INTERVIEW

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Tracks 1-13

Track 1 **Case discussion:** A 78-year-old man with rituximab-refractory follicular lymphoma (FL) achieves a complete response with bendamustine/obinutuzumab on the GADOLIN trial

Track 2 GADOLIN trial: Overall survival benefit with the addition of obinutuzumab to bendamustine followed by obinutuzumab maintenance therapy for patients with rituximab-refractory indolent non-Hodgkin lymphoma (NHL)

Track 3 Primary results of the Phase III GALLIUM study: Obinutuzumab-based induction and maintenance therapy prolongs progression-free survival (PFS) for patients with previously untreated FL

Track 4 Activity of obinutuzumab versus rituximab in B-cell neoplasms

Track 5 Clinical experience with obinutuzumab-associated infusion reactions

Track 6 Activity of FDA-approved (idelalisib) and investigational (copanlisib) PI3K inhibitors in indolent NHL

Track 7 Response to bendamustine/obinutuzumab on a clinical trial

Track 8 **Case discussion:** A 50-year-old man with relapsed mantle cell lymphoma (MCL) receives ibrutinib

Track 9 Sequencing of therapeutic options for relapsed MCL

Track 10 **Case discussion:** A 28-year-old man with Hodgkin lymphoma (HL) receives brentuximab vedotin as consolidation therapy after autologous stem cell transplant

Track 11 Results of the Phase III AETHERA trial: PFS improvement with brentuximab vedotin as consolidation therapy after autologous stem cell transplant in patients with HL at risk of relapse or progression

Track 12 Selection of first-line therapy for chronic lymphocytic leukemia (CLL)

Track 13 Integration of venetoclax into the treatment algorithm for CLL

Select Excerpts from the Interview

Tracks 2-4

DR LOVE: You were the principal investigator of the Phase III GADOLIN study investigating the role of obinutuzumab for rituximab-refractory indolent non-Hodgkin lymphoma (NHL) that was published in *The Lancet Oncology* and updated at ASH 2016 (Sehn 2016; Cheson 2016). Would you talk about the study?

DR SEHN: The GADOLIN trial was designed to evaluate the addition of obinutuzumab to bendamustine versus bendamustine alone for patients with rituximab-refractory indolent NHL. Most of the patients enrolled on the trial had follicular lymphoma (FL). Patients on the obinutuzumab arm whose disease did not progress received obinutuzumab maintenance for 2 years.

1.1

GADOLIN: Results of a Phase III Trial Evaluating Bendamustine with or without Obinutuzumab for Rituximab-Refractory Indolent Non-Hodgkin Lymphoma

Efficacy	Bendamustine + obinutuzumab	Bendamustine	HR, *p*-value
Median progression-free survival			
All patients (n = 204, 209)	25.8 mo	14.1 mo	0.57, <0.0001
Patients with FL (n = 164, 171)	25.3 mo	14.0 mo	0.52, <0.0001
Median overall survival			
All patients (n = 204, 209)	Not reached	Not reached	0.67, 0.0269
Patients with FL (n = 164, 171)	Not reached	53.9 mo	0.58, 0.0061

Select Grade ≥3 adverse events	Bendamustine + obinutuzumab (n = 204)	Bendamustine (n = 203)
Neutropenia	71%	55%
Thrombocytopenia	22%	32%
Infections and infestations	46%	39%
Infusion-related reactions	19%	7%
Neoplasms	12%	11%
Cardiac disorders	9%	3%

HR = hazard ratio; FL = follicular lymphoma

Cheson B et al. *Proc ASH* 2016;**Abstract 615**.

The trial demonstrated a significant improvement in progression-free survival (PFS) for patients who received the combination (Sehn 2016). At the ASH 2016 meeting updated results were reported demonstrating a survival advantage for the obinutuzumab/bendamustine arm (Cheson 2016; [1.1]).

DR LOVE: Would you also comment on the results of the Phase III GALLIUM trial assessing obinutuzumab-based induction and maintenance therapy for patients with newly diagnosed FL?

DR SEHN: Based on the efficacy of obinutuzumab in chronic lymphocytic leukemia (CLL) and the GADOLIN trial in FL, it was logical to investigate this agent in the front-line setting and compare it to rituximab head to head. The GALLIUM trial compared induction therapy with obinutuzumab and chemotherapy followed by maintenance obinutuzumab to rituximab with chemotherapy followed by maintenance rituximab for patients with newly diagnosed FL. The trial met its endpoint with an improvement in PFS on the obinutuzumab arm (Marcus 2016; [1.2]). Because of these results, we might find a shift in the standard up-front approach for FL.

DR LOVE: What is the mechanism of action of obinutuzumab, and how would you compare its efficacy to that of rituximab across the various hematologic histologies?

