

Hematologic Oncology™

U P D A T E

Conversations with Oncology Investigators
Bridging the Gap between Research and Patient Care

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INTERVIEWS

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LAUNCH ISSUE

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Hematologic Oncology Update

A Continuing Medical Education Audio Series

STATEMENT OF NEED/TARGET AUDIENCE

Approximately 135,520 new cases of lymphoid and myeloid cancer and related disorders (eg, myelodysplastic syndrome, myeloproliferative diseases) were identified in the United States in the year 2007, and 52,310 individuals will die from these diseases. Importantly, more than 45 drug products are currently approved for use in the management of hematologic malignancies, comprising more than 55 distinct FDA-approved indications. Although this extensive list of available treatment options is reassuring to patients and oncology healthcare professionals, it poses a challenge to clinicians who must maintain up-to-date knowledge of appropriate clinical management strategies. This activity helps practicing hematologists and oncologists to stay abreast of relevant advances in the treatment of hematologic malignancies so that they can provide optimal patient care.

LEARNING OBJECTIVES

- Utilize available prognostic and predictive clinical and molecular markers to aid in treatment decision-making for patients with hematologic malignancies.
- Design a therapeutic algorithm for the clinical management of indolent and aggressive forms of non-Hodgkin's lymphoma, considering the benefits and risks of induction chemotherapy, radioimmunotherapy, stem cell transplantation, maintenance regimens and emerging molecular-targeted agents.
- Consider emerging clinical research on the use of monoclonal antibodies and immunomodulatory agents when planning primary and consolidation therapy for chronic lymphocytic leukemia (CLL).
- Develop an evidence-based approach to the use of BCR-ABL targeted therapies based on the clinical characteristics of patients with chronic myelogenous leukemia (CML).
- Review the mechanisms of acquired resistance mutations in CML, develop rational clinical strategies for monitoring patients for evidence of disease progression and implement appropriate therapeutic alternatives when warranted.
- Incorporate recent advances in front-line and salvage management of multiple myeloma (MM), including indications and treatment options for autologous stem cell transplantation (ASCT) and non-ASCT candidates.
- Assess ongoing clinical trials evaluating the roles of maintenance and consolidation therapeutic approaches for various hematologic malignancies, including diffuse large B-cell lymphoma, mantle-cell lymphoma, minimal residual disease CLL and MM after successful ASCT.
- Consider the heterogeneous manifestations of myelodysplastic syndrome and the associated cytogenetic markers affecting the initial therapy choice of low-intensity chemotherapy, biologic response modifiers and molecular-targeted agents in specific patient populations.
- Counsel appropriately selected patients with myeloid and lymphoid disorders about clinical research studies incorporating novel treatment approaches.

PURPOSE OF THIS ISSUE OF HEMATOLOGIC ONCOLOGY UPDATE

The purpose of Issue 1 of *Hematologic Oncology Update* is to support the learning objectives by offering the perspectives of Drs O'Brien, Orlowski, Steensma and Maloney on the integration of emerging clinical research data into the management of hematologic malignancies.

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TABLE OF CONTENTS

3 INTERVIEWS

Susan M O'Brien, MD

Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

7 Robert Z Orlowski, MD, PhD

Director, Department of Lymphoma and Myeloma
Associate Professor, Department of Experimental Therapeutics
Division of Cancer Medicine
The University of Texas MD Anderson Cancer Center
Houston, Texas

11 David P Steensma, MD

Associate Professor of Medicine and Oncology
Division of Hematology
Department of Medicine
Mayo Clinic
Rochester, Minnesota

14 David G Maloney, MD, PhD

Associate Member, Clinical Research Division
Fred Hutchinson Cancer Research Center
Associate Professor of Medicine, Division of Oncology
University of Washington
Seattle, Washington

18 POST-TEST

19 EDUCATIONAL ASSESSMENT AND CREDIT FORM

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KEY NEW DATA SETS DISCUSSED IN THIS ISSUE

Cavo M et al. **Bortezomib (Velcade)-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (TD) in preparation for autologous stem-cell (SC) transplantation (ASCT) in newly diagnosed multiple myeloma (MM).** *Proc ASH 2007*; [Abstract 73](#).

Fenaux P et al. **Azacitidine (AZA) treatment prolongs overall survival (OS) in higher risk MDS patients compared with conventional care regimens (CCR): Results of the AZA-001 phase III study.** *Proc ASH 2007*; [Abstract 817](#).

Fisher RI et al. **Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma.** *J Clin Oncol 2006*;24(30):4867-74. [Abstract](#)

Hillmen P et al. **Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia.** *J Clin Oncol 2007*;25(35):5616-23. [Abstract](#)

Hochhaus A et al. **IRIS 6-year follow-up: Sustained survival and declining annual rate of transformation in patients with newly diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) treated with imatinib.** *Proc ASH 2007*; [Abstract 25](#).

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Kantarjian H et al. **Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial.** *Blood 2007*;109(12):5143-50. [Abstract](#)

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Rajkumar SV et al. **A randomized trial of lenalidomide plus high-dose dexamethasone (RD) versus lenalidomide plus low-dose dexamethasone (Rd) in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group.** *Proc ASH 2007*; [Abstract 74](#).

Richardson P et al. **Lenalidomide, bortezomib, and dexamethasone (Rev/Vel/Dex) in patients with relapsed or relapsed/refractory multiple myeloma (MM): Preliminary results of a phase II study.** *Proc ASH 2007*; [Abstract 2714](#).

San Miguel JF et al. **MMY-3002: A phase 3 study comparing bortezomib-melphalan-prednisone (VMP) with melphalan-prednisone (MP) in newly diagnosed multiple myeloma.** *Proc ASH 2007*; [Abstract 76](#).

