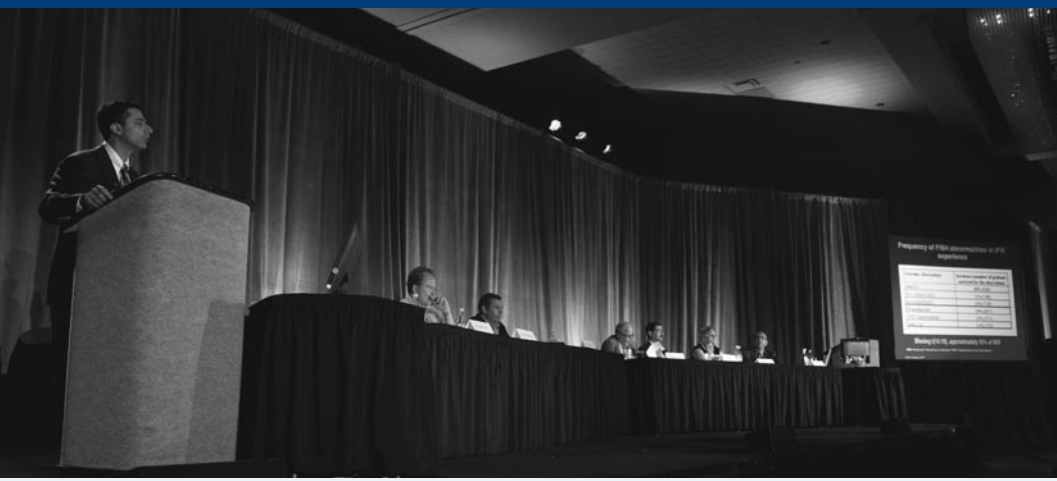
Exploring the Clinical Decisions of Community-Based Oncologists and Hematologists in the Management of **Multiple Myeloma** and **Follicular Lymphoma**



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Proceedings from a Live Event and Faculty Interviews Reviewing an Integrated Patterns of Care Project

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Exploring the Clinical Decisions of Community-Based Oncologists and Hematologists in the Management of Multiple Myeloma and Follicular Lymphoma

A Continuing Medical Education Audio Program

OVERVIEW OF ACTIVITY

It is important for medical oncologists, hematologists and fellows to be aware of similarities and differences between their routine therapeutic strategies and those employed by their colleagues, as well as key opinion leaders in the fields of multiple myeloma (MM) and non-Hodgkin's lymphoma. The heterogeneity that exists within the treating oncology community and the variable pace at which different clinicians incorporate new data sets into their decision-making yield inconsistency in care and likely represent the inability of research evidence to uniformly provide optimal answers for unique clinical situations.

This program focuses on the interpretation of practice patterns collected from 43 hematologists and/or oncologists treating 595 individual cases of MM or follicular lymphoma (FL). The data were analyzed and the care patterns critiqued by prominent clinical investigators in the respective fields. Also included are faculty reviews and discussion of the published data relevant to current therapeutic decision-making for MM and FL. In addition, this activity summarizes the highlights of a live satellite symposium developed from this project and held in Chicago at the ASCO 2010 meeting.

This CME program provides medical oncologists, hematologists and hematology-oncology fellows with a diverse range of practical and research evidence to aid in the delivery of up-to-date clinical management strategies for MM and FL.

LEARNING OBJECTIVES

- Compare treatment strategies employed by community oncologists/hematologists, and apply this knowledge to the routine management of MM and FL.
- Recognize clinical issues for which relative agreement or heterogeneity exists in MM and FL practice patterns, and use this information to refine or validate your existing treatment algorithms.
- Communicate the benefits and risks of evidence-based triplet induction therapy to patients with MM who may or may not be eligible for transplant.
- Critique the clinical evidence, and integrate maintenance rituximab, as appropriate, after initial immunotherapeutic management of newly diagnosed FL.
- Individualize maintenance therapy recommendations for MM according to baseline prognostic and predictive molecular markers.
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation.

ACCREDITATION STATEMENT

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CREDIT DESIGNATION STATEMENT

Research To Practice designates this educational activity for a maximum of 3 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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TABLE OF CONTENTS

TOPICS

CONTENT VALIDATION AND DISCLOSURES

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FACULTY — **Drs Hoffman** and **Hussein** 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 Gregory** — Advisory Committee: Cephalon Inc; Consulting Agreements: Amgen Inc, Genentech BioOncology, Novartis Pharmaceuticals Corporation, Spectrum Pharmaceuticals Inc; Speakers Bureau: Cephalon Inc, Genentech BioOncology. **Dr Lonial** — Advisory Committee, Consulting Agreements and Paid Research: Bristol-Myers Squibb Company, Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation. **Dr Anderson** — Advisory Committee and Consulting Agreements: Celgene Corporation, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation, Onyx Pharmaceuticals Inc. **Dr Cheson** — Advisory Committee: Celgene Corporation, Cephalon Inc, GlaxoSmithKline, Millennium Pharmaceuticals Inc, Pfizer Inc; Speakers Bureau: Celgene Corporation, Cephalon Inc. **Dr Czuczman** — Advisory Committee: Amgen Inc, Biogen Idec, Celgene Corporation, Cephalon Inc, Genentech BioOncology, GlaxoSmithKline, Lilly USA LLC, Millennium Pharmaceuticals Inc, Novartis Pharmaceuticals Corporation; Lectures: Biogen Idec, Genentech BioOncology. **Dr Fonseca** — Consulting Agreements: Amgen Inc, Bristol-Myers Squibb Company, Celgene Corporation, Genzyme Corporation, Medtronic Inc, Otsuka Pharmaceutical Co Ltd; Paid Research: Celgene Corporation, Onyx Pharmaceuticals Inc. **Dr Sabbath** — Paid Research: Amgen Inc, Bristol-Myers Squibb Company, Lilly USA LLC, Novartis Pharmaceuticals Corporation, Sanofi-Aventis; Stock Ownership: Celgene Corporation.

