INTERVIEW

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Tracks 1-12

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Tracks 1-2

DR LOVE: Would you discuss your recent editorial "Follicular lymphoma: Watch and wait is watch and worry" relating to the results of the Phase III trial reported by Ardeshna and colleagues comparing rituximab to the watch and wait approach for patients with low tumor burden follicular lymphoma (FL) (Ansell 2014)?

DR ANSELL: As rituximab has become a standard treatment for FL, the question arose as to whether rituximab therapy was an appropriate approach for patients with low tumor burden disease. The trial by Ardeshna and colleagues initially had 3 arms — patients were randomly assigned to a watch and wait approach or 4 doses of rituximab followed by observation or 4 doses of rituximab followed by rituximab maintenance therapy for 2 years. The second arm was closed early because other studies showed a benefit with maintenance rituximab compared to the watch and wait approach after rituximab induction.

Time to next therapy and progression-free survival were improved with rituximab therapy, but there was no difference in overall survival between the arms. The rationale for stating that watch and wait is watch and worry in the editorial is that patients

on the watch and wait arm experienced a poorer quality of life compared to those who received rituximab (Ardeshna 2014; [1.1]). Patients were more concerned about their disease and visits to their physicians in part because of anxiety about whether their disease had progressed and would require therapy.

DR LOVE: How do you care for patients with FL in your practice outside a protocol setting?

DR ANSELL: My approach in clinical practice is to have a comprehensive conversation with patients because I believe it is important that they participate in the decision-making process. Some patients are comfortable with watching and waiting and monitoring the disease to see what happens, but another population of patients are anxious, and those patients would benefit from receiving rituximab.

In my practice, however, I tend to follow a re-treatment approach for patients with low disease burden receiving rituximab, based on the results of the RESORT trial: I generally administer 4 doses of rituximab, and then at any time the disease looks as if it is beginning to progress, re-treat with 4 more doses at that point.

Patients with bulky disease who have significant constitutional symptoms require chemotherapy. I generally treat those cases with bendamustine/rituximab (BR), based on the fact that the StiL and BRIGHT trials comparing R-CHOP chemotherapy to BR demonstrated good outcomes with BR (Rummel 2013; Flinn 2014).

DR LOVE: How do you approach the issue of rituximab maintenance after rituximab-based chemotherapy for FL?

DR ANSELL: Data suggest that this practice improves time to disease progression and overall outcome, and that is a valid reason for considering it. The optimal duration of rituximab maintenance is still unclear and would require more robust, long-term data for us to make definite conclusions. Toxicities may be exacerbated with a longer duration of rituximab therapy, and the benefit needs to be weighed against potential side effects.

1.1

Phase III Trial of Rituximab versus Watch and Wait for Advanced, Asymptomatic, Nonbulky Follicular Lymphoma

Efficacy	Rituximab maintenance (n = 192)	Watch and wait (n = 187)	Hazard ratio	*p*-value
Median time to start of new treatment	NR	31.1 mo	0.21	<0.0001
Patients who did not need new treatment at 3 years	88%	46%		
Median progression-free survival	NR	24.1 mo	0.23	<0.0001
Three-year overall survival	97%	94%	0.73	0.4

- The rituximab induction arm (n = 84) was closed early.
- Compared to the watchful waiting group, patients in the maintenance rituximab group had significant improvements in the Mental Adjustment to Cancer Scale score ($p = 0.0004$) and Illness Coping Style score ($p = 0.0012$) between baseline and month 7.

NR = not reached

Ardeshna KM et al. *Lancet Oncol* 2014;15(4):424-35.

Tracks 7-9

DR LOVE: Would you discuss the clinical trial findings with brentuximab vedotin in Hodgkin lymphoma (HL)?

DR ANSELL: Brentuximab vedotin has become a key player in the management of HL, particularly in the relapsed setting. In the pivotal Phase II trial of brentuximab vedotin for patients with HL whose disease had progressed after autologous stem cell transplantation (ASCT), the overall response rate was 75% and approximately one third of patients experienced a complete remission (Younes 2012). Long-term follow-up shows that a subgroup of approximately 15% to 20% of patients remain in remission 3 to 4 years later. It is approved for patients after failure of ASCT or multiple chemotherapy regimens and is an appropriate approach in that setting.

It is exciting that this agent is being investigated as front-line therapy for HL. The combination of AVD (doxorubicin, vinblastine, dacarbazine) with brentuximab vedotin was highly effective, with a complete response rate of 96% and a lack of serious pulmonary toxicity (Younes 2013). There is a lot of enthusiasm for this active regimen. The question is whether it will perform better than ABVD alone. An ongoing randomized Phase III trial is comparing AVD with brentuximab vedotin to ABVD as front-line therapy in patients with advanced HL (NCT01712490).

DR LOVE: What do we know about the side effects of brentuximab vedotin?

DR ANSELL: We're still learning about the potential toxicities of brentuximab vedotin. Peripheral neuropathy is a significant side effect and becomes more pronounced with longer administration. Dermatologic toxicities are not common. Infusion reactions have been reported but can be easily managed with the addition of premedication and steroids.

DR LOVE: Would you comment on the efficacy of brentuximab vedotin in systemic anaplastic large cell lymphoma (sALCL)?

DR ANSELL: The treatment of sALCL with brentuximab vedotin has been a huge success story. CD30 is expressed at high levels in sALCL, and response rates have been good. Patients with relapsed or refractory sALCL show continued benefit over time. It is now being investigated in the front-line setting for sALCL. Randomized trials are comparing brentuximab vedotin with CHP — CHOP without vincristine — to standard therapy (NCT01777152).

Track 11

DR LOVE: What are your thoughts on the roles of histone deacetylase (HDAC) inhibitors and pralatrexate in the treatment of peripheral T-cell lymphoma (PTCL)?