Van Oers MH et al. **Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial.** *Blood 2006*;108(10):3295-301. [Abstract](#)

CONTENT VALIDATION AND DISCLOSURES

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INTERVIEW

Susan M O'Brien, MD

Dr O'Brien is Professor of Medicine in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-19

- Track 1** Monitoring patients with chronic myelogenous leukemia (CML) who are receiving tyrosine kinase therapy
- Track 2** Monitoring patients who have achieved a complete cytogenetic remission
- Track 3** Rationale for dose escalation of imatinib in CML
- Track 4** Side effects associated with higher-dose imatinib
- Track 5** Efficacy and toxicity of dasatinib at 100 milligrams per day
- Track 6** Utility of FISH in monitoring patients during treatment
- Track 7** BCR-ABL kinase domain mutation analysis to guide secondary tyrosine kinase inhibitor treatment
- Track 8** Selection of nilotinib or dasatinib after imatinib failure
- Track 9** Null association between imatinib and cardiac abnormalities
- Track 10** IRIS trial six-year follow-up: Sustained survival and declining annual rate of transformation in patients with newly diagnosed, chronic-phase CML treated with imatinib
- Track 11** Historical rationale for observation of patients with newly diagnosed chronic lymphocytic leukemia (CLL)
- Track 12** Prognostic factors for the identification of patients with high-risk CLL
- Track 13** Clinical relevance of prognostic factors to selection of therapy
- Track 14** Use of consolidation alemtuzumab to eliminate residual disease after response to fludarabine-based therapy
- Track 15** Side effects and toxicity of alemtuzumab
- Track 16** Alemtuzumab and cytomegalovirus reactivation
- Track 17** International Phase III trial of bendamustine versus chlorambucil in treatment-naïve B-cell CLL
- Track 18** Utility of consolidation therapy for minimal residual disease in CLL
- Track 19** Future treatment of CML and CLL

Select Excerpts from the Interview

Track 3

▶ **DR LOVE:** What is the role of dose escalation of imatinib for patients with CML?

► **DR O'BRIEN:** In a recently published trial, patients failing imatinib at 400 or 600 milligrams were randomly assigned to either imatinib at 800 milligrams or dasatinib.

The data were analyzed according to which dose of imatinib the patient had failed (Kantarjian 2007). Patients who failed while they were receiving imatinib at 600 milligrams were better off switching to dasatinib. For those who had failed while on imatinib at 400 milligrams, the response rates between the two arms were similar, and the improvement in progression-free survival with dasatinib was of borderline significance (Kantarjian 2007).

This is why the NCCN guidelines consider dose escalation of imatinib as an option (NCCN 2008). However, if a patient has never had a cytogenetic response to imatinib, it's better to switch therapy than to increase the dose.

Track 10

► **DR LOVE:** Would you discuss the six-year follow-up data from the IRIS trial, evaluating imatinib in the treatment of chronic-phase CML (Hochhaus 2007)?

► **DR O'BRIEN:** The failure rate continues to be low, showing imatinib to be excellent in the front-line setting (1.1). One of the most interesting findings is that the number of events per year is declining. In fact, during the sixth year, no patients developed accelerated phase or blast crisis.

To some, these data suggest that early on, a clone of imatinib-resistant cells may develop in some patients that is too small to detect with standard techniques. When imatinib eradicates the sensitive clone, the resistant clone emerges and the patients leave the study and experience an event within a year or two. However, patients without a resistant clone have nothing to cause failure — so the failure rate is decreasing.

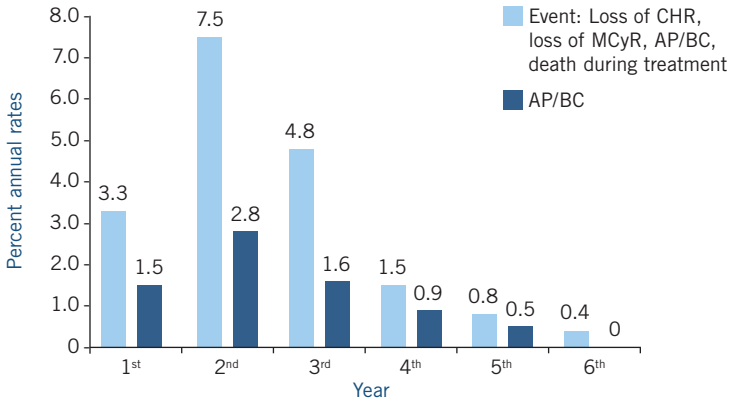
Track 13

► **DR LOVE:** Let's talk about CLL. Are we at a point at which we can use a chromosomal abnormality, such as a 17p deletion, to select therapy?

► **DR O'BRIEN:** The simple answer is no. However, we know that patients with 17p deletions don't respond well to fludarabine-based therapy (Byrd 2006), our mainstay of treatment. Data show that those patients do respond to alemtuzumab. In the trial comparing it to chlorambucil as first-line therapy for CLL, alemtuzumab was better in all groups based on cytogenetic abnormalities (Hillmen 2007; [1.2]).

So patients with 17p deletions fared better on alemtuzumab. Still, their median progression-free survival was 10 months (Hillmen 2007; [1.2]). Alemtuzumab by itself is not the magic bullet for patients with 17p deletions. Steroids also work in these patients, and the British are conducting a Phase II trial combining alemtuzumab with steroids.

IRIS Trial: Declining Annual Event Rates at Six-Year Follow-Up for Patients with Newly Diagnosed, Chronic-Phase CML Treated with Imatinib



CHR = complete hematologic response; MCyR = major cytogenetic response; AP/BC = accelerated-phase/blast crisis

“Conclusions: The 6-year follow-up analysis of the IRIS population indicates that continuous treatment of chronic-phase CML with imatinib induces durable responses in a high percentage of patients with a decreasing rate of relapse and a favorable long-term safety profile.”