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Select Excerpts from the CME Symposium and Interview with Sagar Lonial, MD

INDUCTION THERAPY FOR TRANSPLANT-ELIGIBLE MYELOMA

DR LOVE: What are your thoughts on the choice of induction regimens selected by the participants of our recent Patterns of Care survey (1.1) for patients with transplant-eligible myeloma?

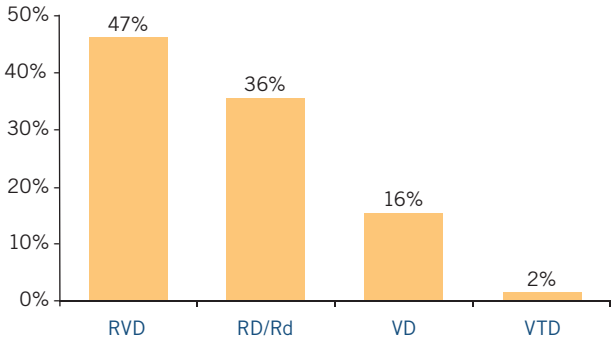
DR LONIAL: I find it intriguing that nearly half of the participants — 47 percent — are recommending triplet therapy of lenalidomide/bortezomib/dexamethasone (RVD). I support the use of triplet therapy. However, the randomized Phase III data supporting the use of these triplet regimens are only now starting to emerge. So I believe these Patterns of Care data are demonstrative of the early adoption of what a large proportion of these physicians regard as effective regimens.

DR HUSSEIN: We use RVD universally for our patients who are transplant eligible. In the community setting, an issue we deal with is the timing of availability of cytogenetic testing results. We order FISH testing for each patient, but we need to decide on the induction regimen before receiving the results. So we haven't figured out the most effective means of incorporating the risk information generated by these tests.

DR LONIAL: This is an important point. Outside of certain referral centers, it is difficult to receive FISH results in a 24- to 48-hour time frame. In the absence of such data, RVD is reasonable as it is clearly effective, regardless of whether a patient has low- or high-risk disease.

1.1

Which of the following systemic regimens is your usual recommendation for initial induction therapy for a patient with multiple myeloma who is eligible for transplant?



Patterns of Care survey of 45 US-based medical oncologists. Research To Practice 2010.

Prior to the ASCO presentations on maintenance therapies, I would have used the risk assessment in determining the need for maintenance therapy.

DR ANDERSON: I believe these Patterns of Care data are relevant as other published data indicate that RVD produces a response in most patients, with approximately three quarters experiencing at least a very good partial response and 57 percent achieving complete or near-complete responses (Anderson 2010; Richardson 2010; [1.2]). This is unprecedented, and though I believe risk stratification is still important, past high-risk markers may no longer be markers of high risk with regimens like RVD. This regimen is effective when the standard treatment for older patients or even transplant does not work. Furthermore, we are seeing repeatedly that biomarkers, such as translocation 4;14 and deletion 13, no longer indicate higher risk for patients receiving these agents.

DR LONIAL: One of the questions we often hear is, if we combine all of the best drugs up front, what can we offer at the time of relapse? In my opinion, this question was probably more relevant with the up-front combination of conventional chemotherapeutic agents. In the case of targeted agents with different mechanisms of action and synergistic activity, administering the drugs together up front rather than in the relapsed or refractory setting may provide more benefit as the number of induced mutations and the amount of drug resistance are much lower up front than they are at the second or third relapse. I believe strong evidence exists to say, "Use these drugs together early to maximize benefit in the long term."

1.2

Efficacy of Lenalidomide/Bortezomib/Dexamethasone (RVD) in a Prospective Phase I/II Study in Newly Diagnosed Myeloma

	CR/nCR	≥VGPR	≥PR	18-month PFS	18-month OS
All patients (n = 66)	39%	67%	100%	75%	97%
Phase II (n = 35)	57%	74%	100%	NR	NR

CR = complete response; nCR = near-complete response; VGPR = very good partial response; PR = partial response; PFS = progression-free survival; OS = overall survival; NR = not reported

Richardson PG et al. *Blood* 2010;116(5):679-86; Anderson KC et al. *Proc ASCO* 2010;**Abstract 8016**.

POST-TRANSPLANT MAINTENANCE TREATMENT FOR MYELOMA

DR LONIAL: Post-transplant maintenance therapy has been a fertile ground for investigation. At ASCO this year, data from two fairly convincing trials demonstrated a significant improvement in progression-free survival favoring lenalidomide as maintenance therapy, regardless of the response to transplant (Attal 2010; [1.3]; McCarthy 2010; [1.4]). In contrast to previous studies with thalidomide, which demonstrated that patients who achieved a complete response with transplant

did not seem to obtain additional benefit from thalidomide maintenance, both lenalidomide studies presented at ASCO seem to suggest that all patients benefit from lenalidomide maintenance, regardless of their response to transplant.

I believe the presentations at ASCO are a pivotal turning point regarding consideration of maintenance therapy after transplant. Our group is currently discussing a standardized recommendation for patients in the post-transplant setting. What I find to be reinforcing is the fact that the maintenance results were corroborated with two independent studies. I feel that the data are robust.

