

Hematologic Oncology™

U P D A T E

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

EDITOR

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INTERVIEWS

Gail J Roboz, MD

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**SPECIAL FEATURE:
BONUS AUDIO**



See page 2 for details about the additional audio from the engaging interview with Dr Garcia-Manero available exclusively online

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OVERVIEW OF ACTIVITY

Over 45 pharmaceutical agents with more than 55 distinct FDA-approved indications are currently available for the management of hematologic cancer. This extensive armamentarium of treatment options poses a challenge to clinicians who must maintain up-to-date knowledge about optimal clinical management strategies. To bridge the gap between research and patient care, this issue of *Hematologic Oncology Update* features one-on-one discussions with leading oncology investigators. By providing information on the latest research developments in the context of expert perspectives, this activity assists medical oncologists, hematologists and hematology-oncology fellows with the formulation of state-of-the-art clinical management strategies to facilitate best-practice patient care.

LEARNING OBJECTIVES

- Develop an algorithm for the evaluation, classification and risk-stratified treatment of myelodysplastic syndrome (MDS).
- Counsel elderly patients with acute myelogenous leukemia (AML) about the efficacy and safety of available treatment options.
- Apply emerging data with novel agents and regimens to the treatment of patients with newly diagnosed or relapsed/refractory indolent and aggressive non-Hodgkin lymphomas (NHL).
- Appraise the role of maintenance therapy in the management of follicular or mantle-cell lymphoma.
- Integrate emerging data with monoclonal antibodies into the evidence-based treatment of chronic lymphocytic leukemia (CLL).
- Communicate the benefits and risks of proteasome inhibitors and IMiD[®]-based therapeutic regimens to patients with newly diagnosed multiple myeloma (MM).
- Formulate up-to-date induction and consolidation treatment strategies for patients with acute promyelocytic leukemia (APL).

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FACULTY — **Dr Garcia-Manero** had no real or apparent conflicts of interest to disclose. The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process: **Dr Roboz** — Lecturing Honoraria: Celgene Corporation, Cephalon Inc, Eisai Inc, Genzyme Corporation. **Dr Gregory** — Advisory Committee: Amgen Inc, Novartis Pharmaceuticals Corporation; Speakers Bureau: Cephalon Inc, Genentech BioOncology, GlaxoSmithKline, Millennium Pharmaceuticals Inc. **Dr Jagannath** — Advisory Committee: Celgene Corporation, Cephalon Inc, Millennium Pharmaceuticals Inc, Ortho Biotech Products LP.

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BONUS AUDIO AVAILABLE EXCLUSIVELY ONLINE



As an added bonus, please visit www.ResearchToPractice.com for continuation of the interview with **Dr Guillermo Garcia-Manero**, reviewing new research developments in the management of MDS. The additional 30 minutes of dialogue is available for download or for online listening. Topics covered include:

- | | |
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INTERVIEW

Gail J Roboz, MD

Dr Roboz is Associate Professor of Medicine and Director of the Leukemia Program at Weill Medical College of Cornell University at The New York Presbyterian Hospital in New York, New York.

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Select Excerpts from the Interview

Tracks 6-8

▶ **DR LOVE:** Would you describe the design and key findings of the landmark study that demonstrated a survival advantage with azacitidine in MDS?

▶ **DR ROBOZ:** Results from the AZA-001 trial have now been presented at the past two major international meetings (Fenaux 2007; List 2008). In this study, patients with IPSS intermediate-2 and high-risk MDS were randomly assigned to treatment with azacitidine or a conventional care regimen (CCR).

The CCR was a choice of three approaches: supportive care, low-dose cytarabine or conventional induction/consolidation chemotherapy. Prior to randomization, the treating physician decided on the approach to CCR — whether

the patient would receive induction chemotherapy, best supportive care with growth factors, antibiotics and transfusions or low-dose cytarabine. Once that decision was made, the patient was then randomly assigned to CCR or azacitidine.

All the important parameters, including survival, transformation to AML and major infections, favored the azacitidine arm (Fenaux 2007; Santini 2008; [1.1]). Evaluating outcomes according to the type of CCR is more difficult statistically.

Doctors and patients are asking, “How many cycles of this do I have to take? How long do I need this? If I’m not seeing a remission, according to the classic definition, is this drug still working?” These are important areas of ongoing research with azacitidine.

For the first time, we have convincing data that show that even if you are not meeting standard leukemia-type remission criteria — such as platelet counts higher than 100,000/ μ L, neutrophil counts higher than 1,000/ mm^3 — it’s possible that the survival benefit and the reduction in transformation to AML persist. As we obtain more data, it appears that we have good reason to maintain patients on azacitidine, even when not meeting conventional response criteria (List 2008; [1.2]).

When I initiate therapy, I don’t tell patients for how many cycles we will continue the treatment. I let them know that I would like them to receive at least four cycles of azacitidine, unless they are not tolerating it well, because I don’t believe that we can assess their response with fewer cycles. After four cycles, we’ll evaluate the counts, the patient’s general condition and how challenging the therapy has been. However, in general, I favor continuing the agent for now.

- ▶ **DR LOVE:** What about the magnitude of the benefit that was observed?
- ▶ **DR ROBOZ:** Survival benefit is so difficult to determine in diseases for which a benefit measured in months rather than weeks already seems huge.

1.1

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

	Azacitidine (n = 179)	CCR (n = 179)
Median overall survival	24.4 months	15 months*
Two-year overall survival	51%	26% [†]
Median time to AML	26.1 months	12.4 months

* Hazard ratio (95% confidence interval) = 0.58 (0.43-0.77), $p = 0.0001$; [†] $p < 0.0001$

AML = acute myelogenous leukemia

SOURCES: Fenaux P et al. *Proc ASH* 2007; [Abstract 817](#); Hellstrom-Lindberg E et al. *Proc ASCO* 2008; [Abstract 7089](#).

For patients with intermediate-2 and high-risk disease, responses that improve survival by close to nine months are significant (Fenaux 2007; List 2008). Oncology agents have been approved in other types of cancer for improvements measured in weeks, so magnitude-wise, this is significant.

It is an impressive number. However, in addition, because azacitidine is associated with an improvement in quality of life, patients are not simply surviving for a few more weeks but are rather experiencing meaningful improvements.

► **DR LOVE:** Does a certain subgroup of patients seem to have prolonged responses, or are all patients only experiencing a small benefit?

► **DR ROBOZ:** We don't know. In the past the patients at higher risk had more profound responses, but the duration of benefit was not as prolonged.