DR ANSELL: HDAC inhibitors like belinostat have shown promising efficacy in the relapsed/refractory setting and are being evaluated up front. These agents can be used in combination with standard CHOP or CHOEP — CHOP with etoposide. The combination of belinostat and CHOP, or BelCHOP, is being investigated as first-line treatment for PTCL (NCT01839097).

Romidepsin is an agent that has a real benefit and is being studied in combination with CHOP in patients with untreated PTCL (NCT01796002). Hopefully the data will show that it provides additional benefit to patients in the long term.

The addition of pralatrexate to CHOP-like chemotherapy has proven to be challenging because of potential toxicities. The T-cell Consortium recently reported the results of a study of CEOP — cyclophosphamide, etoposide, vincristine and prednisone — alternating with pralatrexate. The data were not as promising as what one might have hoped.

DR LOVE: How do you approach the sequencing of pralatrexate and romidepsin outside of a protocol setting?

DR ANSELL: They are both useful agents, and I would commonly use them in the relapsed setting. The choice between the 2 agents would mainly depend on discussions with the patient about the risks and benefits, because they have similar efficacies but different toxicities.

Editor's note: On July 3, 2014, the US Food and Drug Administration (FDA) granted accelerated approval to belinostat for the treatment of relapsed or refractory PTCL.

Track 12

DR LOVE: Would you discuss emerging data with some of the novel therapeutic strategies for Waldenström macroglobulinemia (WM)?

DR ANSELL: The discovery of mutations in the MyD88 adaptor protein, which is present in more than 90% of patients with WM, is interesting and provides us with opportunities to target that pathway. Ibrutinib has shown a high level of activity in initial studies and is a promising agent in WM (Treon 2013; [1.2]). In the future, hopefully combining ibrutinib with other effective agents will be beneficial for patients.

We reported on the lenalidomide, rituximab, cyclophosphamide and dexamethasone (LR-CD) combination at ASH 2013 (Rosenthal 2013; [1.3]). Lenalidomide had been shown to be effective, but patients experienced some issues with anemia. Our goal in this study was to see if combining lenalidomide with a standard regimen would be beneficial. The results were promising, so the hope is in the future to continue to add effective agents to yield a better overall result.

1.2

Prospective Multicenter Study of the Bruton Tyrosine Kinase Inhibitor Ibrutinib in Relapsed or Refractory Waldenström Macroglobulinemia

Efficacy	(n = 63)
Overall response rate	81.0%
Very good partial response	6.3%
Partial response	50.8%
Minor responses	23.8%

- Grade >2 toxicities included neutropenia (19.1%), thrombocytopenia (14.3%), atrial fibrillation (1.6%) and herpes zoster (1.6%).
- Rapid reductions in serum IgM were observed in most patients.
- Attainment of major responses to ibrutinib was affected by mutations in CXCR4 but not MYD88 L265P.

Treon SP et al. *Proc ASH* 2013;**Abstract 251**.

1.3

Phase II Study of Lenalidomide, Rituximab, Cyclophosphamide and Dexamethasone (LR-CD) for Untreated Low-Grade Non-Hodgkin Lymphoma: Waldenström Macroglobulinemia Cohort

Efficacy	(n = 15)
Overall response rate	80.0%
Complete response	6.7%
Partial response	73.3%

- The most common Grade 3 or 4 adverse events were neutropenia (13% Grade 3, 33% Grade 4), anemia (27% Grade 3, 13% Grade 4), and leukopenia (13% Grade 3, 20% Grade 4).
- Grade ≥3 nonhematologic toxicity: 40%
- LR-CD can be safely administered for newly diagnosed symptomatic Waldenström macroglobulinemia.

Rosenthal AC et al. *Proc ASH* 2013;**Abstract 4352**.

1.4

Phase II Study of Carfilzomib, Rituximab and Dexamethasone for Symptomatic Waldenström Macroglobulinemia

Efficacy	(n = 31)
Overall response rate	87.1%
Complete response	3.2%
Very good partial response	32.3%
Partial response	32.3%
Minimal responses	19.3%

- Grade ≥2 toxicities included asymptomatic hyperlipasemia (41.9%), reversible neutropenia (12.9%), cardiomyopathy (3.2%) and peripheral neuropathy (3.2%).

Treon SP et al. *Blood* 2014;124(4):503-10.

Proteasome inhibitors are also effective in WM. They elicit good responses and lower IgM levels. The lower incidence of peripheral neuropathy with carfilzomib, compared to bortezomib, makes it an appealing agent (Treon 2014; [1.4]). If we can find the optimal agent with low toxicity, that would be a welcome addition to the armamentarium for treating this disease. ■

SELECT PUBLICATIONS

Ansell SM. **Follicular lymphoma: Watch and wait is watch and worry.** *Lancet Oncol* 2014;15(4):368-9.

Ansell SM et al. **Frontline therapy with brentuximab vedotin combined with ABVD or AVD in patients with newly diagnosed advanced stage Hodgkin lymphoma.** *Proc ASH* 2012;**Abstract 798**.

Flinn IW et al. **Randomized trial of bendamustine-rituximab or R-CHOP/R-CVP in first-line treatment of indolent NHL or MCL: The BRIGHT study.** *Blood* 2014;123(19):2944-52.

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab as first-line treatment for patients with indolent and mantle-cell lymphomas: An open-label, multicentre, randomised, phase 3 non-inferiority trial.** *Lancet* 2013;381(9873):1203-10.

Younes A et al. **Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: A phase 1, open-label, dose-escalation study.** *Lancet Oncol* 2013;14(13):1348-56.

Younes A et al. **Results of a pivotal Phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma.** *J Clin Oncol* 2012;30(18):2183-9.