DR ANDERSON: These two lenalidomide maintenance trials have completely transformed how we think about maintenance therapy. The benefit also extended into groups of patients with adverse cytogenetics. Perhaps with the exception of the 17p deletion, the other abnormalities did not seem to have an impact on outcome.

DR LONIAL: In the United States a few large randomized trials are in progress in transplant-eligible myeloma, and most of these trials include some form of maintenance therapy. It is tough to have a trial without maintenance therapy as the data from the two trials with maintenance lenalidomide are fairly convincing and hard to ignore.

DR FONSECA: Another aspect related to post-transplant maintenance

1.3

IFM 2005-02 Study: Efficacy of Lenalidomide Maintenance After Transplant in Patients with Myeloma

	Placebo maintenance (n = 307)	Lenalidomide maintenance (n = 307)	Hazard ratio	*p*-value
Disease progression or death	143 (47%)	77 (25%)	—	—
Median progression-free survival (PFS)	24 months	Not reached	Not reported	$<10^{-7}$
Three-year postrandomization PFS	34%	68%	0.46	$<10^{-7}$

Attal M et al. *Proc ASCO* 2010;**Abstract 8018**.

1.4

CALGB-100104: Lenalidomide Maintenance versus Placebo After Transplant for Patients with Myeloma

	Placebo maintenance (n = 208)	Lenalidomide maintenance (n = 210)	Hazard ratio	*p*-value
Disease progression or death	58 (27.9%)	29 (13.8%)	0.42	<0.0001
Median time to disease progression	25.5 months	Not reached	Not reported	<0.0001

McCarthy PL et al. *Proc ASCO* 2010;**Abstract 8017**.

worth mentioning is that weekly bortezomib schedules bring to the forefront the possibility of longer-term administration of bortezomib in the maintenance setting. It is increasingly recognized that a weekly bortezomib schedule does not appear to compromise efficacy, yet the rates of severe peripheral neuropathy or discontinuation because of peripheral neuropathy are much lower with the weekly regimens. I wish we had known this a long time ago because I believe that this schedule can provide a much greater area under the curve for patients. ■

SELECT PUBLICATIONS

Anderson KC et al. **Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma (MM): Final results of a multicenter phase I/II study.** *Proc ASCO* 2010;**Abstract 8016**.

Attal M et al. **Lenalidomide maintenance after transplantation for myeloma.** *Proc ASCO* 2010;**Abstract 8018**.

McCarthy PL et al. **Phase III intergroup study of lenalidomide versus placebo maintenance therapy following single autologous stem cell transplant (ASCT) for multiple myeloma (MM): CALGB 100104.** *Proc ASCO* 2010;**Abstract 8017**.

Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010;116(5):679-86.

Wang M et al. **Rapid control of previously untreated multiple myeloma with bortezomib-lenalidomide-dexamethasone (BLD).** *Hematology* 2010;15(2):70-3.

TRANSPLANT-INELIGIBLE MULTIPLE MYELOMA

Select Excerpts from the CME Symposium and Interview with Dr Lonial

INDUCTION THERAPY FOR TRANSPLANT-INELIGIBLE MYELOMA

DR LOVE: What are your thoughts on the participants' choices of induction regimens in the Patterns of Care survey for patients ineligible for transplant (2.1)?

DR LONIAL: A third of physicians reported melphalan/prednisone/bortezomib (MPV) to be their preferred regimen, and another third said that lenalidomide and dexamethasone was their preference for transplant-ineligible patients.

Currently, one of the important questions in the field is whether melphalan is needed as part of initial therapy for older patients. In the United States we are now redesigning regimens such as RVD for older patients — regimens that use weekly bortezomib with lenalidomide and lower doses of dexamethasone — to see if we can avoid a melphalan-based approach. In the recently published Phase I/II RVD trial, for a small group of patients who did not receive transplant, the median progression-free survival was encouraging (Richardson 2010; Anderson 2010). I believe that the response and survival based on risk stratification were better — or at least better than we would have expected with conventional approaches in this subset of myeloma.

If melphalan is going to be effective in myeloma, it is usually earlier in the disease course, before the clone has an opportunity to develop significant mutations that result in traditional drug resistance. Alkylators such as melphalan are tools we have to work with in myeloma, and I don't simply want to throw them out. However, these are old drugs and we will need to tease out who should receive melphalan and who should not.

DR LOVE: What do you administer outside of a protocol setting?

DR LONIAL: I favor a melphalan-based approach for older patients who are clearly not eligible for stem cell collection. At the borderline ages between 70 and 75, when patients can perhaps undergo transplant, I may favor a nonmelphalan-based approach. However, it is not a simple chronological age decision, and other comorbidities also play a role in determining the possibility of stem cell collection.

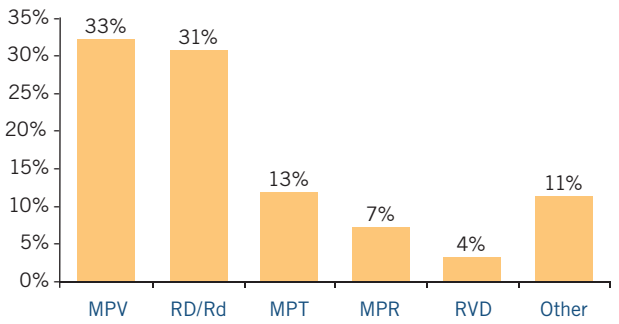
DR LOVE: What melphalan-based regimens do you offer to your patients?