The initial studies with decitabine — another approved hypomethylating agent — included more patients with higher-risk disease, and the responses were good (Wijermans 2000; Kantarjian 2007a, 2007b). Some will argue that it is easier to induce a response in a patient with higher-risk disease due to increased cell turnover. It is easier to achieve remission in a patient with leukemia than one with MDS.

The questions that still come up are, What is the depth of the responses? Are the responses more durable in certain subgroups? We don't know. Although a clear survival benefit has not been demonstrated with decitabine, it is structurally similar to azacitidine, and I've heard much discussion about whether the survival benefit is a class effect of hypomethylating agents or is specific to azacitidine.

► **DR LOVE:** How are you using decitabine in your practice?

► **DR ROBOZ:** Although both drugs are approved for the same indications, patients are aware that azacitidine has demonstrated a survival advantage whereas decitabine has not. One could conjecture that if the clinical trials had been conducted in exactly the same manner, then the results would be more similar. Still, off study it's probably easier to administer azacitidine to the patients with intermediate-2 and high-risk disease, based on the new data.

1.2

AZA-001: Overall Survival (OS) with Azacitidine versus Conventional Care Regimens (CCR) by Best Response for Patients with High-Risk MDS

IWG 2000 response	Two-year OS	p-value*
Hematologic improvement	71.7%	<0.0001
Complete response	78.4%	<0.0001
Partial response	67.5%	0.006
Stable disease	41.3%	0.041

* p-value versus CCR, two-year OS = 26.2%

SOURCE: List AF et al. *Proc ASCO* 2008; **Abstract 7006**.

Decitabine is effective and well tolerated, and I've used it in an off-label manner for older patients with AML, based on some of the preliminary published data demonstrating responses when it's used continuously for 10 days (Blum 2007; [1.3]). ■

1.3

Optimal Biologic Dose of Decitabine and Response in Patients with Acute Myeloid Leukemia: Results of a Phase I Study

"The OBD of decitabine was 20 mg/m²/d intravenously, with limited nonhematologic toxicity...

In an intent-to-treat analysis, the response rate was 44% (11 of 25). Of 21 assessable patients, 11 (52%) responded: four with morphologic and cytogenetic complete remission (CR; each had complex karyotype), four with incomplete CR, and three with partial remission. In untreated AML, four of nine assessable patients achieved CR."

OBD = optimal biologic dose

SOURCE: Blum W et al. *J Clin Oncol* 2007;25(25):3884-91. [Abstract](#)

SELECT PUBLICATIONS

Blum W et al. **Preliminary results of a phase II study of low dose decitabine as a single agent in older patients (age ≥ 60) with previously untreated acute myeloid leukemia (AML).** *Proc ASH* 2008;[Abstract 2957](#).

Blum W et al. **Phase I study of decitabine alone or in combination with valproic acid in acute myeloid leukemia.** *J Clin Oncol* 2007;25(25):3884-91. [Abstract](#)

Borthakur G et al. **Activity of decitabine in patients with myelodysplastic syndrome previously treated with azacitidine.** *Leuk Lymphoma* 2008;49(4):690-5. [Abstract](#)

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Hellstrom-Lindberg E et al. **Relationship of progression to acute myeloid leukemia (AML) from myelodysplastic syndrome (MDS) and cytogenetic status.** *Proc ASCO* 2008;[Abstract 7089](#).

Kantarjian HM et al. **Survival advantage with decitabine versus intensive chemotherapy in patients with higher risk myelodysplastic syndrome: Comparison with historical experience.** *Cancer* 2007a;109(6):1133-7. [Abstract](#)

Kantarjian HM et al. **Update of the decitabine experience in higher risk myelodysplastic syndrome and analysis of prognostic factors associated with outcome.** *Cancer* 2007b;109(2):265-73. [Abstract](#)

List AF et al. **Effect of azacitidine (AZA) on overall survival in higher-risk myelodysplastic syndromes (MDS) without complete remission.** *Proc ASCO* 2008;[Abstract 7006](#).

Santini V et al. **Patient outcome measures prolonged survival in patients with high-risk myelodysplastic syndromes (MDS) treated with azacitidine (AZA).** *Proc ASCO* 2008;[Abstract 7028](#).

Silverman LR et al. **Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the Cancer and Leukemia Group B.** *J Clin Oncol* 2002;20(10):2429-40. [Abstract](#)

Wijermans P et al. **Low-dose 5-aza-2'-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: A multicenter phase II study in elderly patients.** *J Clin Oncol* 2000;18(5):956-62. [Abstract](#)



INTERVIEW

Stephanie A Gregory, MD

Dr Gregory is The Elodia Kehm Chair of Hematology, Professor of Medicine and Director of the Section of Hematology at the Rush University Medical Center/Rush University in Chicago, Illinois.

Tracks 1-22

- Track 1** Case discussion: A 34-year-old woman with asymptomatic, Grade I follicular lymphoma
- Track 2** Role of transplantation for follicular lymphoma
- Track 3** Novel humanized anti-CD20 monoclonal antibody ofatumumab in the treatment of non-Hodgkin lymphoma (NHL)
- Track 4** Clinical experience with ofatumumab with CHOP in the treatment of NHL
- Track 5** Ofatumumab for relapsed/refractory chronic lymphocytic leukemia (CLL)
- Track 6** Future directions for the development of ofatumumab in the treatment of CLL
- Track 7** Phase III trial of R-bendamustine versus R-CHOP as first-line therapy for follicular, indolent or mantle-cell lymphoma (MCL)
- Track 8** First-line therapy for follicular lymphoma
- Track 9** RESORT trial of maintenance rituximab for low tumor burden, indolent lymphoma
- Track 10** Clinical use of maintenance rituximab for follicular lymphoma
- Track 11** Clinical data with bortezomib for follicular lymphoma
- Track 12** Case discussion: An 87-year-old woman with Richter's transformation from CLL
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- Track 14** Case discussion: A 60-year-old man with Stage IV MCL
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- Track 17** Maintenance rituximab for MCL
- Track 18** Case discussion: A 60-year-old woman with diffuse large B-cell lymphoma (DLBCL)
- Track 19** Treatment strategies being evaluated in DLBCL
- Track 20** Clinical use of dose-dense regimens for DLBCL
- Track 21** Utilization of radioimmunotherapy for DLBCL
- Track 22** GCLLSG-CLL8: A Phase III trial of FC versus FCR as first-line therapy for CLL

Select Excerpts from the Interview

Tracks 3, 5

▶ **DR LOVE:** What's new in the treatment of lymphoma?

