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Hematologic Oncology™ UPDATE

Conversations with Oncology Investigators

Bridging the Gap between Research and Patient Care

FACULTY INTERVIEWS

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Hematologic Oncology Update
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OVERVIEW OF ACTIVITY

The treatment of hematologic cancer remains a challenge for many healthcare professionals and patients despite recent gains made in the management of this group of diseases. Determining which treatment approach is most appropriate for a given patient requires careful consideration of patient-specific characteristics, physician expertise and available health system resources. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading hematology-oncology investigators. By providing information on the latest clinical developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of evidence-based and current therapeutic strategies, which in turn facilitates optimal patient care.

LEARNING OBJECTIVES

- Utilize case-based learning to formulate individualized management strategies for patients with hematologic cancer.
- Optimize the management of chronic lymphocytic leukemia and follicular lymphoma through the rational integration of prospective clinical trial results.
- Apply the results of emerging clinical research to the care of patients with myelodysplastic syndromes and acute myeloid leukemia.
- Develop an evidence-based treatment approach for younger and older patients with mantle-cell lymphoma.
- Explain the risks and benefits of evidence-based systemic agents to patients with diverse subtypes of T-cell lymphoma.
- Compare and contrast the benefits and risks of immunomodulatory agents, proteasome inhibitors or both as systemic induction, maintenance and/or relapse treatment of active multiple myeloma.
- Describe the biologic rationale, efficacy and toxicity of novel agents targeting CD30-positive Hodgkin lymphoma and anaplastic large cell lymphoma.
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities.

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INTERVIEW

Julie M Vose, MD

Dr Vose is Neumann M and Mildred E Harris Professor, Chief in the Division of Hematology/Oncology and Professor of Medicine at Nebraska Medical Center in Omaha, Nebraska.

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Track 2 Brentuximab vedotin in relapsed or refractory anaplastic large cell lymphoma (ALCL) and Hodgkin lymphoma (HL)

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Select Excerpts from the Interview

Track 3

DR LOVE: What new systemic therapy strategies are under investigation for patients with non-Hodgkin lymphoma (NHL)?

DR VOSE: An important area of study includes the expanded use of existing agents such as lenalidomide, which appears to have favorable activity in some types of NHL. Lenalidomide is administered orally and has a good toxicity profile. In both mantle-cell lymphoma (MCL) and diffuse large B-cell lymphoma (DLBCL), it appears to have good activity. In some studies, lenalidomide is being evaluated as maintenance therapy, which is another area that seems promising.

DR LOVE: Would you talk about the paper published by your group earlier this year evaluating single-agent lenalidomide for patients with transformed NHL?

DR VOSE: Patients with transformed lymphoma had fairly good, durable responses to lenalidomide (Czuczman 2011). Transformed lymphoma is difficult to treat, and we're always looking for new agents or new combinations to use in this setting. Because lenalidomide has relatively low toxicity, I believe it's a good option for these patients, and it may be of use in combination with other agents.

Track 5

DR LOVE: Would you discuss your study that evaluated survival over the past 3 decades for patients with Grade I or II follicular lymphoma (FL) treated with rituximab?

DR VOSE: After evaluating a number of different patients at our center treated over the past several decades, it appeared that rituximab was associated with continued improvement in outcomes over time with the greatest effect in those patients who received rituximab as initial treatment rather than as salvage therapy (Bociek 2011; [1.1]). The effects were dependent on the different grades of FL.

For symptomatic patients who require treatment, evidence exists that rituximab either alone or in combination is beneficial and improves progression-free survival (PFS) and, in some studies, overall survival (OS).

However, in patients whose disease is asymptomatic, controversy persists with regard to whether improving PFS makes a difference in outcome. At this time, no studies indicate that rituximab improves OS for asymptomatic patients, but it definitely improves the time that patients are in remission.

DR LOVE: What are your thoughts on the use of rituximab maintenance in FL?

DR VOSE: Based on the PRIMA data (Salles 2011; [1.2]), we administer rituximab maintenance after rituximab/chemotherapy using the same schedule the PRIMA study used.

We normally do not treat beyond 2 years because we have no supportive data at this time. Additionally, a small number of patients on rituximab maintenance develop adverse effects, such as infections or low immunoglobulin levels. Although it doesn't occur that often, it does happen to some patients and they develop repeated sinopulmonary infections.