SOURCES: Hochhaus A et al. *Proc ASH* 2007; [Abstract 25](#); Personal communication, Susan M O'Brien, MD, April 2008.

Track 14

► **DR LOVE:** Would you discuss some of the ongoing trials with alemtuzumab for the treatment of CLL?

► **DR O'BRIEN:** We are conducting a study combining alemtuzumab with fludarabine, cyclophosphamide and rituximab (FCR) for patients at high risk (2005-0269). We are also conducting a trial using alemtuzumab to treat minimal residual disease, for which I believe it is particularly effective (2003-0834). Alemtuzumab is not great at treating bulky adenopathy, but it's excellent at clearing bone marrow disease.

Emerging data show that we need a certain period of time — probably three to six months — between treatment with fludarabine and consolidation with alemtuzumab to allow recovery of the immune system (Hainsworth 2008). Patients with a reasonable response to first-line therapy do not experience disease progression that quickly, so we have time to wait, repeat the bone marrow biopsy and then use alemtuzumab if needed to eradicate residual disease. In a German randomized trial, this approach was shown to have a major impact on progression-free survival (Wendtner 2004). ■

Treatment response as assessed by Independent Response Review Panel (IRRP)

	A (n = 149)	C (n = 148)	p-value
Overall response	83.2%	55.4%	<0.0001
Complete response (CR)	24.2%	2.0%	<0.0001
MRD-negative*	7.4%	0%	0.0008

Overall response rate and progression-free survival according to cytogenetic abnormality

	Overall response rate			Median progression-free survival		
	A	C	p-value	A	C	p-value
17p deletion	64%	20%	0.0805	10.7mo	2.2mo	0.4066
11q deletion (no 17p deletion)	87%	29%	<0.0001	8.5mo	8.5mo	0.4338
Trisomy 12 (no 17p deletion, no 11q deletion)	83%	80%	1.0000	18.3mo	12.9mo	0.0915
Normal	84%	69%	0.3238	19.9mo	14.3mo	0.5582
Sole 13q	91%	62%	0.0087	24.4mo	13.0mo	0.0170
17p deletion or 11q deletion	79%	27%	<0.0001	9.4mo	7.7mo	0.1602

A = alemtuzumab; C = chlorambucil; MRD = minimal residual disease

* Two patients with MRD-negative CR were determined by the IRRP to have Rai Stage 0 disease at study entry.

SOURCE: Hillmen P et al. *J Clin Oncol* 2007;25(35):5616-23. [Abstract](#)

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Hillmen P et al. **Alemtuzumab compared with chlorambucil as first-line therapy for chronic lymphocytic leukemia.** *J Clin Oncol* 2007;25(35):5616-23. [Abstract](#)

Hochhaus A et al. **IRIS 6-year follow-up: Sustained survival and declining annual rate of transformation in patients with newly diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) treated with imatinib.** *Proc ASH* 2007;[Abstract 25](#).

Kantarjian H et al. **Dasatinib or high-dose imatinib for chronic-phase chronic myeloid leukemia after failure of first-line imatinib: A randomized phase 2 trial.** *Blood* 2007;109(12):5143-50. [Abstract](#)

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INTERVIEW

Robert Z Orlowski, MD, PhD

Dr Orlowski is Director of the Department of Lymphoma and Myeloma and is Associate Professor in the Department of Experimental Therapeutics in the Division of Cancer Medicine at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-17

- Track 1** Emergence of Phase III data with novel agents as first-line therapy for multiple myeloma (MM)
- Track 2** SWOG-S0232: Superiority of lenalidomide with high-dose dexamethasone compared to dexamethasone alone for newly diagnosed MM
- Track 3** ECOG-E4A03: Lenalidomide with high-dose or low-dose dexamethasone in newly diagnosed MM
- Track 4** Induction bortezomib/dexamethasone versus vincristine/doxorubicin/dexamethasone (VAD) prior to autologous stem cell transplantation (ASCT) for newly diagnosed MM
- Track 5** Italian study of induction thalidomide/dexamethasone with or without bortezomib in preparation for ASCT in newly diagnosed MM
- Track 6** Mechanism(s) of action of proteasome inhibitors
- Track 7** Melphalan/prednisone with or without thalidomide for patients with newly diagnosed MM who are ineligible for transplantation
- Track 8** VISTA trial results: Melphalan/prednisone with or without bortezomib for newly diagnosed MM
- Track 9** Use of “IMiD”-based (thalidomide or lenalidomide) regimens versus bortezomib-based regimens for newly diagnosed MM
- Track 10** Efficacy and tolerability of lenalidomide/dexamethasone and thalidomide/dexamethasone
- Track 11** International Myeloma Working Group consensus on prophylaxis for IMiD-associated thrombosis
- Track 12** Safety and efficacy of bortezomib/lenalidomide with dexamethasone for newly diagnosed MM
- Track 13** Potential impact of novel agents on the future role of transplantation in MM
- Track 14** Role of maintenance therapy after transplantation
- Track 15** Improved time to progression with pegylated liposomal doxorubicin with bortezomib compared to bortezomib alone in relapsed or refractory MM
- Track 16** Selection of patients for treatment with liposomal doxorubicin and bortezomib
- Track 17** Key ongoing trials in MM

Select Excerpts from the Interview

Tracks 2-3

▶ **DR LOVE:** Can you discuss the ECOG trial evaluating lenalidomide combined with high- and low-dose dexamethasone?