► **DR GREGORY:** I've seen many new developments, although I'm uncertain whether any of them will replace our standard treatment approaches. Everyone is trying to improve upon rituximab, but how do you do that with a monoclonal antibody? Perhaps we can improve the attachment of the monoclonal antibody to the FC-gamma receptors from the monocyte-macrophage system to enhance cell destruction. We can add cytokines, such as GM-CSF or interleukin, to the monoclonal antibody or humanize it to achieve more effective antibody-dependent cellular toxicity or to complement cellular lysis.

The novel agent ofatumumab is a humanized anti-CD20 monoclonal antibody currently in clinical trials for NHL and CLL. The data with ofatumumab mainly involve patients with relapsed/refractory CLL, and it appeared to be effective in some of the patients for whom a fludarabine/cyclophosphamide/rituximab (FCR)-type regimen had failed. It also appeared to work well for some of the patients with the poorer prognostic factors of CLL (Osterborg 2008; [2.1]).

In the front-line treatment of CLL, investigators will be conducting a trial comparing ofatumumab to chlorambucil, which is how bendamustine received FDA approval (Knauf 2008). They're also evaluating ofatumumab in combination with fludarabine/cyclophosphamide in the relapsed setting.

2.1

Ofatumumab for Fludarabine- and Alemtuzumab-Refractory or Bulky Fludarabine-Refractory CLL

	Fludarabine- and alemtuzumab-refractory CLL (n = 59)	Bulky fludarabine-refractory CLL (n = 79)
Received prior rituximab	59%	54%
Overall response rate	51%	44%
Complete response rate	0%	1%
Partial response rate	51%	43%
Stable disease rate	39%	43%
Median overall survival	13.7 months	15.4 months
Median time to next CLL therapy	9.0 months	7.9 months

“These results demonstrate the effectiveness of ofatumumab in patients with double-refractory CLL or bulky fludarabine-refractory disease. Ofatumumab was well tolerated with no unexpected toxicities. This monoclonal antibody potentially represents an active treatment option with clinical benefit for patients with poor prognosis who have exhausted standard treatment options.”

SOURCE: Osterborg A et al. *Proc ASH* 2008; **Abstract 328**.

 **Track 7**

► **DR LOVE:** What are some recently reported data sets with bendamustine in lymphoma?

► **DR GREGORY:** One impressive study, reported by Dr Rummel, compared bendamustine/rituximab to R-CHOP as front-line therapy for advanced follicular or mantle-cell lymphoma. It was a noninferiority study, and he demonstrated that bendamustine/rituximab appeared — at least in the interim analysis — to be as effective as R-CHOP with less toxicity (Rummel 2008; [2.2]).

If those results hold up, we may replace CHOP with bendamustine as front-line therapy. Many physicians in the United States are still administering R-CHOP as front-line therapy for follicular lymphoma. It would be nice if we had a less toxic replacement for that regimen, and bendamustine may work.

Brad Kahl’s study of 100 patients with rituximab-refractory, indolent NHL led to the approval of bendamustine in the relapsed setting. That trial reported impressive overall response rates and durations of response. Bendamustine works for patients with rituximab-refractory disease (Kahl 2007).

2.2 Phase III Randomized Trial of Rituximab/Bendamustine (R-B) versus R-CHOP as First-Line Therapy for Follicular, Indolent or Mantle-Cell Lymphoma

Second interim analysis (median follow-up of 28 months)

Efficacy

	R-B (n = 221)	R-CHOP (n = 212)
Overall response rate	94%	93%
Complete response rate	41%	33%
Median event-free survival	Not reached	39 months*

* No statistical difference

Safety

	R-B (n = 221)	R-CHOP (n = 212)
Alopecia	0%	89%
Any grade infection	25%	37%
Grade III/IV leukopenia	19%	36%

“In this second interim analysis, the combination of bendamustine and rituximab appears to be noninferior to the standard R-CHOP while showing a better tolerability profile.”

SOURCE: Rummel MJ et al. *Proc ASH* 2008; [Abstract 2596](#).

 **Track 9**

► **DR LOVE:** What about the use of maintenance rituximab for patients with indolent lymphomas? What studies are evaluating this issue?

► **DR GREGORY:** The RESORT trial (ECOG-E4402) recently closed to accrual. This study is evaluating four weeks of rituximab for patients with asymptom-

atic indolent lymphomas, including follicular lymphomas with a low tumor burden. If the patient demonstrates a partial or complete response after four weeks of rituximab, he or she is randomly assigned to one of two arms (2.3).

One arm offers maintenance rituximab with one infusion every three months until the disease progresses. The other arm involves waiting until the patient experiences disease progression and then re-treating with four weeks of rituximab. If the disease progresses again, they re-treat again with four weeks of rituximab until the patient's disease no longer responds.

At Rush University, we have enrolled five or six patients on this trial. We have four patients who are on the maintenance arm, and some of them have been receiving rituximab every three months and remain in complete remission for 4.5 to 5 years, which is impressive.

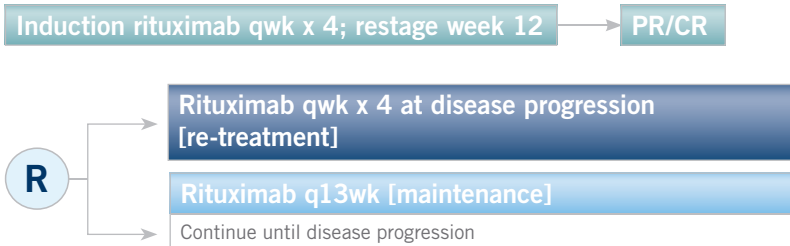
Is it better to keep patients on maintenance therapy or wait until the disease progresses and then re-treat? You'll use much less rituximab with the second choice.

If it takes the same amount of time to become refractory to rituximab, what's the sense in administering it every three months, spending money, suppressing the immune system and risking infection? As this question is currently being evaluated in the RESORT trial, I don't have a conclusion.

2.3

RESORT: A Phase III Randomized Study of Rituximab for Patients with Low Tumor Burden Indolent Non-Hodgkin Lymphoma (NHL)

Protocol ID: ECOG-E4402
Target Accrual: 389 (Closed)



PR = partial response
CR = complete response

Select Eligibility Criteria

- Low-grade NHL, previously untreated
- Measurable disease
- Low tumor burden
- Stage III/IV disease
- ECOG PS 0 or 1

Study Contacts

Eastern Cooperative Oncology Group
Brad Kahl, MD, Tel: 608-263-1836
Michael Williams, MD, Tel: 434-924-9637

SOURCE: NCI Physician Data Query, January 2009.

