INTERVIEW

Sonali M Smith, MD

Dr Smith is Associate Professor in the Section of Hematology/Oncology and Director of the Lymphoma Program at The University of Chicago in Chicago, Illinois.

Tracks 1-14

Track 1 Activity, side effects and mechanism of action of brentuximab vedotin in CD30-positive lymphomas

Track 2 Clinical investigation of up-front chemotherapy in combination with brentuximab vedotin for elderly patients with HL

Track 3 Activity of lenalidomide in relapsed or refractory DLBCL

Track 4 **Case 6 discussion:** A healthy 71-year-old man with profound lymphocytosis and splenomegaly is diagnosed with MCL with t(11;14) translocation

Track 5 Aggressive induction immunochemotherapy including cytarabine followed by ASCT for younger patients with MCL

Track 6 Age, performance status or geriatric assessment in treatment decision-making for newly diagnosed lymphoma

Track 7 BR for relapsed MCL

Track 8 Investigational agents — Btk and PI3-kinase inhibitors — in MCL

Track 9 Emerging data with the second-generation proteasome inhibitor carfilzomib in NHL

Track 10 ECOG study of induction BR with or without bortezomib for elderly patients with untreated MCL

Track 11 Translating recent clinical trial data to the front-line treatment of PTCL

Track 12 Pralatrexate for relapsed or refractory PTCL in the pivotal PROPEL study

Track 13 Shifting treatment of cutaneous T-cell lymphoma to biologic therapies — retinoids, HDAC inhibitors and denileukin diftitox

Track 14 Emerging role of epigenetics in identifying risk factors and treatment approaches in lymphomas

Select Excerpts from the Interview

Tracks 1-2

DR LOVE: What are your thoughts on the antibody-drug conjugate brentuximab vedotin, which was recently approved by the FDA for relapsed/refractory Hodgkin lymphoma (HL) and relapsed/refractory anaplastic large cell lymphoma (ALCL)?

DR SMITH: Brentuximab vedotin, also known as SGN-35, is a monoclonal antibody that binds CD30, which is an activation marker present on classical

HL but also present in certain other lymphomas, such as ALCL. DLBCL even has a CD30-positive variant. When brentuximab vedotin binds a CD30-positive tumor cell, it releases an auristatin analog, which is an antitubulin agent that leads to apoptosis.

The brentuximab vedotin story is fascinating, and for the first time we have a targeted therapy for patients with HL. Phase I data with brentuximab vedotin primarily in patients with HL and ALCL have already been published in *The New England Journal of Medicine* (Younes 2010). This agent can be used in the relapsed/refractory setting, but it also should be taken forward into trials in the up-front setting. Brentuximab vedotin's safety profile and the ability to combine it with other chemotherapy regimens make it a promising agent for patients with HL.

In patients with relapsed/refractory ALCL, the Phase II data are also extremely promising because the vast majority of patients experienced a response, and many of those responses were durable (Shustov 2010; [4.1]). This agent also seems to be well tolerated, with the only toxicity being some hepatotoxicity and neuropathy.

Researchers are evaluating brentuximab vedotin in a number of different settings. Perhaps one of the biggest areas of unmet need is among patients older than age 60 with classical HL. This population represents about 15% of all patients with HL, and they tend to have poor outcomes. They've been under-represented on the vast majority of studies, probably because of low tolerance to bleomycin and other augmented regimens. I believe this is a setting in which brentuximab vedotin can make a difference (Chen 2010; [4.1]).

4.1

Response and Maximum Tumor Reduction with Brentuximab Vedotin (SGN-35) in Relapsed/Refractory Hodgkin Lymphoma (HL) and Anaplastic Large Cell Lymphoma (ALCL)*

	HL[1] (n = 102)	ALCL[2] (n = 58)
Overall response rate	75%	86%
Complete remission	34%	53%
Partial remission	40%	33%
Maximum tumor reduction (n = 96, 57)	94%	97%

* By independent review facility

[1] Chen R et al. *Proc ASH* 2010;**Abstract 283**; [2] Shustov AR et al. *Proc ASH* 2010;**Abstract 961**.

Track 5

DR LOVE: What is your up-front treatment approach for patients with MCL?

DR SMITH: At our institution, a fit and relatively young patient with MCL would be considered for an aggressive induction therapy followed by consoli-

dative autologous stem cell transplant (ASCT) based on data from the German Group and the CALGB experience, which reported that patients who enter a good remission with induction chemotherapy and receive an ASCT have an approximately 70% to 80% survival rate (Damon 2009; Dreyling 2005). The challenge is that this type of aggressive therapy is not appropriate for all patients, and controversy exists over the best induction therapy prior to ASCT.