► **DR ORLOWSKI:** ECOG-E4A03 randomly assigned patients with newly diagnosed myeloma to lenalidomide with high-dose dexamethasone or lenalidomide with low-dose dexamethasone. The overall response rate was about 12 percent lower with low-dose dexamethasone compared to high-dose dexamethasone, but overall survival was better with low-dose dexamethasone (Rajkumar 2007). Less intensive therapy, which patients can tolerate better and benefit from a better overall survival rate, represents an advance in the field.

Track 5

► **DR LOVE:** Can you describe the key first-line induction studies with bortezomib-based regimens reported at ASH 2007?

► **DR ORLOWSKI:** In an important study from the Italian Myeloma Group, patients with newly diagnosed multiple myeloma were randomly assigned to thalidomide/dexamethasone with or without bortezomib (VTD or TD) prior to ASCT (Cavo 2007). This study was designed to administer only three cycles of three-week induction therapy before patients went on to ASCT — a reduction in the amount of therapy patients receive prior to transplant, which is always positive. The patients who received VTD had a higher overall response rate and better response quality than those receiving TD. Interestingly, VTD was associated with a better complete and overall response rate than TD in patients with deletions of chromosome 13 or translocations between 4 and 14 compared to those without the high-risk features.

The overall toxicity profile of the two regimens was comparable, with a little more neuropathy associated with VTD but more thromboembolic complications with TD. In general, when bortezomib is incorporated into a regimen, fewer thromboembolic complications occur. We don't know why this occurs, but it's a welcome development.

Tracks 7-8

► **DR LOVE:** Can you discuss recent studies of first-line therapy for patients who are not candidates for transplantation?

► **DR ORLOWSKI:** A study from France evaluated melphalan/prednisone (MP) or MP with thalidomide (MP-T) for patients with newly diagnosed myeloma who were more than 75 years old and were not considered by most of us as candidates for transplantation. The patients who received MP-T had a significant improvement in overall response rate, response quality and time to progression. Overall survival was improved by 18 months among patients treated with MP-T (Hulin 2007).

A second trial — VISTA — evaluated MP versus bortezomib with MP (VMP). The patients who received VMP had a superior overall response rate compared to those treated with MP, and adverse cytogenetic effects did not have an impact on overall response or durability of response. The complete

response rate was five percent with MP compared to 35 percent with VMP (San Miguel 2007; [2.1]).

For older patients, two good options are now available: MP with bortezomib or MP with thalidomide. These are probably the two best standard treatments for patients who may not be transplant candidates.

2.1

VISTA Trial: Superior Efficacy of Bortezomib/Melphalan/Prednisone (VMP) versus Melphalan/Prednisone (MP) in Newly Diagnosed Multiple Myeloma

	Hazard ratio	95% CI	p-value
Time to progression	0.54	0.42-0.70	0.000002
Progression-free survival	0.61	0.49-0.76	0.00001
Overall survival	0.61	0.42-0.88	0.0078
Time to next therapy	0.52	0.39-0.70	0.000009
Complete response	11.2*	6.1-20.6	<0.000001

Hazard ratio < 1.0 favors VMP; * odds ratio, favors VMP; CI = confidence interval

SOURCE: San Miguel JF et al. *Proc ASH* 2007; [Abstract 76](#).

Tracks 9, 12

► **DR LOVE:** How do you decide between IMiD-based and bortezomib-based regimens?

► **DR ORLOWSKI:** I believe that patients with adverse cytogenetic features or those with moderate to high-stage disease according to the International Staging System should receive a bortezomib-containing regimen. We also know that bortezomib is safe, effective and doesn't require dose reductions for patients with renal failure, which occurs in a substantial proportion of patients with multiple myeloma. For patients with good-risk cytogenetics, the best approach is to present both IMiD-based and bortezomib-based options and to obtain input from the patient. However, I would still argue that the higher complete response rates with bortezomib-based regimens are worth considering strongly.

► **DR LOVE:** What do we know about combining an IMiD and bortezomib?

► **DR ORLOWSKI:** Paul Richardson made a great presentation at ASH of a Phase I/II study evaluating bortezomib with lenalidomide and dexamethasone for patients with relapsed or refractory multiple myeloma. They were able to identify a tolerable dosage, which was safe and had an overall response rate of more than 90 percent (Richardson 2007). In the future, bortezomib/lenalidomide and dexamethasone may prove to be an optimal regimen for all patients. Being able to achieve response rates close to 100 percent with shorter durations of therapy is quite encouraging.

Track 15

► **DR LOVE:** Would you comment on your Phase III study of liposomal doxorubicin and bortezomib in relapsed or refractory multiple myeloma?

► **DR ORLOWSKI:** This was the first trial demonstrating that an anthracycline in combination with bortezomib had a better overall response rate and quality of response than bortezomib alone. The very good partial response plus complete response rate went from about 20 percent to 30 percent, which was a 50 percent improvement (Orlowski 2007; [2.2]). We also saw a trend toward better overall survival, which I believe will continue as the data mature. The data show that the benefits of bortezomib and pegylated liposomal doxorubicin were maintained regardless of the patients' age, prior transplant or exposure to thalidomide. ■

2.2

Pegylated Liposomal Doxorubicin (PLD) and Bortezomib (V) versus Bortezomib Alone in Relapsed or Refractory Multiple Myeloma

Efficacy endpoint	V (n = 310)	V + PLD (n = 303)	Hazard ratio	p-value
Median time to progression	6.5mo	9.3mo	1.82	0.000004
Overall survival (15 months)	75%	82%	1.41	<0.05
CR + PR	41%	44%	—	0.43
CR + VGPR	19%	27%	—	0.0157

CR = complete response; PR = partial response; VGPR = very good partial response

SOURCE: Orlowski RZ et al. *J Clin Oncol* 2007;25(25):3892-901. [Abstract](#)

SELECT PUBLICATIONS

Cavo M et al. **Bortezomib (Velcade)-thalidomide-dexamethasone (VTD) vs thalidomide-dexamethasone (TD) in preparation for autologous stem-cell (SC) transplantation (ASCT) in newly diagnosed multiple myeloma (MM).** *Proc ASH* 2007; [Abstract 73](#).