Track 11

▶ **DR LOVE:** What other new agents are being evaluated for follicular lymphoma?

▶ **DR GREGORY:** Lenalidomide is being evaluated, and bortezomib was recently compared to bortezomib in combination with rituximab in relapsed/refractory follicular lymphoma. An upcoming study will evaluate the combination of rituximab, bendamustine and bortezomib. That should be an interesting trial.

▶ **DR LOVE:** Would you discuss what we know about bortezomib in follicular lymphoma?

▶ **DR GREGORY:** The trial with bortezomib/rituximab evaluated two different ways of administering bortezomib to patients with relapsed/refractory disease. One regimen was a weekly dose of bortezomib, and the other regimen was the schedule used in multiple myeloma — on days one, four, eight and 11. Both regimens seemed to yield good response rates, and it appeared that the weekly infusion was less toxic (De Vos 2006).

Track 16

▶ **DR LOVE:** How do you use bortezomib in the treatment of mantle-cell lymphoma?

▶ **DR GREGORY:** I have used it a great deal in the relapsed setting on days one, four, eight and 11. I often add rituximab on day one. I try to administer at least six to eight cycles because I believe that if you give up after the first couple of cycles, you haven't completed an adequate trial period.

I have been relatively impressed with bortezomib in the relapsed setting. We're not talking about long responses. We're talking about months, not years, but it's something to offer a patient who has experienced relapse. If the patient is young, we try to find an allogeneic donor and perhaps perform a nonmyeloablative allotransplant.

Track 22

▶ **DR LOVE:** What else happened at ASH that's important to know about?

▶ **DR GREGORY:** The German CLL data were interesting. It was the first randomized trial evaluating fludarabine/cyclophosphamide/rituximab (FCR) versus fludarabine/cyclophosphamide (FC) as first-line therapy for CLL. The results certainly favored FCR (Hallek 2008; [2.4]). ■

**Phase III Randomized Trial of Fludarabine/Cyclophosphamide/
Rituximab (FCR) versus Fludarabine/Cyclophosphamide
(FC) as First-Line Therapy for CLL (N = 817)**

Median follow-up of 25.5 months

Efficacy

	FCR	FC	p-value
Overall response rate	95.0%	88.0%	0.001
Complete response rate	52.0%	27.0%	<0.0001
Two-year PFS	76.6%	62.3%	<0.0001
Two-year OS	91.0%	98.0%	0.18

PFS = progression-free survival; OS = overall survival

Safety

	FCR	FC	p-value
Neutropenia	33.6%	20.9%	0.0001
Leukopenia	24.0%	12.1%	<0.0001
Grade III/IV infections	18.8%	14.8%	0.68

“Treatment with FCR chemoimmunotherapy improves response rates and PFS when compared to FC chemotherapy. FCR caused more neutropenia/leukopenia without increasing the incidence of severe infections. These results suggest that FCR chemoimmunotherapy might become the new standard first-line treatment for physically fit patients with CLL.”

SOURCE: Hallek M et al. *Proc ASH* 2008; [Abstract 325](#).

SELECT PUBLICATIONS

De Vos S et al. **Phase 2 study of bortezomib weekly or twice weekly plus rituximab in patients with follicular (FL) or marginal zone (MZL) lymphoma: Final results.** *Proc ASH* 2006; [Abstract 694](#).

Hallek M et al. **Immunochemotherapy with fludarabine (F), cyclophosphamide (C), and rituximab (R) (FCR) versus fludarabine and cyclophosphamide (FC) improves response rates and progression-free survival (PFS) of previously untreated patients (pts) with advanced chronic lymphocytic leukemia (CLL).** *Proc ASH* 2008; [Abstract 325](#).

Kahl B et al. **Bendamustine is safe and effective in patients with rituximab-refractory, indolent B-cell non-Hodgkin lymphoma.** *Proc ASH* 2007; [Abstract 1351](#).

Knauf WU et al. **Bendamustine versus chlorambucil as first-line treatment in B cell chronic lymphocytic leukemia: An updated analysis from an international phase III study.** *Proc ASH* 2008; [Abstract 2091](#).

Osterborg A et al. **Ofatumumab (HuMax-CD20), a novel CD20 monoclonal antibody, is an active treatment for patients with CLL refractory to both fludarabine and alemtuzumab or bulky fludarabine-refractory disease: Results from the planned interim analysis of an international pivotal trial.** *Proc ASH* 2008; [Abstract 328](#).

Rummel MJ et al. **Bendamustine plus rituximab versus CHOP plus rituximab in the first-line-treatment of patients with follicular, indolent and mantle cell lymphomas: Results of a randomized phase III study of the study group indolent lymphomas (StiL).** *Proc ASH* 2008; [Abstract 2596](#).



INTERVIEW

Sundar Jagannath, MD

Dr Jagannath is Chief of the Multiple Myeloma and Stem Cell Transplantation Program at St Vincent's Comprehensive Cancer Center in New York, New York and Professor of Medicine at New York Medical College in Valhalla, New York.

Tracks 1-9

- | | | | |
|----------------|---|----------------|--|
| Track 1 | Combination regimens incorporating bortezomib for patients with newly diagnosed multiple myeloma (MM) | Track 5 | Clinical trial of lenalidomide/dexamethasone with elotuzumab for relapsed MM |
| Track 2 | Clinical use of bortezomib-containing regimens in patients with high-risk MM | Track 6 | Clinical trial of bortezomib with vorinostat for relapsed/refractory MM |
| Track 3 | Safety and efficacy of lenalidomide/bortezomib/dexamethasone (RVD) in patients with newly diagnosed MM | Track 7 | Case discussion: An 80-year-old man with newly diagnosed Stage II MM |
| Track 4 | Case discussion: Therapeutic approach for a 68-year-old woman with relapsed MM four years after treatment with VAD followed by a stem cell transplant | Track 8 | Case discussion: A 55-year-old man with slowly progressing MM |
| | | Track 9 | Case discussion: A 68-year-old woman with relapsed MM who previously received front-line VAD induction therapy |

Select Excerpts from the Interview

Track 1

► **DR LOVE:** Can you discuss some of the important Phase III data sets presented at the 2008 ASH meeting?