The CALGB-59909 study used augmented CHOP with a methotrexate-based induction regimen. I would consider it a hybrid of R-hyper-CVAD, but the difference is that on the CALGB regimen the induction courses are limited. They only administer 2 or at most 3 courses of induction therapy prior to collecting stem cells and proceeding to transplant.

At ASH 2010 Martin Dreyling and colleagues reported that the addition of cytarabine to induction therapy provides a substantial improvement in complete response rates and time to treatment failure after transplant (Hermine 2010). The addition of cytarabine did not translate to an improvement in OS, but the follow-up is still relatively short. Now I believe that any patient who is being considered for an ASCT in first remission should consider cytarabine as part of his or her induction therapy.

Track 10

DR LOVE: What is known about the use of BR for patients with MCL?

DR SMITH: In the NHL 1-2003 study, a subanalysis of patients with indolent lymphoma who received BR versus R-CHOP was performed, and BR appeared to be equivalent to R-CHOP (Burchardt 2009). I believe cytarabine is important, but I also feel that not every patient can tolerate high-dose cytarabine. Some patients probably fare better with an outpatient regimen, whether it's R-CHOP or BR, and may still be considered for an ASCT.

DR LOVE: What are your thoughts on the combination of BR and bortezomib that's being compared to BR in a Phase II ECOG study for patients with MCL who are not eligible for transplant?

4.2

VERTICAL Study: Bendamustine, Bortezomib and Rituximab (BVR) in Patients with Relapsed/Refractory Follicular Lymphoma

Efficacy	BVR (n = 63)
Overall response rate	88%
Complete response rate	53%
Median duration of response	11.7 months
Median progression-free survival	14.9 months

Fowler N et al. *J Clin Oncol* 2011;29(25):3389-95.

DR SMITH: The bendamustine/bortezomib/rituximab (BVR) regimen has also been referred to as the "VERTICAL regimen" (Fowler 2011; [4.2]). It's a well-tolerated regimen and I believe it's appropriate to compare it to BR to ascertain exactly what bortezomib contributes to the BR regimen (4.3). ■

4.3

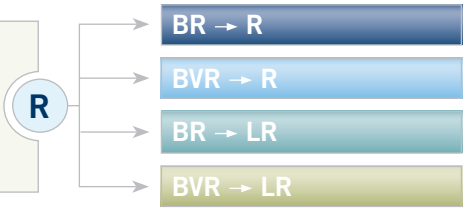
Bendamustine (B), Bortezomib (V) and Rituximab (R) Followed by R and Lenalidomide (L) for Older Patients with Previously Untreated Mantle-Cell Lymphoma (MCL)

Protocol IDs: ECOG-E1411

Target Accrual: 332 (Open)

Eligibility

- Histologically confirmed untreated MCL
- ECOG PS 0 to 2
- No CNS metastasis



www.clinicaltrials.gov.

SELECT PUBLICATIONS

Burchardt CA et al. **Peripheral blood stem cell mobilization after bendamustine containing chemotherapy in indolent lymphomas is possible. Results from the phase III study of B-R vs CHOP-R (NHL 1-2003 trial) of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 2679**.

Chen R et al. **Results of a pivotal Phase 2 study of brentuximab vedotin (SGN-35) in patients with relapsed or refractory Hodgkin lymphoma.** *Proc ASH* 2010;**Abstract 283**.

Damon LE et al. **Immunochemotherapy and autologous stem-cell transplantation for untreated patients with mantle-cell lymphoma: CALGB 59909.** *J Clin Oncol* 2009;27(36):6101-8.

Dreyling M et al. **Early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation in first remission significantly prolongs progression-free survival in mantle-cell lymphoma: Results of a prospective randomized trial of the European MCL Network.** *Blood* 2005;105(7):2677-84.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: The Phase II VERTICAL study.** *J Clin Oncol* 2011;29(25):3389-95.

Hermine O et al. **Alternating courses of 3x CHOP and 3x DHAP plus rituximab followed by a high dose ARA-C containing myeloablative regimen and autologous stem cell transplantation (ASCT) is superior to 6 courses CHOP plus rituximab followed by myeloablative radiochemotherapy and ASCT in mantle cell lymphoma: Results of the MCL Younger Trial of the European Mantle Cell Lymphoma Network (MCL net).** *Proc ASH* 2010;**Abstract 110**.

Shustov AR et al. **Complete remissions with brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large cell lymphoma.** *Proc ASH* 2010;**Abstract 961**.

Younes A et al. **Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas.** *N Engl J Med* 2010;363(19):1812-21.