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INTERVIEW

David P Steensma, MD

Dr Steensma is Associate Professor of Medicine and Oncology in the Department of Medicine's Division of Hematology at the Mayo Clinic in Rochester, Minnesota.

Tracks 1-14

- | | | | |
|----------------|---|-----------------|--|
| Track 1 | AZA-001: Azacitidine prolongs overall survival in higher-risk myelodysplastic syndrome (MDS) compared to conventional care regimens | Track 8 | Case discussion: A man in his seventies with high-risk (INT-2) platelet transfusion-dependent MDS |
| Track 2 | Clinical trials evaluating azacitidine in combination with histone deacetylase inhibitors | Track 9 | Case follow-up: Complete remission and freedom from transfusion after treatment on a demethylating agent |
| Track 3 | Counseling patients about the similarities and differences between MDS and cancer | Track 10 | Case discussion: A 75-year-old woman with isolated del(5q) syndrome |
| Track 4 | Common questions about the treatment of MDS | Track 11 | Case follow-up: Two-year response to lenalidomide on a clinical trial |
| Track 5 | Treatment algorithm for patients with newly diagnosed MDS | Track 12 | Case discussion: A 60-year-old man with high-risk MDS |
| Track 6 | Newly recognized cytogenetic abnormalities not included in the International Prognostic Scoring System | Track 13 | Case follow-up: Azacitidine followed by umbilical cord transplantation |
| Track 7 | Incidence of MDS in the US | Track 14 | Emerging treatment options in MDS |

Select Excerpts from the Interview

Track 1

► **DR LOVE:** Where are we right now in terms of therapy for myelodysplastic syndrome (MDS)?

► **DR STEENSMASMA:** The biggest news, which came from the 2007 ASH meeting, was the presentation of data from a study comparing azacitidine to the conventional care regimens of best supportive care, low-dose cytarabine or standard chemotherapy. Azacitidine was shown to improve overall survival by about nine months and delay transformation to leukemia. It was also well tolerated (Fenaux 2007; [3.1]). Patients received an average of nine cycles of therapy, so they were able to receive the drug for a longer period than we've seen in the past.

Another drug in the same class, decitabine, is approved for myelodysplasia. A multicenter study with a five-day outpatient regimen of decitabine — which is more convenient than the regimen on the package labeling — demonstrated a 32 percent complete response rate. That is better than what we have seen before azacitidine and decitabine were available (Steensma 2007).

► **DR LOVE:** How would you compare the available data for azacitidine and decitabine?

► **DR STEENSMASMA:** We have survival data for azacitidine (Fenaux 2007; [3.1]) but not yet for decitabine. EORTC-06011 is an ongoing study of decitabine in which survival is the endpoint. We're likely to hear those results later this year or perhaps in early 2009. The trial is taking place in Europe, with a study design similar to the azacitidine trial. Azacitidine and decitabine have never been compared directly, so we have to extrapolate by comparing studies side by side.

3.1 AZA-001: Azacitidine versus Conventional Care Regimens (CCR) for Patients with High-Risk MDS

Protocol ID: AZA-001; Accrual: 358 (Closed)

	Azacitidine (n = 179)	CCR (n = 179)
Median overall survival	24.4 months	15 months*
Median time to AML	26 months	12 months

* Hazard ratio (95% confidence interval) = 0.58 (0.43-0.77), p = 0.001

SOURCE: Fenaux P et al. *Proc ASH* 2007; [Abstract 817](#).

Track 2

► **DR LOVE:** What current clinical research for MDS do you expect to have the greatest impact on clinical practice during the next three to five years?

► **DR STEENSMASMA:** One interesting area is combining azacitidine or decitabine with other classes of drugs. People are most excited about the combinations with the histone deacetylase (HDAC) inhibitors. One of those, vorinostat, is already approved for cutaneous T-cell lymphoma. Several others are being evaluated specifically in MDS. ECOG-E1905 is comparing azacitidine to azacitidine with an HDAC inhibitor called MS-275. A Phase II multicenter

trial is evaluating another HDAC inhibitor, belinostat. If it shows efficacy as a single agent, we may have a good rationale to combine it.

Combining azacitidine and decitabine with the HDAC inhibitors is attractive because the side-effect profiles are different. With the HDAC inhibitors, cytopenias don't seem to be an issue as much as QT-interval prolongation and fatigue (Byrd 2005). Perhaps we could use the agents together and not find much overlap of the adverse events.

► **DR LOVE:** What do we know about the side effects and toxicities of azacitidine and decitabine?

► **DR STEENSMASMA:** With azacitidine, the biggest issue has been cytopenias. Neutropenia is manageable for some patients, but it lands others in the hospital with febrile neutropenia. In the Phase II multicenter study of decitabine, 17 percent of the patients had febrile neutropenia (Steenasma 2007). That was not as high as with some of the leukemia induction regimens, but it's not negligible either.

The other adverse events associated with azacitidine and decitabine, which are similar, are mild: Gastrointestinal toxicities and rash.

Track 5

► **DR LOVE:** Would you discuss your clinical approach to the treatment of patients with MDS?

► **DR STEENSMASMA:** I start by risk stratifying. Is the patient at high or low risk of progression to leukemia and death? If the patient is at low risk, you have time to try different approaches, such as growth factors. If the patient is at high risk, then the question is whether he or she is a transplant candidate. I find that assessment difficult.

The transplant centers are accepting sicker and older patients now. I don't automatically rule out someone who is 63 or 64 years old. I send them to the transplant physician to hear the specialist's opinion.