► **DR JAGANNATH:** Paul Richardson from the Dana-Farber Cancer Institute presented data on the RVD combination in patients with newly diagnosed multiple myeloma (Richardson 2008).

The previous year he presented data on the same regimen in patients with relapsed and refractory myeloma (Richardson 2007b), so the 2008 data were more of an update. The overall response rate for newly diagnosed patients who received the maximum planned dose was 100 percent (3.1).

Similarly, Bill Bensinger presented data from a multi-institutional trial on the combination of bortezomib, cyclophosphamide and dexamethasone followed by bortezomib, thalidomide and dexamethasone as first-line therapy for

multiple myeloma. In this trial, 90 percent of patients responded to the treatment (Bensinger 2008; [3.2]).

Another regimen consisting of bortezomib, thalidomide and dexamethasone as induction therapy for patients with symptomatic myeloma also demonstrated a good response rate (Kaufman 2007; [3.3]).

The data show that almost 100 percent of patients respond to these combinations, so for the first time we have agents in our armamentarium that have high response rates among newly diagnosed patients, and that is good news.

3.1

Phase I/II Trial of Lenalidomide, Bortezomib and Dexamethasone (RVD) for Patients with Newly Diagnosed Multiple Myeloma (MM)

Efficacy data (n = 66)

	All patients	Patients receiving MPD
ORR	98%	100%

Responses by ISS stage

	ISS I (n = 33)	ISS II (n = 21)	ISS III (n = 10)	p-value
≥PR	97%	100%	100%	0.385
≥VGPR	51%	57%	80%	0.421

Responses by cytogenetic status

	Normal (n = 39)	Abnormal (n = 24)	No 13q deletion (n = 52)	13q deletion (n = 7)	No trans 4;14 (n = 49)	Trans 4;14 (n = 10)
≥PR	100% p = 0.381	96%	100% p = 0.119	86%	98% p = 1.00	100%
≥VGPR	69% p = 0.560	79%	75% p = 0.375	57%	73% p = 1.00	70%

“RVD produces high quality responses and is well tolerated in newly diagnosed MM pts, regardless of their cytogenetic status or ISS stage. MPD has been reached at Len 25 mg, Bz 1.3 mg/m², and Dex 20 mg, with phase II enrollment now complete and 100% ORR reported at the MPD.

Stem cell mobilization has been successful in almost all pts, with transplant course in pts otherwise unremarkable.”

MPD = maximum planned dose; ORR = overall response rate; ISS = International Staging System; PR = partial response; VGPR = very good partial response

SOURCE: Richardson P et al. *Proc ASH* 2008; **Abstract 92**.

3.2

Response Rate for Sequential Bortezomib, Cyclophosphamide and Dexamethasone (VCD) Followed by Bortezomib, Thalidomide and Dexamethasone (VTD) as First-Line Therapy for Multiple Myeloma (N = 30)

	Response rate
Overall response rate (\geq PR)	90%
CR + VGPR	60%
CR	33%
PR	30%
Stable disease or not evaluable	10%

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

“This bortezomib/cyclophosphamide/dexamethasone (VCD) based combination induction therapy followed by VTD is a promising addition to the treatment armamentarium for previously untreated patients. The response rates: ORR 90%; VGPR (60%) and CR (33%) are extremely encouraging and improve over our bortezomib/dexamethasone 2-drug experience which produced 90% PR and 38% VGPR. This very well tolerated new regimen is potentially an important step forward in induction therapy with presentation of more mature data.”

SOURCE: Bensing W et al. *Proc ASH* 2008; [Abstract 94](#).

3.3

Bortezomib, Thalidomide and Dexamethasone as Induction Therapy for Patients with Symptomatic Multiple Myeloma

“After a median follow up of 373 days, median progression free survival and overall survival have not been reached. One year overall survival is 97%. One-year progression-free survival is 87%. In conclusion, we report a very high response rate with a short course of bortezomib, thalidomide and dexamethasone with an acceptable toxicity profile. Follow up of patients in CR treated without high dose therapy and autologous transplant is in progress. Further studies of this active regimen are warranted.”

SOURCE: Kaufman JL et al. *Proc ASH* 2007; [Abstract 3605](#).

Track 2

► **DR LOVE:** What do we know about the effectiveness of bortezomib in patients with high-risk disease?

► **DR JAGANNATH:** The robust information that is being reported with bortezomib shows that patients with multiple myeloma who are at high risk — such as those who have 4;14 translocation, cytogenetically detected chromosome 13 deletion, 14;16 translocation or 17p13 deletion — benefit from the addition of this agent (Jagannath 2007; [3.4]). These patients have poor outcomes when they are treated with traditional chemotherapy and simple

autologous transplants, but whenever bortezomib is added to the mix, their outcomes dramatically improve.

We saw the benefit of this agent in the trial evaluating melphalan/prednisone with or without bortezomib as initial treatment for multiple myeloma (San Miguel 2008). The French Francophone Myeloma Intergroup (IFM) has also observed this in its trials of bortezomib/dexamethasone as induction therapy (Harousseau 2006, 2008).

As the addition of bortezomib apparently overcomes a poor prognosis, more and more physicians are using it for their patients who are at high risk. They are also using it for patients who have renal impairment or other comorbidities that increase their risk of developing deep venous thromboses, as that risk is minimal with bortezomib.

Physicians now have a choice of regimens when treating their patients with multiple myeloma. The Mayo Clinic website recommends that patients at high risk receive bortezomib and patients at low risk receive lenalidomide. However, I believe that will be questioned because we can now treat with the combination of bortezomib/lenalidomide/dexamethasone, and we don't have to base our selection on whether the prognosis is good or poor.

3.4

Bortezomib Overcomes the Poor Prognosis Conferred by Chromosome 13 Deletion

“In multiple myeloma, deletion of chromosome 13 (del(13)) is associated with poor prognosis regardless of treatment. This study analyzed the impact of del(13) status on response and survival following treatment with either bortezomib or high-dose dexamethasone in patients in the SUMMIT and APEX trials. Additionally, matched-pairs subset analyses were conducted of patients with and without del(13), balanced for age and International Staging System parameters. In both SUMMIT and APEX, prognosis appeared to be poorer in bortezomib-treated patients with del(13) compared with patients with no del(13) by metaphase cytogenetics.