DR LONIAL: In the protocol setting, ECOG has an ongoing Phase III trial comparing MPT to MPR. Another melphalan-based regimen is VMP, which requires a weekly office visit. Depending on the patients and the distance they must travel, we may choose MPR or VMP outside of a protocol setting.

In addition to the triplets, at ASCO this year an update was presented of the Phase III trial comparing VMPT followed by bortezomib-based maintenance therapy to VMP without maintenance therapy (Boccadoro 2010; [2.2]). The investigational regimen of VMPT → VT continues to be more successful than VMP.

2.1

Which of the following systemic regimens is your usual recommendation for initial induction therapy for a patient with multiple myeloma who is not eligible for transplant?



Patterns of Care survey of 45 US-based medical oncologists. Research To Practice 2010.

MAINTENANCE THERAPY FOR TRANSPLANT-INELIGIBLE MYELOMA

DR LOVE: What about the issue of maintenance therapy for transplant-ineligible patients?

DR LONIAL: I believe that what was presented at ASCO begins to address the question of maintenance therapy

for transplant-ineligible patients (Boccadoro 2010; [2.2]). Europeans clearly believe that maintenance therapy is important regardless of the patient's age. The maintenance concept did not affect us here in the United States until six months ago, when we saw data at the ASH plenary session suggesting that bortezomib could be administered as maintenance therapy in a regular cycle every three months (Mateos 2009) or as one dose every two weeks (Palumbo 2009b). Data with maintenance lenalidomide in the MPR → R regimen were also presented at ASH 2009 (Palumbo 2009a).

All of these maintenance regimens are for transplant-ineligible patients, and thus these kinds of maintenance regimens also will be incorporated into the care of older patients.

DR LOVE: How do you approach the long-term management of elderly patients outside of a protocol setting?

DR LONIAL: In terms of the initial treatment, if the regimen contains melphalan, we don't typically administer it for more than nine to 12 months. Beyond that, we start to consider maintenance therapy. My choice of maintenance therapy depends on how well the patient tolerates the initial induction therapy. Before the current maintenance data, I would allow the patient to take a break before starting treatment again.

2.2

Phase III Trial Comparing VMPT → VT to VMP Followed by Observation for Elderly Patients with Multiple Myeloma

	VMPT → VT	VMP	*p*-value
CR	38%	24%	0.0008
≥VGPR	59%	50%	0.03
>PR	89%	81%	0.01
Three-year PFS	54%	40%	0.006

CR = complete response; VGPR = very good partial response; PR = partial response; PFS = progression-free survival

Boccadoro M et al. *Proc ASCO* 2010;**Abstract 8013**.

MANAGEMENT OF BORTEZOMIB-ASSOCIATED NEUROPATHY

DR LOVE: Where are we currently regarding management of neuropathy and the issue of weekly versus twice-weekly dosing of bortezomib?

DR LONIAL: In terms of managing and minimizing neuropathy, the keys are early recognition and dose modification. In combination regimens, weekly bortezomib therapy makes a lot of sense. Also, for the older patient, weekly bortezomib with melphalan allows you to administer treatment longer and have significantly less neuropathy in that context (Palumbo 2009b; [2.3]). I believe that we are only now starting to learn the best way to use bortezomib as part of a combination.

DR FONSECA: I agree that the theme is clear that weekly bortezomib

appears not to compromise efficacy, yet the rates of severe peripheral neuropathy and discontinuation because of peripheral neuropathy are much lower with that schedule.

DR LOVE: What about prevention and management of neuropathy?

DR LONIAL: At our institution, we have created a questionnaire for our infusion nurse. With every dose of bortezomib, the infusion center nurse asks the patients about pain, numbness and aching or cramping in the calves. This provides us with a heightened awareness of the symptomatology related to neuropathy, and thus we know at each dose what's happening. By using the questionnaire, we are alerted more frequently in the middle of the cycle, which is often when these issues arise. If we wait for the every third-week visit, we miss it.

2.3

Italian Phase III Study of VMPT versus VMP for Newly Diagnosed Multiple Myeloma: Efficacy and Sensory Peripheral Neuropathy (PN) According to Bortezomib (V) Infusion Schedule

	VMP — V twice weekly (n = 63)*	VMP — V once weekly (n = 190)*
Complete response	25%	23%
Progression-free survival, two years	56%	58%
Sensory PN Any Grade Grade III/IV	 43% 14%	 21% 2%
PN discontinuation	16%	4%
Total planned dose	67.6 mg/m^2	46.8 mg/m^2
Total delivered dose	41 mg/m^2	40 mg/m^2

* Three patients in the twice-weekly and one patient in the once-weekly group are not evaluable because they never started therapy.

Palumbo A et al. *Proc ASH* 2009b;**Abstract 128**.

TREATMENT TOLERABILITY AND RESPONSES IN ELDERLY PATIENTS WITH MYELOMA

DR LOVE: We also recently conducted a cross-sectional case survey of unselected cases from the practices of the Patterns of Care participants. What are your thoughts on the unselected case data provided by the participants and outcomes by age?

DR LONIAL: What is important to me from an educational perspective is that patients older than age 75 had a similar symptomatology to those younger than 75 (2.4). In addition, with appropriate tailoring of induction regimens, the response rate and tolerance to therapy seem similar to those in the younger age groups.

DR FONSECA: I find these data encouraging because they appear to be consistent with the literature.

DR LOVE: What about the actual regimens chosen by age (2.5)?