If the transplant physician recommends it, then for higher-risk disease, transplant is the treatment of choice. We may need to prepare the patient for the transplant and decrease the blast count with azacitidine, but transplant is the definitive therapy. ■

SELECT PUBLICATIONS

Byrd JC et al. **A Phase I and pharmacodynamic study of depsipeptide (FK228) in chronic lymphocytic leukemia and acute myeloid leukemia.** *Blood* 2005;105(3):959-67. [Abstract](#)

Fenaux P et al. **Azacitidine (AZA) treatment prolongs overall survival (OS) in higher-risk MDS patients compared with conventional care regimens (CCR): Results of the AZA-001 phase III study.** *Proc ASH* 2007;[Abstract 817](#).

Steenasma DP et al. **Preliminary results of a phase II study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndrome (MDS).** *Proc ASH* 2007;[Abstract 1450](#).



INTERVIEW

David G Maloney, MD, PhD

Dr Maloney is Associate Member in the Clinical Research Division of the Fred Hutchinson Cancer Research Center and is Associate Professor of Medicine in the Division of Oncology at the University of Washington in Seattle, Washington.

Tracks 1-12

- | | | | |
|----------------|---|-----------------|--|
| Track 1 | Advances associated with the use of rituximab for follicular lymphoma | Track 7 | R-CHOP versus R-hyper-CVAD in the treatment of mantle-cell lymphoma |
| Track 2 | Radiolabeled antibody therapy in the treatment of follicular lymphoma | Track 8 | Incorporation of bortezomib into the treatment of mantle-cell lymphoma |
| Track 3 | Potential role of bendamustine in the treatment of follicular lymphoma | Track 9 | Safety and efficacy of nonmyeloablative allogeneic stem cell transplantation in mantle-cell lymphoma |
| Track 4 | Improved clinical outcomes with maintenance rituximab in follicular lymphoma | Track 10 | R-CHOP-14 versus R-CHOP-21 for diffuse large B-cell lymphoma (DLBCL) |
| Track 5 | Ongoing clinical trials evaluating maintenance rituximab in follicular lymphoma | Track 11 | Development of novel antibodies for the treatment of DLBCL |
| Track 6 | Clinical algorithm for the use of maintenance rituximab | Track 12 | Clinical utility of allogeneic hematopoietic cell transplantation in the lymphomas and CLL |

Select Excerpts from the Interview

Track 1

► **DR LOVE:** Would you discuss recent research advances in the management of follicular lymphoma?

► **DR MALONEY:** I believe we're now clearly demonstrating that a number of strategies are beginning to improve survival. This has predominantly been accomplished through the inclusion of anti-CD20 antibody targeted therapies. Rituximab has played the biggest role in this setting.

We have five trials indicating that by simply adding rituximab to standard chemotherapy, you obtain a better result (Czuczman 2005, 2004; Forstpointner 2004; Hiddemann 2005; Marcus 2005). This result has generally been in terms of improved progression-free survival, but several of the studies are beginning to show improved survival.

Track 4

► **DR LOVE:** Would you discuss the use of maintenance rituximab?

► **DR MALONEY:** I believe the role of maintenance rituximab is one of the key unanswered questions in follicular lymphoma. It's been shown that if you use four doses of single-agent rituximab, then maintenance rituximab extends progression-free survival (Ghielmini 2004; [4.1]). In that setting, we know maintenance rituximab works.

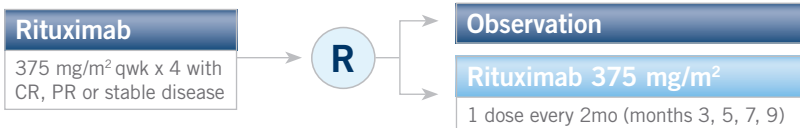
Regarding patients with relapsed disease, van Oers recently published one of the most important studies, evaluating patients with relapsed follicular lymphoma who were still eligible to receive an anthracycline-containing regimen, which meant that they had received chlorambucil, CVP or a fludarabine-based regimen. The patients received CHOP or R-CHOP, and R-CHOP proved to be better, which was not a surprise (van Oers 2006; [4.2]).

A secondary randomization to two years of maintenance rituximab versus observation was also included. The group of patients who received CHOP benefited from maintenance rituximab, as did the group of patients who received R-CHOP.

That's the closest we have come to suggesting that maintenance rituximab will work in follicular lymphoma. We even saw a survival advantage for the overall group in that trial (van Oers 2006; [4.2]).

4.1

Phase III Randomized Trial Comparing Maintenance Rituximab to Observation in Patients with Follicular Lymphoma



	Maintenance rituximab (n = 73)	Observation (n = 78)	p-value
Median event-free survival (mo)	23.2	11.8	0.024
Chemotherapy-naïve patients	36	19	0.009
Pretreated patients	15	10	0.081
Median remission duration (mo)	36	16	0.004

CR = complete response; PR = partial response

"This trial shows that prolonged treatment with rituximab, compared to the standard rituximab schedule, improves outcomes for patients with follicular lymphoma in terms of both event-free survival and response duration, without causing additional toxicity."

SOURCE: Ghielmini M et al. *Blood* 2004;103(12):4416-23. [Abstract](#)

Phase III Randomized Trial of CHOP versus R-CHOP with or without Rituximab (R) Maintenance for Patients with Relapsed Follicular Lymphoma (FL)

“The final analysis of the European Organisation for Research and Treatment of Cancer (EORTC) 20981 Intergroup study has shown several important findings. Firstly, in patients with relapsed/resistant FL, remission induction with R-CHOP results in a highly significant increase in CR rate as compared with CHOP; secondly, R maintenance treatment significantly improves PFS and OS in patients responding to induction treatment; thirdly, R maintenance treatment achieves a considerable increase in PFS not only after remission induction with chemotherapy (CHOP) but also after immunochemotherapy (R-CHOP).”