In the SUMMIT and APEX matched-pairs analysis, response and survival appeared comparable in bortezomib-treated patients with or without del(13) by metaphase cytogenetics. However, patients with del(13) receiving dexamethasone in APEX appeared to have markedly decreased survival compared with those without del(13) by metaphase cytogenetics. These matched-pairs analyses suggest that bortezomib may overcome some of the poor impact of del(13) as an independent prognostic factor.”

SOURCE: Jagannath S et al. *Leukemia* 2007;21(1):151-7. [Abstract](#)

Track 3

► **DR LOVE:** What have you observed in terms of the toxicity associated with RVD?

► **DR JAGANNATH:** In the clinical trial evaluating RVD in patients with newly diagnosed multiple myeloma, the regimen was well tolerated.

For some of the patients from whom we were able to collect stem cells, the effect of the lenalidomide persisted and cyclophosphamide was required for mobilization. So when lenalidomide is incorporated up front, collecting stem cells with filgrastim alone is not effective, but if you use two grams per meter squared of cyclophosphamide and the growth factor, it works well.

I believe that the RVD regimen is effective. Many of the patients on the trial have chosen not to undergo the stem cell transplant but rather to stay on the regimen and continue it at a lower dose as a maintenance phase.

This is an important clinical trial, and moving forward a study is being designed in which patients will receive four cycles of RVD and then either stay on the regimen or proceed to stem cell transplant followed by additional RVD, so all the patients will receive one year of this combination. We will be participating in this multi-institutional trial, along with the Dana-Farber and IFM groups, so I anticipate that patient accrual will be robust and quick. ■

SELECT PUBLICATIONS

Bensinger W et al. **A Phase II study of bortezomib (Velcade®), cyclophosphamide (Cytosan®), thalidomide (Thalomid®) and dexamethasone as first-line therapy for multiple myeloma.** *Proc ASH* 2008;[Abstract 94](#).

Dimopoulos MA et al. **Treatment of patients with relapsed/refractory multiple myeloma (MM) with lenalidomide and dexamethasone with or without bortezomib depending on prior neurotoxicity: Prospective evaluation of the impact of cytogenetic abnormalities and assessment of bone met.** *Proc ASH* 2008;[Abstract 1726](#).

Harousseau JL et al. **Bortezomib/dexamethasone versus VAD as induction prior to autologous stem cell transplantation (ASCT) in previously untreated multiple myeloma (MM): Updated data from IFM 2005/01 trial.** *Proc ASCO* 2008;[Abstract 8505](#).

Harousseau JL et al. **Bortezomib plus dexamethasone as induction treatment prior to autologous stem cell transplantation in patients with newly diagnosed multiple myeloma: Results of an IFM phase II study.** *Haematologica* 2006;91(11):1498-505. [Abstract](#)

Jagannath S et al. **Bortezomib appears to overcome the poor prognosis conferred by chromosome 13 deletion in phase 2 and 3 trials.** *Leukemia* 2007;21(1):151-7. [Abstract](#)

Kaufman JL et al. **Bortezomib, thalidomide, and dexamethasone as induction therapy for patients with symptomatic multiple myeloma.** *Proc ASH* 2007;[Abstract 3605](#).

Lonial S et al. **Characterisation of haematological profiles and low risk of thromboembolic events with bortezomib in patients with relapsed multiple myeloma.** *Br J Haematol* 2008;143(2):222-9. [Abstract](#)

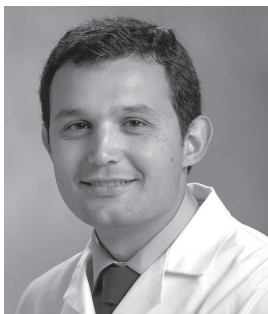
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Richardson P et al. **Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma: Encouraging efficacy in high risk groups with updated results of a Phase I/II study.** *Proc ASH* 2008;[Abstract 92](#).

Richardson P et al. **Lenalidomide, bortezomib, and dexamethasone (Rev/Vel/Dex) as front-line therapy for patients with multiple myeloma (MM): Preliminary results of a Phase 1/2 study.** *Proc ASH* 2007a;[Abstract 187](#).

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* 2007b;[Abstract 2714](#).

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. [Abstract](#)



INTERVIEW

Guillermo Garcia-Manero, MD

Dr Garcia-Manero is Associate Professor of Medicine and Chief of the Section of Myelodysplastic Syndromes in the Department of Leukemia at The University of Texas MD Anderson Cancer Center in Houston, Texas.

Tracks 1-10

- | | | | |
|----------------|---|-----------------|---|
| Track 1 | Therapeutic approaches for elderly patients with AML | Track 6 | All-trans retinoic acid (ATRA) and arsenic trioxide for APL |
| Track 2 | Clinical trial data with clofarabine for AML and MDS | Track 7 | Side effects and toxicities associated with ATRA and arsenic trioxide |
| Track 3 | Clinical use of clofarabine off protocol for MDS or AML | Track 8 | Induction and consolidation with ATRA and arsenic trioxide for APL |
| Track 4 | Side effects and toxicities associated with clofarabine | Track 9 | Molecular monitoring for APL |
| Track 5 | Acute promyelocytic leukemia (APL) | Track 10 | Key published data sets in APL |

Select Excerpts from the Interview

Track 2

► **DR LOVE:** Would you discuss the data on clofarabine as treatment for AML and MDS?

► **DR GARCIA-MANERO:** We have published data from Phase I and Phase II studies in AML with Dr Faderl from MD Anderson as lead author in a number of papers in *Blood* (Faderl 2005, 2006, 2008a). Response rates with clofarabine or clofarabine/ara-C are similar to those for patients with the same characteristics treated with idarubicin/ara-C (IA)-type chemotherapy.

Studies of clofarabine in older patients are ongoing, and data from a key study are now being analyzed. It's possible that lower doses — 10 mg/m² to 30 mg/m² — may be well tolerated, with mortality rates of approximately five or 10 percent, which is lower than with the standard approaches of the past. We have to wait and see whether that translates into a meaningful improvement in survival.

The question is, can you extrapolate data in AML to MDS? We are involved in a number of studies, both at MD Anderson and in cooperative studies,

evaluating lower doses and oral schedules of clofarabine for patients with MDS.

The data are exciting and have been presented at the last two ASH annual meetings (Faderl 2007, 2008c). The response rate is approximately 40 to 50 percent. I have seen a strong signal that clofarabine may allow rescue of some patients for whom 5-azacitidine or decitabine fails (Faderl 2008c; [4.1]). I believe that this may be a major breakthrough in helping control the disease for patients who have not been helped by hypomethylating agents.