DR SEHN: Obinutuzumab is classified as a Type II anti-CD20 monoclonal antibody. Its primary advantage compared to rituximab is its enhanced ability to stimulate direct cell death and antibody-dependent cellular cytotoxicity. It has a different mechanism of action from that of rituximab and may be superior, depending on tumor histology. A big advantage relative to rituximab was observed in the GALLIUM trial in FL and

1.2 **Primary Results of the Phase III GALLIUM Trial Evaluating Rituximab or Obinutuzumab in Combination with Chemotherapy for Newly Diagnosed Follicular Lymphoma**

Efficacy	Rituximab/ chemotherapy (n = 601)	Obinutuzumab/ chemotherapy (n = 601)	HR, *p*-value
Three-year PFS	73.3%	80%	0.66, 0.0012
Three-year OS	92.1%	94%	0.75, 0.21
Three-year TTNT	81.2%	87.1%	0.68, 0.0094
Select Grade ≥3 adverse events	**Rituximab/chemotherapy (n = 597)**	**Obinutuzumab/chemotherapy (n = 595)**	
Leukopenia	8.4%	8.6%	
Neutropenia	37.9%	43.9%	
Febrile neutropenia	4.9%	6.9%	
Infections	15.6%	20%	
Infusion-related reactions	6.7%	12.4%	
Thrombocytopenia	2.7%	6.1%	
Second neoplasms	2.7%	4.7%	

HR = hazard ratio; PFS = progression-free survival; OS = overall survival; TTNT = time to next treatment

Marcus R et al. *Proc ASH* 2016;**Abstract 6**.

in the CLL11 trial in CLL (Goede 2014). However, the GOYA trial for patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) did not show an advantage with obinutuzumab (Vitolo 2016).

Track 9

DR LOVE: How do you approach sequencing treatment for patients with mantle cell lymphoma (MCL)?

DR SEHN: The management of MCL is complicated with all the available options. Ideally, we want to administer the agents that are most effective and least toxic in the earlier settings. It is likely that novel compounds like ibrutinib and possibly lenalidomide may move into the front-line setting because they have a better toxicity profile than our current therapies.

Currently chemoimmunotherapy is still the standard for up-front treatment. For younger patients, autologous stem cell transplant (ASCT) is recommended. I would offer patients ibrutinib in the second line because it is highly effective. After ibrutinib I would recommend bendamustine or bendamustine/rituximab (BR). Lenalidomide either alone or with rituximab is also an option, but I believe it is not as effective as ibrutinib, so I would consider it in a later-line setting. Venetoclax is one of the exciting agents in development for MCL, but we must await further data with this agent.

All of these options will likely be used because we don't have a cure for this disease. We do not have a right or wrong sequence, and in my practice I consider the patient's clinical condition, choose the agent with the highest efficacy and balance that with the toxicity.

Tracks 12-13

DR LOVE: What is your approach to newly diagnosed CLL?

DR SEHN: In my practice in Canada my recommendations are partly dependent on funding. Currently purine analogue-based therapy, like FCR (fludarabine/cyclophosphamide/rituximab), is usually the front-line choice for most patients. In my clinic I generally offer patients fludarabine/rituximab. BR has been shown to be as effective as FCR and has better tolerability, so for many patients BR is a reasonable standard.

We are excited about targeted agents like ibrutinib, which have lower toxicity. Ibrutinib is now a mainstay of therapy in the relapsed setting and may be considered for elderly patients for whom we want to avoid chemotherapy. For patients with 17p deletion chemotherapy is not highly effective and ibrutinib has now become the standard therapy. In my practice we can access ibrutinib for patients with 17p deletion, but it's much more difficult for us to access for elderly patients.

The obinutuzumab/chlorambucil combination is effective for older patients for whom toxicity is an additional concern. In the future I believe we will move away from the more toxic, high-intensity therapies. Novel targeted agents are going to make their way into the front-line setting.

DR LOVE: What is your clinical experience with venetoclax in the management of CLL?

DR SEHN: Venetoclax is on the verge of approval in Canada, and I've only had access to it in my clinic in the context of clinical trials. For patients with CLL, tumor lysis syndrome (TLS) is a definite risk. As venetoclax is starting to be used more commonly, oncologists will need a strategy for identifying and monitoring patients at high risk for TLS and managing care accordingly. TLS is generally a risk only at the initiation of treatment.

Tools and guidelines are available for physicians to aid in the care of these patients. Some patients may need to be admitted to a hospital or receive treatment in centers where sequential laboratory investigations can be obtained to monitor for TLS. We're currently trying to create algorithms and management strategies that allow us to better identify patients at high risk. ■

SELECT PUBLICATIONS

Cheson B et al. **Obinutuzumab plus bendamustine followed by obinutuzumab maintenance prolongs overall survival compared with bendamustine alone in patients with rituximab-refractory indolent non-Hodgkin lymphoma: Updated results of the GADOLIN study.** *Proc ASH* 2016;**Abstract 615**.

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

Marcus R et al. **Obinutuzumab-based induction and maintenance prolongs progression-free survival (PFS) in patients with previously untreated follicular lymphoma: Primary results of the randomized Phase III GALLIUM study.** *Proc ASH* 2016;**Abstract 6**.

Sehn L et al. **Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): A randomised, controlled, open-label, multicentre, phase 3 trial.** *Lancet Oncol* 2016;17(8):1081-93.

Vitolo U et al. **Obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: Final results from an open-label, randomized phase 3 study (GOYA).** *Proc ASH* 2016;**Abstract 470**.