1.1

Effect of Rituximab (R) on Survival in Patients with Grade 1 or 2 Follicular Lymphoma Treated over the Past 3 Decades*

	No R	Initial R	Salvage R	*p*-value
Five-year probability of survival	72% Reference	89% HR = 0.33	90% HR = 0.60	<0.001

HR = hazard ratio

Conclusions: In this analysis, patients with Grade 1 or 2 follicular lymphoma in the Nebraska Lymphoma Study Group database who received initial or salvage R experienced prolonged survival compared to those who never received R. This effect was independent of FLIPI score, and the effect was greatest for patients who received R starting with their initial therapy.

* Retrospective analysis of patients in the Nebraska Lymphoma Study Group database who received therapy between June 1981 and January 2008

Bociek G et al. *Proc ASCO* 2011;**Abstract e18509**.

1.2

Rituximab (R) Maintenance for Patients with Follicular Lymphoma Responding to Immunochemotherapy: Survival and Adverse Events (AEs) in the PRIMA Study at 36 Months Median Follow-Up

	R maintenance	Observation	Hazard ratio (HR) or risk ratio (RR)	*p*-value
Three-year PFS (n = 505, 513)	74.9%	57.6%	0.55 (HR)	<0.0001
Grade 3 or 4 AEs (n = 501, 508)	24%	17%	1.46 (RR)	0.0026
Grade 2 to 4 infections	39%	24%	1.62 (RR)	<0.0001
Treatment discontinued because of AE	4%	2%	2.41 (RR)	0.029

PFS = progression-free survival

Salles G et al. *Lancet* 2011;377(9759):42-51.

Track 21

DR LOVE: What is your usual approach to first-line treatment of chronic lymphocytic leukemia (CLL)?

DR VOSE: For up-front therapy with an asymptomatic patient, we use a watch-and-wait approach. In general, we have been administering fludarabine/cyclophosphamide/rituximab (FCR) to a younger patient who has cytopenias or is otherwise symptomatic, although bendamustine/rituximab (BR) is now being used more often because of the decreased toxicity profile. For younger patients with relapsed disease, we consider an allogeneic transplant, especially for patients with high-risk cytogenetics.

We are also currently enrolling patients in the CALGB-10404 study — which is a randomized Phase II trial — that is evaluating the addition of cyclophosphamide and/or lenalidomide to fludarabine/rituximab (FR) in CLL (1.3).

DR LOVE: What has been your experience with tumor lysis syndrome in patients with CLL — particularly those with a high white blood cell count — and how do you approach it clinically?

DR VOSE: Tumor lysis syndrome is often easily managed, so we generally don't have to discontinue treatment. Patients with a high white blood cell count and those with large, bulky disease or a large tumor burden are definitely at higher risk, so we carefully monitor these patients.

Unless a patient with CLL has transformed disease, I would not necessarily administer rasburicase. However, in other types of aggressive lymphomas — Burkitt's lymphoma or lymphoblastic lymphoma, which have a high proliferation rate — we administer rasburicase to patients with a high risk of tumor lysis, and we have had excellent experiences with it. ■

1.3

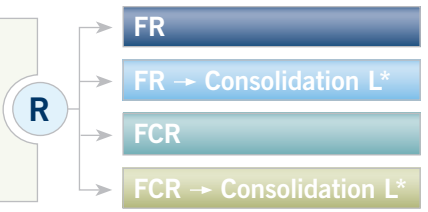
Fludarabine (F) and Rituximab (R) with or without Lenalidomide (L) and/or Cyclophosphamide (C) for Patients with Symptomatic, Previously Untreated Chronic Lymphocytic Leukemia (CLL)

Protocol IDs: CALGB-10404; ECOG-10404; NCIC-CTG-C10404; SWOG-C10404

Target Accrual: 405 (Open)

Eligibility

- ≥18 years old with untreated B-cell CLL
- Symptomatic
- PS 0 to 2
- Intermediate or high risk (Rai stage)

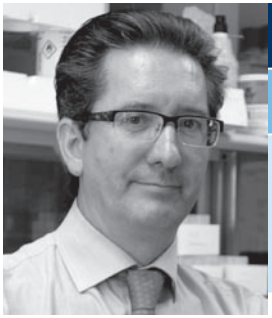


* Consolidation therapy for patients with complete or partial response or stable disease after induction therapy

www.clinicaltrials.gov. Identifier NCT00602459.