4.1

Response Rates with Oral (PO) and Intravenous (IV) Clofarabine among Patients* with High-Risk MDS

	PO [†] (n = 24)	IV 15 mg/m ² (n = 20)	IV 30 mg/m ² (n = 16)
CR, n (%)	7 (29)	7 (35)	4 (25)
CRp, n (%)	2 (8)	3 (15)	2 (13)

CR = complete remission; CRp = complete remission with incomplete platelet recovery

* Thirty-nine (64%) patients failed prior hypomethylator therapy with either decitabine or azacitidine (22 [61%] patients treated IV and 17 [68%] patients treated with PO clofarabine).

[†] Starting dose of 40 mg/m² orally daily x 5 every 4 to 6 weeks, decreased to 30 mg/m² orally daily x 5 after six patients had been treated on the higher dose

SOURCE: Faderl S et al. *Proc ASH 2008c*; [Abstract 222](#).

Tracks 3-4

► **DR LOVE:** Cost and reimbursement issues aside, how would you use clofarabine as treatment for AML and MDS?

► **DR GARCIA-MANERO:** Clofarabine would be my first choice for a patient with MDS for whom either 5-azacitidine or decitabine has failed. In AML, clofarabine would also be a consideration. However, the reality is that we have more experience with other approaches with which cost issues are not so relevant, such as fludarabine-containing regimens.

The study of clofarabine versus clofarabine/ara-C as front-line therapy for patients age 60 or older with AML or high-risk MDS was published recently (Faderl 2008a). Although this may be a major breakthrough for clofarabine, I would not yet recommend it as front-line therapy for AML. We need to evaluate the data before we start replacing “7 + 3” (anthracycline-based therapy with cytarabine) with clofarabine.

I feel better now using a hypomethylating agent off protocol for a patient with AML in the front-line setting. In this setting, the mortality rates are lower and the toxicity profiles are better with hypomethylating agents.

► **DR LOVE:** What are the side effects and toxicities with clofarabine, either alone or in combination with ara-C?

► **DR GARCIA-MANERO:** It is a powerful cytotoxic agent, so when we induce patients with clofarabine we do so in the hospital in a protected environment, not that different from the “7 + 3”-type approach, as opposed to induction with a hypomethylating agent, which can be administered on an outpatient basis. So that doesn’t change much.

Patients exhibit significant myelosuppression and neutropenic fever similar to those seen with an ara-C-containing regimen, in addition to the characteristic rash typically appearing on the patient’s upper body, which can be treated with steroids and topical care.

What changes is that the induction mortality drops from the 30 to 40 percent reported with a “7 + 3” regimen to approximately 10 percent with clofarabine (Atallah 2007; Faderl 2006), perhaps due to less mucosal damage that can lead to death from infection in patients receiving high-dose ara-C regimens. I believe that is what makes clofarabine attractive.

Tracks 6-8

► **DR LOVE:** Would you comment on the all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) combination therapy that’s used to treat acute promyelocytic leukemia (APL)?

► **DR GARCIA-MANERO:** The ATRA/ATO combination was rapidly moved into clinical trials of front-line therapy, and now it is becoming the standard treatment for APL. Molecular responses are robust, and the disease-free survival is approximately 90 percent in the median follow-up data we currently have available. This is satisfactory, as this is a nonchemotherapy approach for APL.

The patients with higher-risk APL still pose a problem, largely because many of them die or develop a bleed in their brains before we can enroll them on studies. We do have a promising strategy of combining gemtuzumab ozogamicin with this ATRA/ATO regimen, and the outcomes are dramatic (Ravandi 2009).

The treatment protocols for the ATRA/ATO regimen with and without gemtuzumab ozogamicin are all available in the published literature. That being said, molecular monitoring is key in the treatment of these patients and you need access to a good RT-PCR assay for translocation 15;17 or the PML/RARalpha fusions, otherwise you will be treating the patient blindly. Those tests are strong predictors of what will happen to the patient and should be repeated regularly during the course of therapy.

► **DR LOVE:** What do you see in terms of side effects and toxicity with this therapy?

► **DR GARCIA-MANERO:** The most important side effect of ATRA would be the retinoic acid syndrome, which is basically a capillary-type syndrome with

which, after a few days of therapy, patients develop pulmonary edema, shortness of breath, et cetera. Nowadays this is rare, partly because the therapy is changing the natural history of the disease and also because we heavily premedicate patients with steroids. If the syndrome does occur, you can stop therapy and treat them with the steroids, and most will fare well.

One peculiar toxicity exists with ATO, which is QT prolongation and torsades de pointes. This occurs infrequently and is more common in African-Americans than in Caucasians. Guidelines suggest that you can rechallenge patients with ATO, but I would not feel comfortable with that. The good news is that I have a number of such patients whom I have switched to idarubicin/anthracycline or gemtuzumab ozogamicin/ATRA, and they are now five to six years out and are faring extremely well. ■

SELECT PUBLICATIONS

Atallah E et al. **Establishment of baseline toxicity expectations with standard frontline chemotherapy in acute myelogenous leukemia.** *Blood* 2007;110(10):3547-51. [Abstract](#)

Estey E et al. **Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia.** *Blood* 2006;107(9):3469-73. [Abstract](#)

Faderl S et al. **A randomized study of clofarabine versus clofarabine plus low-dose cytarabine as front-line therapy for patients aged 60 years and older with acute myeloid leukemia and high-risk myelodysplastic syndrome.** *Blood* 2008a;112(5):1638-45. [Abstract](#)

Faderl S et al. **Clofarabine combinations as acute myeloid leukemia salvage therapy.** *Cancer* 2008b;113(8):2090-6. [Abstract](#)

Faderl S et al. **Oral (PO) and intravenous (IV) clofarabine for patients (pts) with myelodysplastic syndrome (MDS).** *Proc ASH* 2008c;[Abstract 222](#).

Faderl S et al. **Results of an exploratory study of oral (PO) and intravenous (IV) clofarabine in patients with myelodysplastic syndrome.** *Proc ASH* 2007;[Abstract 1455](#).