DR LONIAL: Among patients who are older than 75 years of age, the most frequently used regimens were predominantly the doublets. RD or VD were the two that were chosen with the highest frequency, with each being used in approximately one quarter of cases. For the patients younger than age 75, who I believe in many ways represent those one might consider for high-dose therapy, RD was administered approximately one fifth of the time, VD approximately one quarter and RVD approximately one fifth.

In aggregate, the melphalan-based regimens were administered to 40 to 45 percent of patients older than age 75.

I believe it is relatively clear based on the published data that with appropriate dose modifications patients older than age 75 can fare well with either MPT or MPV.

DR LOVE: Would you also comment on treatment tolerability by age and whether such data have been shown elsewhere (2.6)?

DR LONIAL: I don't know if any other data set has shown what we have here. These results perhaps

2.4

Symptomatology at the Time Treatment Was Initiated

	Overall (n = 276)	Age <65 (n = 95)	Age 65-74 (n = 98)	Age ≥75 (n = 83)
Very symptomatic	30%	33%	28%	28%
Moderately symptomatic	37%	34%	37%	42%
Mildly symptomatic	26%	25%	30%	24%
Not at all symptomatic	7%	8%	5%	6%

Love N et al. *Proc ASH* 2010;**Abstract 1516**.

2.5

Induction Regimen by Age

	Overall (n = 269)	Age <65 (n = 94)	Age 65-74 (n = 98)	Age ≥75 (n = 77)
Rd/RD	24%	29%	23%	21%
VD	24%	24%	24%	22%
RVD	13%	29%	8%	1%
MPT	10%	0%	9%	22%
MPV	8%	0%	10%	16%
MP	5%	2%	4%	10%
TD	4%	5%	5%	3%
Other	12%	11%	17%	5%

Cross-sectional case survey from the practices of 45 US-based medical oncologists. Research To Practice 2010.

reflect the experience of the physicians that were taking the survey.

One could argue that tolerance to therapy may be so similar here because the treatments may have been different for the older versus the younger patients. In our group, I would imagine that no more than one quarter walked away with nothing at all and approximately three quarters would not experience any major problems. ■

2.6

Clinician-Reported Side Effects and Toxicities by Age*

	Overall (n = 269)	Age <65 (n = 94)	Age 65-74 (n = 98)	Age ≥75 (n = 77)
Things went very well: Same or fewer problems than expected	38%	40%	37%	36%
Things went fairly well: Minor or moderate problems, not difficult to manage	44%	49%	41%	42%
Significant problems that were difficult to manage	15%	8%	20%	18%
Major problems with significant consequences	3%	3%	2%	4%

* Excludes patients not receiving treatment or in early treatment and not yet evaluated

Love N et al. *Proc ASH* 2010;**Abstract 1516**.

SELECT PUBLICATIONS

Anderson KC et al. **Lenalidomide, bortezomib, and dexamethasone in patients with newly diagnosed multiple myeloma (MM): Final results of a multicenter phase I/II study.** *Proc ASCO* 2010;**Abstract 8016**.

Boccadoro M et al. **Bortezomib, melphalan, prednisone, and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide (VT) for initial treatment of elderly multiple myeloma patients.** *Proc ASCO* 2010;**Abstract 8013**.

Love N et al. **Tolerance and response to initial systemic therapy in younger and older patients with multiple myeloma: A cross-sectional case survey with 276 unselected recent cases in the practices of US-based medical oncologists.** *Proc ASH* 2010;**Abstract 1516**.

Mateos MV et al. **A prospective, multicenter, randomized, trial of bortezomib/melphalan/prednisone (VMP) versus bortezomib/thalidomide/prednisone (VTP) as induction therapy followed by maintenance treatment with bortezomib/thalidomide (VT) versus bortezomib/prednisone (VP) in elderly untreated patients with multiple myeloma older than 65 years.** *Proc ASH* 2009;**Abstract 3**.

Palumbo A et al. **A phase III study to determine the efficacy and safety of lenalidomide in combination with melphalan and prednisone (MPR) in elderly patients with newly diagnosed multiple myeloma.** *Proc ASH* 2009a;**Abstract 613**.

Palumbo A et al. **Bortezomib, melphalan, prednisone and thalidomide (VMPT) followed by maintenance with bortezomib and thalidomide for initial treatment of elderly multiple myeloma patients.** *Proc ASH* 2009b;**Abstract 128**.

Richardson PG et al. **Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.** *Blood* 2010;116(5):679-86.

Select Excerpts from the CME Symposium and Interview with Stephanie A Gregory, MD

FRONT-LINE INDUCTION THERAPY FOR NEWLY DIAGNOSED FL

DR LOVE: What do you think about the choice of initial induction therapy from our recent cross-sectional case survey (3.1)?

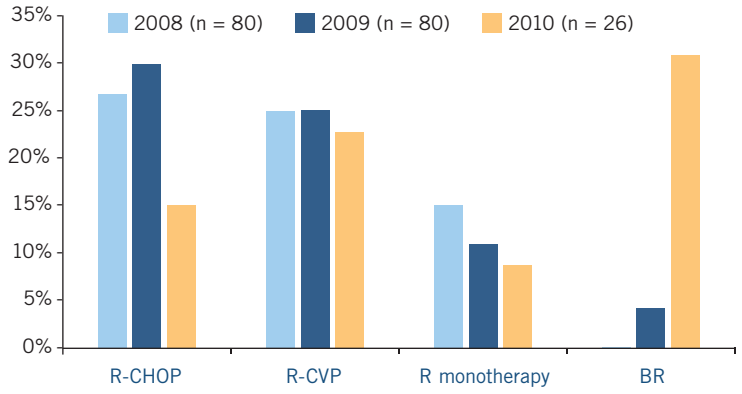
DR GREGORY: It appears that R-CVP or R-CHOP was used more often in 2008 and 2009, and it is interesting that in the group of patients who received initial treatment in 2010, bendamustine/rituximab (BR) was used significantly more frequently than other regimens (3.1).