SELECT PUBLICATION

Czuczman MS et al. **The differential effect of lenalidomide monotherapy in patients with relapsed or refractory transformed non-Hodgkin lymphoma of distinct histological origin.** *Br J Haematol* 2011;154(4):477-81.



INTERVIEW

Jesus F San-Miguel, MD, PhD

Dr San-Miguel is Professor of Hematology and Head of the Hematology Department at the University Hospital of Salamanca and Director of the Biomedical Research Institute of Salamanca in Salamanca, Spain.

Tracks 1-15

Select Excerpts from the Interview

Track 5

DR LOVE: Would you comment on the use of post-transplant maintenance lenalidomide in multiple myeloma (MM), what we've learned from the updated data presented in Paris by the CALGB and the issue of secondary cancer?

DR SAN-MIGUEL: The post-transplant lenalidomide maintenance data in patients with MM are attractive. The duration of PFS was nearly doubled

in both the French and CALGB trials (Attal 2010; McCarthy 2011; [2.1]). Although no benefit has been observed in the French trial with regard to OS, a benefit is already evident in the reduced number of deaths with lenalidomide maintenance in the CALGB. However, the enthusiasm for these benefits was initially somewhat counteracted by the issue of second cancers.

Most of the agents we use to treat cancer can induce a higher risk of secondary tumors, and so far in the French trial the incidence in the treatment arm is between 7% and 8%. In the control arm, the incidence is significantly lower. Ultimately, though, the event-free survival continues to be in favor of lenalidomide maintenance.

2.1

Post-transplant Lenalidomide Maintenance Therapy for Patients with Multiple Myeloma

	IFM 2005-02[1]		CALGB-100104[2]	
	Lenalidomide (n = 307)	**Placebo** (n = 307)	**Lenalidomide** (n = 231)	**Placebo** (n = 229)
Median PFS[1] or TTP[2]	41 mo	24 mo	48 mo	31 mo
	$p < 10^{-8}$		$p < 0.0001$	
Deaths	19%*	17%*	9%	16%

PFS = progression-free survival; TTP = time to progression
* Difference not significant

[1] Attal M et al. *Proc 13th International Myeloma Workshop* 2011; [2] McCarthy PL et al. *Proc 13th International Myeloma Workshop* 2011.

Track 7

DR LOVE: Would you discuss the options for initial up-front therapy for transplant-ineligible patients with MM?

DR SAN-MIGUEL: For the elderly, melphalan/prednisone (MP) has been standard for more than 30 years. However, now we have 3 agents — thalidomide (T), lenalidomide (R) and bortezomib (V) — that, in combination with MP or corticosteroids, have become the new treatment standard.

The addition of thalidomide to MP (MPT) yields a significant benefit in terms of response rate and PFS in at least 5 of the 6 randomized trials, and in 3 of them a benefit is also apparent in OS, leading to an approximate 6-month prolongation in both OS and PFS (Fayers 2011).

Lenalidomide in combination with MP (MPR) has been recently tested in a large randomized trial. This trial compared MP to MPR with a third arm evaluating lenalidomide as continuous treatment until disease progression, and the response rate was significantly higher with the lenalidomide-based regimens. Furthermore, an additional significant benefit was observed in PFS for patients receiving continuous lenalidomide compared to MP and MPR. No difference in OS was observed (Palumbo 2010).

Bortezomib was evaluated in the VISTA study, which was a large randomized trial that compared MPV to MP alone. The difference in response rate was significant, with an 8-month benefit in PFS and a significant benefit in OS observed with the addition of bortezomib. These data were striking because benefit in PFS was clear almost from the outset (San Miguel 2008).

Nevertheless, bortezomib was associated with some toxicity, particularly peripheral neuropathy. For this reason, the Spanish group pioneered the concept of reducing the dose by moving to a weekly dosing schedule from a twice-weekly dosing schedule. In the GEM-2005 trial, by reducing the dose of bortezomib from twice weekly to weekly we were able to significantly decrease the peripheral neuropathy. Gastrointestinal symptoms were also significantly reduced. Most important, we were able to maintain, if not increase, the efficacy of the regimen (Mateos 2010b).

