolerability of idelalisib and ABT-199 in CLL also?

DR LACASCE: Idelalisib is a PI3 kinase delta inhibitor, and that is downstream of the BTK enzyme, which is the target of ibrutinib. Idelalisib has been studied in both indolent B-cell lymphomas and CLL and yields good response rates, though I believe the response rates are probably a little lower than with ibrutinib in CLL. It is also associated with the same phenomenon of peripheral lymphocytosis when you initiate therapy.

The toxicity profile is a little different. You see a fair number of cases of pneumonitis and LFT abnormalities, but we are able to administer treatment to most patients through those. Cases of colitis have also been reported recently in patients who've received idelalisib for a period of time. But it is an active drug, and I believe we'll be seeing other PI3 kinase inhibitors being studied in CLL.

The second-generation BCL2 inhibitor ABT-199 is also an interesting agent. The first-generation agent also inhibited BCL-XL and thus caused significant thrombocytopenia. That is not an issue with ABT-199, however. The major issue with ABT-199 is that it's associated with tumor lysis, so studies of this agent have used careful dose escalation. I've observed patients in whom LDH rose within a short time after starting ABT-199 therapy, so it's simply a matter of prophylaxis for tumor lysis.

But it is an active and well-tolerated agent in CLL and NHL, based on data from Matt Davids at our institution (Davids 2013, 2014). Combining it with antibodies and other agents will be interesting. I believe a study is planned of ABT-199 with R-CHOP in large cell lymphoma, and because of their favorable toxicity profiles, these agents are perfect to study in combination with chemotherapy. ■

Editor's note: On July 23, 2014, the US FDA approved idelalisib for the treatment of relapsed CLL, in combination with rituximab, for patients in whom rituximab alone would be considered appropriate therapy because of comorbidities.

The FDA also granted accelerated approval to idelalisib for the treatment of relapsed FL or relapsed small lymphocytic lymphoma (SLL) in patients who have received at least 2 prior systemic therapies.

SELECT PUBLICATIONS

Davids MS et al. **Phase I study of ABT-199 (GDC-0199) in patients with relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL): Responses observed in diffuse large B-cell (DLBCL) and follicular lymphoma (FL) at higher cohort doses.** *Proc ASCO* 2014;**Abstract 8522**.

Davids MS et al. **Overcoming stroma-mediated treatment resistance in chronic lymphocytic leukemia through BCL-2 inhibition.** *Leuk Lymphoma* 2013;54(8):1823-5.

Eichhorst B et al. **Chemoimmunotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus bendamustine and rituximab (BR) in previously untreated and physically fit patients (pts) with advanced chronic lymphocytic leukemia (CLL): Results of a planned interim analysis of the CLL10 trial, an international, randomized study of the German CLL Study Group (GCLLSG).** *Proc ASH* 2013;**Abstract 526**.