I believe the practice change seen in 2010 may be a reflection of the Phase III trial results presented at ASH 2009 (Rummel 2009; [3.2]). It is amazing that the community seems to have jumped on the bandwagon right away.

DR CZUCZMAN: Though everybody got on the bandwagon right away, I am still waiting for the final publication from the Rummel trial. I believe we should also keep in mind the characteristics of the patients in the trial. Only patients with Grade I or II FL were enrolled, and those with Grade IIIa or b disease were excluded. We also need to be mindful of the potential long-term toxicities, and I believe that we don't have a final answer yet.

DR CHESON: In my practice I use BR as initial induction therapy for most patients with FL, including those with Grade IIIa disease. We examined our own data, and the

3.1 Initial Systemic Treatment of Follicular Lymphoma by Year Initiated



R = rituximab; B = bendamustine

Cross-sectional case survey from the practices of 45 US-based medical oncologists. Research To Practice 2010.

curve was superimposable, if not even a little better than the German data. Regarding side effects, in our data BR appears to be better than R-CHOP with respect to cardiotoxicity and infections (3.3). If you want to be cautious, then you can select certain patients, such as those who are older or have comorbidities or cardiac issues — they are the perfect candidates. But I believe its use will extend more and more into other patient populations. I have seen the first draft of the manuscript, and every subset that has been examined fares better with BR, whether they have bulky disease, low FLIPI scores or high FLIPI scores. So when the results are published, the practice patterns will change dramatically.

DR GREGORY: I believe that in the long run, BR will win out. Though right now we don't have that long-term follow-up, in a straightforward case of FL without a question of transformation, I will recommend BR.

DR LONIAL: Do any concerns about myelodysplastic syndromes (MDS) or chronic myelosuppression arise with BR?

DR CHESON: With more than three years of follow-up, one patient in the BR arm developed MDS and one patient in the R-CHOP arm developed acute myeloid leukemia (AML). Again, this is short follow-up for AML/MDS. We need another two to

3.2 **Efficacy Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Indolent Lymphomas**

	Overall response	Complete response	Progression-free survival	Time to next treatment
BR (n = 260)	92.7%	39.6%	54.9 months	Not reached
R-CHOP (n = 253)	91.3%	30%	34.8 months	40.7 months
p-value	—	0.0262	0.00012	0.0002

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

3.3 **Safety Data from the Phase III Study Comparing Bendamustine/Rituximab (BR) to R-CHOP in the Front-Line Treatment of Indolent Lymphomas**

	Grade III/IV neutropenia	Infectious complications	Peripheral neuropathy	Stomatitis	Rash	Alopecia
BR (n = 260)	10.7%	36.5%	6.9%	6.2%	16.2%	15.0%
R-CHOP (n = 253)	46.5%	50.2%	28.8%	18.6%	9.1%	62.0%
p-value	<0.0001	0.0025	<0.0001	<0.0001	0.0122	Not reported

Rummel MJ et al. *Proc ASH* 2009;**Abstract 405**.

four years before we can definitively say anything.

DR LOVE: What about stem cell collection?

DR CHESON: It appears that stem cells can be collected, and it has been done in a small number of patients on this trial (Burchardt 2009).

ONGOING CLINICAL TRIALS INCORPORATING PROTEASOME INHIBITORS AND IMMUNOMODULATORS AS COMPONENTS OF INITIAL TREATMENT FOR FL

DR LOVE: What about trials evaluating bortezomib in the up-front setting?

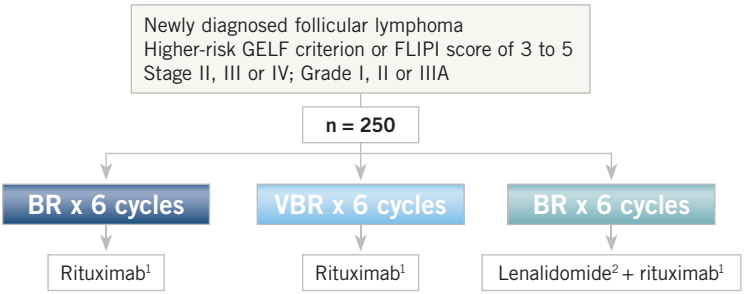
DR CHESON: Two separate trials reported on bortezomib, bendamustine and rituximab (VBR) in relapsed or refractory FL (Fowler 2009b; Friedberg 2009), and the response rates were approximately 80 to 85 percent, with a significant proportion of patients achieving complete remissions. The regimen was also well tolerated, and that's why we would like to conduct a BR versus VBR study in the up-front setting. A couple of trials in the cooperative group setting are evaluating the role of bortezomib in the initial management of FL. An ECOG-sponsored randomized trial evaluating bortezomib is also being initiated (3.4).

DR LOVE: What about lenalidomide as part of initial induction therapy for FL?