Track 8

DR LOVE: Would you discuss the Phase III study evaluating subcutaneous versus intravenous (IV) bortezomib in MM that was recently published in *The Lancet Oncology* (Moreau 2011; [2.2])?

DR SAN-MIGUEL: The study was a 2-to-1 randomization comparing subcutaneous administration of bortezomib to IV treatment, and approximately 220 patients were randomly assigned. The data are attractive for several reasons. First, the incidence of Grade 3 or higher peripheral sensory neuropathy is quite low with subcutaneous administration, 6% or less.

Second, the response rate was near 55%, and the PFS was almost 11 months, which is longer than the 6-month PFS reported previously in the APEX trial. Interestingly, even on the IV arm, it was more than 9 months in this study. The question is, why is the PFS longer, even with IV administration? I believe it's because physicians now know how to use bortezomib better. They are reducing the toxicity by decreasing dose as soon as a signal indicates to do so. This allows the patient to stay on treatment which results in prolonged survival.

2.2

MMY-3021: A Phase III Trial of Subcutaneous (SC) versus Intravenous (IV) Administration of Bortezomib in Relapsed Multiple Myeloma

Response	Bortezomib SC (n = 145)	Bortezomib IV (n = 73)
Overall response rate	42%	42%
Complete response	6%	8%
Nonhematologic adverse events		
Any peripheral neuropathy (any grade)	38%	53%
Any peripheral neuropathy (Grade ≥3)	6%	16%

Moreau P et al. *Lancet Oncol* 2011;12(5):431-40.

Tracks 12, 14

DR LOVE: Would you talk a little about some of the new agents that are emerging in MM?

DR SAN-MIGUEL: Pomalidomide is a third-generation IMiD with efficacy similar to lenalidomide — about 60% of patients at high risk responded, and a PFS of approximately 11 months was achieved. Even patients with lenalidomide-refractory disease respond to pomalidomide — 20% to 30% respond, with a 5- to 7-month PFS (Lacy 2010).

Carfilzomib is a second-generation proteasome inhibitor and is similar to bortezomib in terms of response, with a PFS of around 1 year in bortezomib-naïve disease in patients who achieved VGPR. In patients with bortezomib-refractory disease, approximately 20% respond to carfilzomib. Another important point is the lack of associated peripheral neuropathy.

At ASH 2010, Dr Jakubowiak presented data on carfilzomib, lenalidomide and dexamethasone (CRd) in newly diagnosed MM. The response rate to CRd was 100% (Jakubowiak 2010). Almost 40% are complete responses, which is similar to the RVD regimen, so I believe these agents will move quickly to the up-front setting. ■

SELECT PUBLICATIONS

Attal M et al. **Maintenance treatment with lenalidomide after transplantation for MYELOMA: Final analysis of the IFM 2005-02.** *Proc ASH* 2010;**Abstract 310**.

Fayers PM et al. **Thalidomide for previously untreated elderly patients with multiple myeloma: Meta-analysis of 1685 individual patient data from 6 randomized clinical trials.** *Blood* 2011;118:1239-47.

Jakubowiak AJ et al. **Carfilzomib, lenalidomide, and dexamethasone in newly diagnosed multiple myeloma: Initial results of Phase I/II MMRC trial.** *Proc ASH* 2010;**Abstract 862**.

Lacy MQ et al. **Pomalidomide (CC4047) plus low dose dexamethasone (pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM).** *Leukemia* 2010;24(11):1934-9.

Mateos MV et al. **Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial.** *Lancet Oncol* 2010a;11(10):934-41.

Mateos MV et al. **Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the Phase III VISTA trial.** *J Clin Oncol* 2010b;28(13):2259-66.

McCarthy P et al. **Phase III Intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB ECOG BMT-CTN 100104.** *Proc 13th International Myeloma Workshop* 2011.

Palumbo A et al. **A Phase 3 study to determine the efficacy and safety of lenalidomide combined with melphalan and prednisone in patients ≥ 65 years with newly diagnosed multiple myeloma.** *Haematologica* 2010;95(51);**Abstract 0566**.

San Miguel JF et al. **Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma.** *N Engl J Med* 2008;359(9):906-17.

INTERVIEW

Pierre Fenaux, MD

Dr Fenaux is Professor of Hematology at the Hôpital Avicenne, University Paris 13 in Bobigny, France.