CR = complete response; PFS = progression-free survival; OS = overall survival

SOURCE: Van Oers MH et al. *Blood* 2006;108(10):3295-301. [Abstract](#)

Track 5

▶ **DR LOVE:** Can you discuss the ongoing clinical trials of maintenance rituximab in follicular lymphoma?

▶ **DR MALONEY:** Two interesting trials are ongoing. The first is the PRIMA study, which has completed accrual. Patients with follicular lymphoma were treated with dealer’s choice for induction — R-CVP, R-CHOP, R-MCP or R-FCM — and were then randomly assigned to either observation or maintenance rituximab for two years. We are eagerly awaiting those results.

The RESORT study (ECOG-E4402) is a different approach, building on the Swiss trial that used four doses of rituximab followed by extended rituximab or not (Ghielmini 2004). The RESORT trial uses one dose of rituximab every three months indefinitely until tumor progression. The endpoint is to determine how long it takes to develop rituximab resistance. Does it occur faster in patients who are continuously exposed to rituximab compared to those who are treated only as needed, when they experience relapse?

Track 8

▶ **DR LOVE:** Where are we right now in the treatment of mantle-cell lymphoma?

▶ **DR MALONEY:** The use of bortezomib is causing the most excitement (Fisher 2006; [4.3]). The FDA has approved it for relapsed mantle-cell lymphoma. People are trying to figure out how best to incorporate bortezomib earlier into therapy. Many regimens are being reported with CHOP, in which vincristine is dropped and bortezomib is added in various weekly or twice-weekly schedules.

▶ **DR LOVE:** In your practice, how are you incorporating bortezomib?

▶ **DR MALONEY:** Generally speaking, I’m using it only for patients with relapsed

disease. I'm not using it in the front-line setting. I haven't seen anything yet that makes me change my approach. ■

4.3

Multicenter Phase II Study of Bortezomib in Patients with Relapsed or Refractory Mantle-Cell Lymphoma (MCL)

"This study represents the largest prospective study to date in patients with relapsed MCL. In a population typical of the relapsed MCL population, the results demonstrate that bortezomib is effective, with a 33% response rate, including 8% CR/CRu. The median DORs in all responding patients (9.2 months) and patients achieving CR/CRu (13.5 months) are considerable given the median expected survival of 1 to 2 years after initial relapse, suggesting important clinical benefit. Similarly, median TTP was 10.6 months among responders, 14.6 months in patients achieving CR/CRu, and 6.2 months in all patients. These data are supported by similar results from phase I and II studies of single-agent bortezomib in relapsed MCL."

SOURCE: Fisher RI et al. *J Clin Oncol* 2006;24(30):4867-74. [Abstract](#)

SELECT PUBLICATIONS

Belch A et al. **A phase II study of bortezomib in mantle cell lymphoma: The National Cancer Institute of Canada Clinical Trials Group trial IND.150.** *Ann Oncol* 2007;18(1):116-21. [Abstract](#)

Czuczman MS et al. **Rituximab in combination with fludarabine chemotherapy in low-grade or follicular lymphoma.** *J Clin Oncol* 2005;23(4):694-704. [Abstract](#)

Czuczman MS et al. **Prolonged clinical and molecular remission in patients with low-grade or follicular non-Hodgkin's lymphoma treated with rituximab plus CHOP chemotherapy: 9-year follow-up.** *J Clin Oncol* 2004;22(23):4711-6. [Abstract](#)

Fisher RI et al. **Multicenter phase II study of bortezomib in patients with relapsed or refractory mantle cell lymphoma.** *J Clin Oncol* 2006;24(30):4867-74. [Abstract](#)

Forstpointner R et al. **The addition of rituximab to a combination of fludarabine, cyclophosphamide, mitoxantrone (FCM) significantly increases the response rate and prolongs survival as compared with FCM alone in patients with relapsed and refractory follicular and mantle cell lymphomas: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group.** *Blood* 2004;104(10):3064-71. [Abstract](#)

Ghielmini M et al. **Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule.** *Blood* 2004;103(12):4416-23. [Abstract](#)

Goy A et al. **Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-cell non-Hodgkin's lymphoma.** *J Clin Oncol* 2005;23(4):667-75. [Abstract](#)

Hiddemann W et al. **Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group.** *Blood* 2005;106(12):3725-32. [Abstract](#)

Marcus R et al. **CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma.** *Blood* 2005;105(4):1417-23. [Abstract](#)

Van Oers MH et al. **Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: Results of a prospective randomized phase 3 intergroup trial.** *Blood* 2006;108(10):3295-301. [Abstract](#)