DR GREGORY: Results of a Phase II study of lenalidomide/rituximab in the up-front treatment of indolent lymphomas were recently presented (Fowler 2009a; [3.5]). The results were impressive. I would like to point out that patients were required only to have a lymph node larger than 1.5 centimeters. Apparently these patients did not necessarily have to be experiencing symptoms or be in need of treatment. The patients received rituximab on day one and lenalidomide on

3.4

Phase II ECOG Trial Evaluating the Role of Bortezomib as Part of Initial Induction Therapy and Rituximab and Lenalidomide as Maintenance Therapy



[1] Rituximab q8wk x 2 years; [2] Oral lenalidomide days 1 to 21 q28d x 1 year
B = bendamustine; R = rituximab; V = bortezomib

www.clinicaltrials.gov. Identifier NCT01216683.

days one through 21 of a 28-day cycle and could receive up to six cycles.

The overall response rate was 84 percent, with a complete response rate of 79 percent, and in the subgroup of patients with FL the complete response rate was 94 percent. These are clearly impressive findings.

The study continues to enroll and so far has accrued approximately 58 patients. Patients fared well without much neurotoxicity. Many patients developed a diffuse erythematous rash typical with lenalidomide, which usually goes away if the dose is decreased or the drug is stopped.

Currently, many oncologists use single-agent rituximab for patients with low tumor burdens, and this combination may be a newer approach for such patients.

DR CZUCZMAN: The lenalidomide/rituximab combination has shown good activity in the up-front setting (Fowler 2009a; [3.5]).

A CALGB study randomly assigning patients to lenalidomide alone versus lenalidomide with rituximab is also showing promising results. ■

3.5

Activity of Lenalidomide/Rituximab in the Up-Front Treatment of Indolent B-Cell Non-Hodgkin's Lymphoma*

Overall response	Complete response	Partial response	Stable disease
84%	79%	5%	16%

* n = 20 evaluable patients: follicular lymphoma n = 10, marginal zone lymphoma n = 8, small lymphocytic lymphoma n = 2

Fowler N et al. *Proc ASH* 2009;**Abstract 1714**.

SELECT PUBLICATIONS

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

Fowler N et al. **A biologic combination of lenalidomide and rituximab for front-line therapy of indolent B-cell non-Hodgkin's lymphoma.** *Proc ASH* 2009a;**Abstract 1714**.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: Encouraging activity in the phase 2 VERTICAL study.** *Proc ASH* 2009b;**Abstract 933**.

Friedberg JW et al. **Bendamustine, bortezomib and rituximab in patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma (NHL): A multicenter phase II clinical trial.** *Proc ASH* 2009;**Abstract 924**.

Rummel MJ et al. **Bendamustine plus rituximab is superior in respect of progression free survival and CR rate when compared to R-CHOP as first-line treatment of patients with advanced follicular, indolent, and mantle cell lymphomas: Final results of a randomized phase III study of the StiL (Study Group Indolent Lymphomas, Germany).** *Proc ASH* 2009;**Abstract 405**.

Salles GA et al. **Rituximab maintenance for 2 years in patients with untreated high tumor burden follicular lymphoma after response to immunochemotherapy.** *Proc ASCO* 2010;**Abstract 8004**.

Select Excerpts from the CME Symposium and Interview with Dr Gregory

MANAGEMENT OF RELAPSED OR REFRACTORY FL

DR LOVE: Can you comment on the reported use of various regimens in relapsed FL in the Patterns of Care survey?

DR GREGORY: The data reflect an impressive use of BR in relapsed FL (4.1). I believe clinicians may not know which bendamustine dose to use yet because the FDA-approved dose is 120 mg/m^2 on days one and two of a 21-day cycle. This dose causes profound neutropenia, and I believe 40 percent of patients did not get through the required number of cycles on that study.

I always start at a lower dose, somewhere between 70 to 90 mg/m^2 on days one and two, and you can optimally use this in the relapsed setting.

DR LOVE: What about bortezomib-based regimens in relapsed FL?

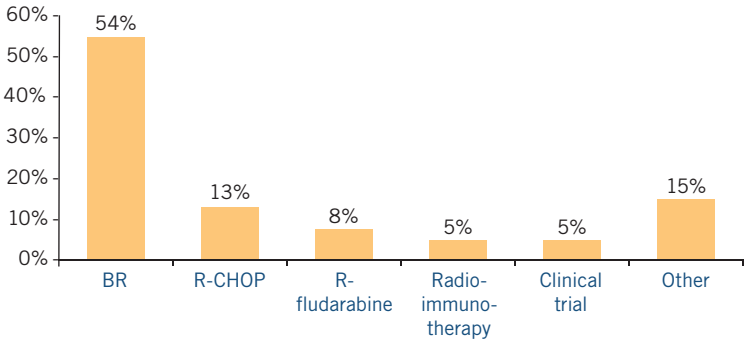
DR CHESON: VBR has been investigated in two separate regimens (Fowler 2009; [4.2]; Friedberg 2009; [4.3]). We presented the VERTICAL trial, in which VBR was administered every five weeks, and Jonathan Friedberg's VBR is administered every four weeks.

The results are comparable, with responses in the range of 80 to 85 percent, a significant proportion of which are complete remissions.

Follow-up is not sufficient to provide progression-free survival. However, both of these regimens were reasonably well tolerated. ■

4.1

Which of the following systemic regimens is your usual recommendation for relapsed follicular lymphoma?



Patterns of Care survey of 45 US-based medical oncologists. Research To Practice 2010.

4.2 Phase II VERTICAL Study: Efficacy and Safety of Bortezomib/Bendamustine/Rituximab in Relapsed or Refractory Follicular Lymphoma*

Overall response	Complete response	Partial response	≥Grade III peripheral neuropathy
86%	53%	34%	10%

* n = 59 of 63 patients with at least one postbaseline response assessment

"Additional follow-up is required to assess long-term outcomes, including progression-free and overall survival. VBR is active in this heavily pre-treated, high-risk population, with high CR rates, and was generally well tolerated."