Tracks 1-9

Track 1 Advances in understanding the biology of myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML)

Track 2 Evaluation and initial treatment for patients with MDS

Track 3 Selection of hypomethylating agent — azacitidine or decitabine — for the treatment of MDS

Track 4 Monitoring and management of treatment-related neutropenia and anemia during early cycles of hypomethylating agents

Track 5 Schedule and duration of administration with hypomethylating agents in MDS

Track 6 Lenalidomide in MDS with or without del(5q)

Track 7 Novel markers for risk stratification and treatment approach for older patients with AML

Track 8 Induction chemotherapy/all-trans retinoic acid (ATRA) with arsenic trioxide consolidation therapy as up-front treatment of acute promyelocytic leukemia (APL)

Track 9 High early death rate in APL despite ATRA

Select Excerpts from the Interview

Track 3

DR LOVE: How do you choose between the hypomethylating agents, azacitidine and decitabine, when treating myelodysplastic syndromes (MDS)?

DR FENAUX: It's difficult. At least 1 study has shown a survival advantage with azacitidine (Fenaux 2009a; [3.1]), but that's not yet been shown with decitabine. This might be related to a difference between the agents, but it may also be that the schedule used in the decitabine trials was not optimal. Since those data were presented, a new schedule of 20 mg/m^2 per day for 5 days every month has been approved by the FDA. This may be more active than the schedule evaluated in the initial trials, and it's used in most centers in the United States.

Another reason why the decitabine studies were not conclusive for a survival advantage may be that the number of cycles administered was not adequate. It

3.1

Azacitidine versus Conventional Care Regimens (CCR) for Patients with Higher-Risk Myelodysplastic Syndromes: Efficacy Data

	Azacitidine (n = 179)	CCR (n = 179)	Hazard ratio	*p*-value
Median overall survival	24.5 months	15 months	0.58	0.0001
Median time to AML transformation	17.8 months	11.5 months	0.50	<0.0001

AML = acute myeloid leukemia

Fenaux P et al. *Lancet Oncol* 2009;10(3):223-32.

appears that prolonged treatment is key. The azacitidine trial that reported a survival improvement had a median number of 9 cycles overall and 15 cycles in responders, which is probably significant in terms of outcome.

Track 4

DR LOVE: What common side effects and toxicities are seen with hypomethylating agents?

DR FENAUX: The most significant problem is related to cytopenias during the first cycles. Hypomethylating agents lead to fewer cytopenias compared to chemotherapy, but MDS occurs in patients who are typically older than those who would receive chemotherapy, so it remains an issue in these patients. Protracted neutropenia also occurs in many of these patients, in addition to defects in neutrophil function. These patients are prone to infections, and patients must be carefully monitored during the first cycles.

When necessary, we transfuse the patients or administer prophylactic antibiotics. Oncologists need to be aware in advance that these agents are associated with cytopenias and treat accordingly. Otherwise, the risk may be stopping too early, lowering the dose too rapidly or increasing the interval too quickly between cycles.

Track 6

DR LOVE: What are your thoughts on lenalidomide for patients with MDS and 5q deletions?

DR FENAUX: The MDS-003 and MDS-004 trials (List 2006; Fenaux 2009b; [3.2]) demonstrated that a sufficient dose of lenalidomide initially — 10 mg rather than 5 mg daily — is necessary to achieve transfusion independence. More patients who received the higher dose achieved cytogenetic responses, which is associated with fewer cases of progression from MDS to acute myeloid leukemia (AML). This analysis showed that the more you eradicate the disease in terms of cytogenetic response, the longer the remissions are and the fewer the cases of progression to AML.

3.2

MDS-003 and MDS-004 Trials: Efficacy of and Transfusion Independence with Lenalidomide 10 Mg for Patients with Myelodysplastic Syndromes and Del(5q)

	MDS-003[1]	MDS-004[2]
Transfusion independence	67%	56%
Complete cytogenetic response	45%	24%

[1] List A et al. *N Engl J Med* 2006;355(14):1456-65; [2] Fenaux P et al. *Proc ASH* 2009b;**Abstract 944**.

Track 8

DR LOVE: What's new in acute promyelocytic leukemia (APL)?