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In a trial for patients with CML who were failing on imatinib at 400 or 600 milligrams, those who were treated with _____ had better outcomes than those who were treated with imatinib at 800 milligrams.
 - a. Alemtuzumab
 - b. Dasatinib
 - c. Nilotinib
 - d. Any of the above
2. The six-year follow-up data from the IRIS trial indicate that continuous treatment of chronic-phase CML with imatinib induces durable responses in a high percentage of patients, with a decreasing annual rate of relapse.
 - a. True
 - b. False
3. A trial comparing alemtuzumab to chlorambucil as first-line therapy for CLL demonstrated that patients with the 17p deletion who received _____ had better outcomes.
 - a. Alemtuzumab
 - b. Chlorambucil
4. In ECOG-E4A03, induction therapy with lenalidomide and low-dose dexamethasone resulted in a lower overall response rate but higher overall survival compared to lenalidomide with high-dose dexamethasone.
 - a. True
 - b. False
5. In the VISTA trial, bortezomib/melphalan/prednisone (VMP) resulted in significant improvements in the overall response rate compared to _____ among patients with newly diagnosed multiple myeloma.
 - a. Bortezomib alone
 - b. Lenalidomide
 - c. Melphalan/prednisone
 - d. All of the above
6. Which of the following are HDAC inhibitors?
 - a. MS-275
 - b. Vorinostat
 - c. Belinostat
 - d. Both b and c
 - e. All of the above
7. Among patients with relapsed or refractory multiple myeloma, pegylated liposomal doxorubicin in combination with bortezomib resulted in significant improvements in _____ compared to bortezomib alone.
 - a. Very good partial response plus complete response rate
 - b. Overall survival
 - c. Both a and b
8. Compared to best supportive care, azacitidine improves overall survival among patients with MDS by approximately _____.
 - a. Three months
 - b. Six months
 - c. Nine months
 - d. 15 months
9. Maintenance rituximab was found to improve outcomes for patients with relapsed follicular lymphoma who had received induction therapy with _____.
 - a. CHOP
 - b. R-CHOP
 - c. Either a or b
 - d. None of the above
10. The PRIMA study allows the use of which of the following regimens as induction therapy for patients with follicular lymphoma?
 - a. R-CVP
 - b. R-CHOP
 - c. R-MCP
 - d. Any of the above
11. In the RESORT trial, patients receive induction therapy with _____.
 - a. CVP
 - b. R-CVP
 - c. Rituximab alone
 - d. Any of the above
12. Bortezomib has been FDA approved for the treatment of _____ lymphoma.
 - a. Follicular
 - b. Mantle-cell
 - c. Diffuse large B-cell
 - d. None of the above

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

BEFORE completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- Dose escalation of imatinib in CML.....4 3 2 1
- Evolving role of alemtuzumab in chronic lymphocytic leukemia.....4 3 2 1
- New front-line therapy options in multiple myeloma.....4 3 2 1
- Azacitidine in the treatment of high-risk myelodysplastic syndrome.....4 3 2 1
- Benefits of rituximab in the treatment of follicular lymphoma.....4 3 2 1

AFTER completion of this activity, how would you characterize your level of knowledge on the following topics?

4 = Expert 3 = Above average 2 = Competent 1 = Insufficient

- Dose escalation of imatinib in CML.....4 3 2 1
- Evolving role of alemtuzumab in chronic lymphocytic leukemia.....4 3 2 1
- New front-line therapy options in multiple myeloma.....4 3 2 1
- Azacitidine in the treatment of high-risk myelodysplastic syndrome.....4 3 2 1
- Benefits of rituximab in the treatment of follicular lymphoma.....4 3 2 1

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

Yes No

Please explain:

Will this activity help you improve patient care?

Yes No Not applicable

If no, please explain:

Did the activity meet your educational needs and expectations?

Yes No

If no, please explain:

Please respond to the following LEARNER statements by circling the appropriate selection:

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

As a result of this activity, I will:

- Utilize available prognostic and predictive clinical and molecular markers to aid in treatment decision-making for patients with hematologic malignancies.....4 3 2 1 N/M N/A
- Design a therapeutic algorithm for the clinical management of indolent and aggressive forms of non-Hodgkin's lymphoma, considering the benefits and risks of induction chemotherapy, radioimmunotherapy, stem cell transplantation, maintenance regimens and emerging molecular-targeted agents.....4 3 2 1 N/M N/A
- Consider emerging clinical research on the use of monoclonal antibodies and immunomodulatory agents when planning primary and consolidation therapy for chronic lymphocytic leukemia (CLL).....4 3 2 1 N/M N/A
- Develop an evidence-based approach to the use of BCR-ABL targeted therapies based on the clinical characteristics of patients with chronic myelogenous leukemia (CML).....4 3 2 1 N/M N/A
- Review the mechanisms of acquired resistance mutations in CML, develop rational clinical strategies for monitoring patients for evidence of disease progression and implement appropriate therapeutic alternatives when warranted.....4 3 2 1 N/M N/A
- Incorporate recent advances in front-line and salvage management of multiple myeloma (MM), including indications and treatment options for autologous stem cell transplantation (ASCT) and non-ASCT candidates.....4 3 2 1 N/M N/A
- Assess ongoing clinical trials evaluating the roles of maintenance and consolidation therapeutic approaches for various hematologic malignancies, including diffuse large B-cell lymphoma, mantle-cell lymphoma, minimal residual disease CLL and MM after successful ASCT.....4 3 2 1 N/M N/A
- Consider the heterogeneous manifestations of myelodysplastic syndrome and the associated cytogenetic markers affecting the initial therapy choice of low-intensity chemotherapy, biologic response modifiers and molecular-targeted agents in specific patient populations.....4 3 2 1 N/M N/A
- Counsel appropriately selected patients with myeloid and lymphoid disorders about clinical research studies incorporating novel treatment approaches.....4 3 2 1 N/M N/A

EDUCATIONAL ASSESSMENT AND CREDIT FORM (continued)

What other practice changes will you make or consider making as a result of this activity?

.....

What additional information or training do you need on the activity topics or other oncology-related topics?

.....

Additional comments about this activity:

.....

.....

May we include you in future assessments to evaluate the effectiveness of this activity?

Yes No

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

Faculty	4 = Expert				3 = Above average				2 = Competent				1 = Insufficient			
	Knowledge of subject matter								Effectiveness as an educator							
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Robert Z Orlowski, MD, PhD	4	3	2	1	4	3	2	1	4	3	2	1	4	3	2	1
David P Steensma, MD	4	3	2	1	4	3	2	1	4	3	2	1	4	3	2	1
David G Maloney, MD, PhD	4	3	2	1	4	3	2	1	4	3	2	1	4	3	2	1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty for this activity:

.....

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