Faderl S et al. **Clofarabine and cytarabine combination as induction therapy for acute myeloid leukemia (AML) in patients 50 years of age or older.** *Blood* 2006;108(1):45-51. [Abstract](#)

Faderl S et al. **Results of a phase 1-2 study of clofarabine in combination with cytarabine (ara-C) in relapsed and refractory acute leukemias.** *Blood* 2005;105(3):940-7. [Abstract](#)

Kantarjian H et al. **Phase 2 clinical and pharmacologic study of clofarabine in patients with refractory or relapsed acute leukemia.** *Blood* 2003a;102(7):2379-86. [Abstract](#)

Kantarjian HM et al. **Phase I clinical and pharmacology study of clofarabine in patients with solid and hematologic cancers.** *J Clin Oncol* 2003b;21(6):1167-73. [Abstract](#)

Raffoux E et al. **Combined treatment with arsenic trioxide and all-trans-retinoic acid in patients with relapsed acute promyelocytic leukemia.** *J Clin Oncol* 2003;21(12):2326-34. [Abstract](#)

Ravandi F et al. **Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin.** *J Clin Oncol* 2009;27(4):504-10. [Abstract](#)

Shen ZX et al. **All-trans retinoic acid/As₂O₃ combination yields a high quality remission and survival in newly diagnosed acute promyelocytic leukemia.** *Proc Natl Acad Sci USA* 2004;101(15):5328-35. [Abstract](#)

Tsimberidou AM et al. **All-trans retinoic acid (ATRA) and arsenic trioxide (As₂O₃) combination therapy induces high rates of durable molecular remission in newly diagnosed acute promyelocytic leukemia (APL).** *Proc ASH* 2007;[Abstract 1834](#).

QUESTIONS (PLEASE CIRCLE ANSWER):

1. In the AZA-001 trial, treatment with azacitidine compared to conventional care regimens (CCR) improved median overall survival by approximately _____ for patients with high-risk MDS.
 - a. Three months
 - b. Six months
 - c. Nine months
 - d. 12 months
2. In the AZA-001 trial, treatment with azacitidine delayed the transformation to AML by approximately _____ compared to CCR for patients with high-risk MDS.
 - a. Four months
 - b. Eight months
 - c. 13 months
 - d. 17 months
3. In the AZA-001 trial, azacitidine was associated with significant improvements in overall survival compared to CCR among patients who achieved _____.
 - a. Complete response only
 - b. Complete response or partial response only
 - c. Complete response, partial response or stable disease
 - d. None of the above
4. Ofatumumab monotherapy has demonstrated efficacy in _____ CLL.
 - a. Relapsed/refractory
 - b. Newly diagnosed
 - c. Both a and b
 - d. None of the above
5. An interim analysis of a Phase III randomized trial demonstrated that in terms of efficacy, R-CHOP was _____ rituximab/bendamustine as first-line therapy for follicular, indolent or mantle-cell lymphoma.
 - a. More effective than
 - b. Less effective than
 - c. Comparable to
6. In a German Phase III randomized trial, which of the following regimens was found to be superior to fludarabine/cyclophosphamide as first-line therapy for CLL?
 - a. Fludarabine/rituximab
 - b. Fludarabine/cyclophosphamide/rituximab
 - c. Fludarabine/cyclophosphamide/ofatumumab
 - d. Both b and c
 - e. None of the above
7. In the Phase I/II trial of lenalidomide, bortezomib and dexamethasone for patients with newly diagnosed multiple myeloma, the overall response rate was _____ for patients who received the maximum planned dose.
 - a. 70 percent
 - b. 80 percent
 - c. 90 percent
 - d. 100 percent
8. In the Phase I/II trial of lenalidomide, bortezomib and dexamethasone for patients with newly diagnosed multiple myeloma, stem cell mobilization was unsuccessful in all patients.
 - a. True
 - b. False
9. Response rates (CR + CRp) of approximately 40 to 50 percent were reported with clofarabine in the treatment of high-risk MDS.
 - a. True
 - b. False
10. Patients who received prior hypomethylation therapy (decitabine or azacitidine) did not benefit from treatment with clofarabine in a study of high-risk MDS.
 - a. True
 - b. False

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

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

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

Impact of azacitidine on overall survival in MDS	4	3	2	1
Activity of ofatumumab in relapsed/refractory CLL	4	3	2	1
Efficacy of FCR for newly diagnosed CLL	4	3	2	1
Efficacy of bendamustine/rituximab as first-line therapy for indolent NHL	4	3	2	1
Activity of bortezomib in follicular or mantle-cell lymphoma	4	3	2	1
Safety and efficacy of RVD as first-line therapy for multiple myeloma	4	3	2	1
Data for clofarabine in AML or MDS	4	3	2	1

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

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

Impact of azacitidine on overall survival in MDS	4	3	2	1
Activity of ofatumumab in relapsed/refractory CLL	4	3	2	1
Efficacy of FCR for newly diagnosed CLL	4	3	2	1
Efficacy of bendamustine/rituximab as first-line therapy for indolent NHL	4	3	2	1
Activity of bortezomib in follicular or mantle-cell lymphoma	4	3	2	1
Safety and efficacy of RVD as first-line therapy for multiple myeloma	4	3	2	1
Data for clofarabine in AML or MDS	4	3	2	1

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

Yes No

If 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 be able to:

- Develop an algorithm for the evaluation, classification and risk-stratified treatment of myelodysplastic syndrome (MDS)
- Counsel elderly patients with acute myelogenous leukemia (AML) about the efficacy and safety of available treatment options
- Apply emerging data with novel agents and regimens to the treatment of patients with newly diagnosed or relapsed/refractory indolent and aggressive non-Hodgkin lymphomas (NHL)
- Appraise the role of maintenance therapy in the management of follicular or mantle-cell lymphoma
- Integrate emerging data with monoclonal antibodies into the evidence-based treatment of chronic lymphocytic leukemia (CLL)
- Communicate the benefits and risks of proteasome inhibitors and IMiD®-based therapeutic regimens to patients with newly diagnosed multiple myeloma (MM)
- Formulate up-to-date induction and consolidation treatment strategies for patients with acute promyelocytic leukemia (APL)

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:

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 editor and faculty for this educational activity

	4 = Excellent	3 = Good	2 = Adequate	1 = Suboptimal	
Faculty	Knowledge of subject matter				Effectiveness as an educator
Gail J Roboz, MD	4	3	2	1	4 3 2 1
Stephanie A Gregory, MD	4	3	2	1	4 3 2 1
Sundar Jagannath, MD	4	3	2	1	4 3 2 1
Guillermo Garcia-Manero, 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 editor and faculty for this activity:

REQUEST FOR CREDIT — Please print clearly

Name:..... Specialty:.....

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Medical License/ME Number:..... Last 4 Digits of SSN (required):.....

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