DR FENAUX: APL can be cured in the majority of patients. Combination chemotherapy/all-trans retinoic acid (ATRA) leads to an 80% event-free survival and a 90% disease-free survival (Powell 2010; [3.3]). Arsenic trioxide (ATO) can also be used as consolidation to reduce the risk of mortality in remission. Some physicians use ATO up front without chemotherapy, in combination with ATRA, but this approach can be potentially dangerous due to significant differentiation syndrome. I believe the Intergroup trial used a wise approach in keeping the anthracycline/ATRA combination for induction and using arsenic derivatives for consolidation and/or maintenance. ■

3.3

Intergroup Study C9710: Arsenic Trioxide (ATO) with Standard Induction/Consolidation Therapy* for Acute Promyelocytic Leukemia

Endpoint	Induction → consolidation (n = 237)	Induction → consolidation + ATO† (n = 244)	*p*-value
Three-year event-free survival	63%	80%	<0.0001
Three-year overall survival	81%	86%	0.059
Three-year disease-free survival	70%	90%	<0.0001

* Induction (ATRA, Ara-C, daunorubicin); 2 courses consolidation (ATRA, daunorubicin)
† Two 25-day courses of ATO consolidation immediately after induction

Powell BL et al. *Blood* 2010;116(19):3751-7.

SELECT PUBLICATIONS

Fenaux P et al. **Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: A randomised, open-label, phase III study.** *Lancet Oncol* 2009a;10(3):223-32.

Fenaux P et al. **RBC transfusion independence and safety profile of lenalidomide 5 or 10 mg in pts with low- or int-1-risk MDS with del5q: Results from a randomized Phase III trial (MDS-004).** *Proc ASH* 2009b;**Abstract 944**.

List A et al. **Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion.** *N Engl J Med* 2006;355(14):1456-65.

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

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

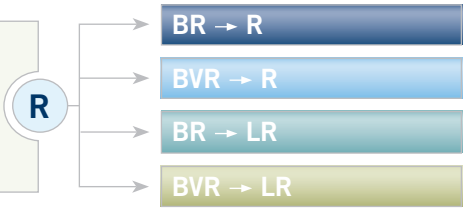
Bendamustine (B), Bortezomib (V) and Rituximab (R) Followed by R and Lenalidomide (L) for Older Patients with Previously Untreated Mantle-Cell Lymphoma (MCL)

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.

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **The PRIMA study of maintenance rituximab versus observation for patients with FL responding to immunochemotherapy demonstrated that the use of maintenance rituximab was not associated with an improvement in PFS.**
   a. True
   b. False
2. **In the CALGB-100104 and IFM 2005-02 trials, post-transplant lenalidomide maintenance therapy for patients with newly diagnosed MM resulted in significant improvements in time to disease progression and PFS, respectively.**
   a. True
   b. False
3. **Updated data presented by the CALGB at the 13th International Myeloma Workshop indicate that patients receiving lenalidomide maintenance therapy experienced improved overall survival.**
   a. True
   b. False
4. **Data from the Phase III MMY-3021 trial evaluating subcutaneous versus intravenous administration of bortezomib for patients with relapsed MM reported equivalent response rates and a(n) _____ incidence of peripheral neuropathy with subcutaneous bortezomib administration.**
   a. Decreased
   b. Equivalent
   c. Increased
5. **The ECOG-E1411 trial is evaluating BR or BVR followed by rituximab or lenalidomide/rituximab maintenance therapy for older patients with previously untreated MCL.**
   a. True
   b. False
6. **Study data with brentuximab vedotin presented at ASH 2010 demonstrated an overall response rate of 75% or higher for patients with _____.**
   a. Hodgkin lymphoma
   b. Anaplastic large T-cell lymphoma
   c. Both a and b
7. **Brentuximab vedotin is an antibody-drug conjugate that targets _____ tumor cells.**
   a. CD20-positive
   b. CD30-positive
   c. CD5-positive
8. **In the VERTICAL study for patients with relapsed/refractory FL, treatment with BVR resulted in an overall response rate of approximately 90%.**
   a. True
   b. False
9. **An assessment of a small number of patients on the NHL 1-2003 study indicated that mobilizing stem cells after a patient has received BR is _____.**
   a. Feasible, with results similar to post-R-CHOP mobilization
   b. Not feasible to the extent required for transplantation
10. **In the Phase III MDS-004 placebo-controlled study of lenalidomide for patients with MDS and del(5q), higher rates of transfusion independence and complete cytogenetic response were achieved with a lenalidomide starting dose of 10 mg compared to 5 mg.**
    a. True
    b. False

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Hematologic Oncology Update — Issue 3, 2011

Research To Practice is committed to providing valuable continuing education for oncology clinicians, and your input is critical to helping us achieve this important goal. Please take the time to assess the activity you just completed, with the assurance that your answers and suggestions are strictly confidential.

PART ONE — Please tell us about your experience with this educational activity

How would you characterize your level of knowledge on the following topics?

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

	BEFORE	AFTER
Efficacy of brentuximab vedotin in relapsed HL and ALCL	4 3 2 1	4 3 2 1
Proposed Intergroup trials of BR-based up-front therapy in MCL	4 3 2 1	4 3 2 1
Activity of pralatrexate and romidepsin in relapsed PTCL	4 3 2 1	4 3 2 1
Second primary cancer with maintenance lenalidomide in MM	4 3 2 1	4 3 2 1
Subcutaneous versus intravenous administration of bortezomib	4 3 2 1	4 3 2 1
Duration of hypomethylating agents in MDS	4 3 2 1	4 3 2 1

Was the activity evidence based, fair, balanced and free from commercial bias?

☐ Yes ☐ No If no, please explain: .....

Please identify how you will change your practice as a result of completing this activity (select all that apply).

☐ This activity validated my current practice; no changes will be made
☐ Create/revise protocols, policies and/or procedures
☐ Change the management and/or treatment of my patients
☐ Other (please explain): .....

If you intend to implement any changes in your practice, please provide 1 or more examples:

.....

The content of this activity matched my current (or potential) scope of practice.

☐ Yes ☐ No If no, please explain: .....

Please respond to the following learning objectives (LOs) by circling the appropriate selection:

4 = Yes 3 = Will consider 2 = No 1 = Already doing N/M = LO not met N/A = Not applicable

As a result of this activity, I will be able to:

- Utilize case-based learning to formulate individualized management strategies for patients with hematologic cancer. . . . . 4 3 2 1 N/M N/A
- Optimize the management of chronic lymphocytic leukemia and follicular lymphoma through the rational integration of prospective clinical trial results. . . . . 4 3 2 1 N/M N/A
- Apply the results of emerging clinical research to the care of patients with myelodysplastic syndromes and acute myeloid leukemia. . . . . 4 3 2 1 N/M N/A
- Develop an evidence-based treatment approach for younger and older patients with mantle-cell lymphoma. . . . . 4 3 2 1 N/M N/A
- Explain the risks and benefits of evidence-based systemic agents to patients with diverse subtypes of T-cell lymphoma. . . . . 4 3 2 1 N/M N/A
- Compare and contrast the benefits and risks of immunomodulatory agents, proteasome inhibitors or both as systemic induction, maintenance and/or relapse treatment of active multiple myeloma. . . . . 4 3 2 1 N/M N/A
- Describe the biologic rationale, efficacy and toxicity of novel agents targeting CD30-positive Hodgkin lymphoma and anaplastic large cell lymphoma. . . . . 4 3 2 1 N/M N/A
- Facilitate patient access to clinical trial participation through communication of ongoing research opportunities. . . . . 4 3 2 1 N/M N/A

Please describe any clinical situations that you find difficult to manage or resolve that you would like to see addressed in future educational activities:

.....

Would you recommend this activity to a colleague?

☐ Yes ☐ No

If no, please explain:.....

Additional comments about this activity:

.....

As part of our ongoing, continuous quality-improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey.

☐ Yes, I am willing to participate in a follow-up survey.

☐ No, I am not willing to participate in a follow-up survey.

PART TWO — Please tell us about the faculty and editor for this educational activity

4 = Excellent 3 = Good 2 = Adequate 1 = Suboptimal

Faculty	Knowledge of subject matter	Effectiveness as an educator
Julie M Vose, MD	4 3 2 1	4 3 2 1
Jesus F San-Miguel, MD, PhD	4 3 2 1	4 3 2 1
Pierre Fenaux, MD	4 3 2 1	4 3 2 1
Sonali M Smith, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

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Professional Designation:

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UPDATE

This activity is supported by educational grants from Allos Therapeutics, Celgene Corporation, Cephalon Inc, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Onyx Pharmaceuticals Inc, Sanofi and Seattle Genetics.

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