VBR = bortezomib/bendamustine/rituximab; CR = complete response

Fowler N et al. *Proc ASH* 2009;**Abstract 933**.

4.3 Efficacy of Bendamustine/Bortezomib/Rituximab in Relapsed or Refractory Mantle-Cell Lymphoma (MCL) and Indolent Lymphomas

	Overall response
All patients (n = 29*)	79%
Relapsed or refractory FL (n = 16)	85%
Relapsed or refractory MCL (n = 7)	71%

* Remaining patients had marginal-zone non-Hodgkin's lymphoma, small lymphocytic lymphoma or lymphoplasmacytic lymphomas.

"...in this heavily pretreated population (as compared with prior studies of BR, including 33% rituximab-refractory pts), the BVR regimen is highly active, with over half of evaluable pts achieving CR/CRu. It appears more toxic than BR alone, with expected additive toxicities from V. Prophylaxis against varicella zoster reactivation is indicated when using this regimen. Further follow-up will determine whether the high CR/CRu rate corresponds to prolonged PFS. These promising results warrant additional evaluation of this regimen in *de novo* disease."

FL = follicular lymphoma; BR = bendamustine/rituximab; BVR = bendamustine/bortezomib/rituximab; CR/CRu = complete response/unconfirmed complete response; V = bortezomib; PFS = progression-free survival

Friedberg JW et al. *Proc ASH* 2009;**Abstract 924**.

SELECT PUBLICATIONS

Agathocleous A et al. **Weekly versus twice weekly bortezomib given in conjunction with rituximab, in patients with recurrent follicular lymphoma, mantle cell lymphoma and Waldenström macroglobulinaemia.** *Br J Haematol* 2010;151(4):346-53.

Di Bella N et al. **Results of a phase 2 study of bortezomib in patients with relapsed or refractory indolent lymphoma.** *Blood* 2010;115(3):475-80.

Fowler N et al. **Bortezomib, bendamustine, and rituximab in patients with relapsed or refractory follicular lymphoma: Encouraging activity in the phase 2 VERTICAL study.** *Proc ASH* 2009;**Abstract 933**.

Friedberg JW et al. **Bendamustine, bortezomib and rituximab in patients with relapsed/refractory indolent and mantle cell non-Hodgkin lymphoma (NHL): A multicenter phase II clinical trial.** *Proc ASH* 2009;**Abstract 924**.

POST-TEST

Exploring the Clinical Decisions of Community-Based Oncologists and Hematologists in the Management of Multiple Myeloma and Follicular Lymphoma

QUESTIONS (PLEASE CIRCLE ANSWER):

1. **Patients with which of the following lymphomas were not included in the Phase III German trial comparing BR to R-CHOP as initial therapy for indolent lymphomas?**
   a. Diffuse large B-cell lymphoma
   b. Grade III follicular lymphoma
   c. Mantle-cell lymphoma
   d. Both a and b
2. **What proportion of patients with myeloma have been reported to have experienced at least a partial remission with RVD in a Phase I/II study?**
   a. 20 percent
   b. 50 percent
   c. 100 percent
3. **Which of the following improvements has been demonstrated with maintenance lenalidomide for patients with myeloma who have received transplants?**
   a. Improved progression-free survival
   b. Improved overall survival
   c. Both of the above
   d. None of the above
4. **Which of the following subsets of patients derived clinical benefit from maintenance lenalidomide after transplant?**
   a. Those who achieved a complete response with transplant
   b. Those who did not achieve a complete response with transplant
   c. Both of the above
5. **Which of the following improvements was demonstrated by the investigational regimen VMP → VT compared to VMP for elderly patients with myeloma?**
   a. Improved progression-free survival
   b. Improved complete response rates
   c. Improved overall survival
   d. Both a and b
6. **Compared to a biweekly schedule, weekly bortezomib in combination regimens for myeloma is associated with _____.**
   a. Improved efficacy
   b. Similar efficacy
   c. Decreased efficacy
7. **Which of the following results was similar in the two arms of the Phase III German trial comparing BR to R-CHOP as initial therapy for follicular and other indolent lymphomas?**
   a. Complete response rate
   b. Overall response rate
   c. Progression-free survival
   d. Time to next treatment
8. **Which of the following regimens has demonstrated improved efficacy and safety over R-CHOP in the initial treatment of FL?**
   a. BR
   b. Rituximab alone
   c. Radioimmunotherapy
   d. FCR
9. **Patients with which of the following non-Hodgkin's lymphomas were included in the Phase III German study comparing BR to R-CHOP?**
   a. FL
   b. Mantle-cell lymphoma
   c. Waldenström macroglobulinemia
   d. All of the above
10. **All of the following side effects except _____ were reported at much lower frequencies with BR than with R-CHOP.**
    a. Grade III/IV neutropenia
    b. Infectious complications
    c. Peripheral neuropathy
    d. Rash
    e. Alopecia
11. **Preliminary data suggest that adequate stem cell mobilization is possible after exposure to BR.**
    a. True
    b. False

Post-test answer key: 1d, 2c, 3a, 4c, 5d, 6b, 7b, 8a, 9d, 10d, 11a

EDUCATIONAL ASSESSMENT AND CREDIT FORM

Exploring the Clinical Decisions of Community-Based Oncologists and Hematologists in the Management of Multiple Myeloma and Follicular Lymphoma

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

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

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

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

	BEFORE	AFTER
Clinical use of maintenance therapy for patients with multiple myeloma who have or have not received transplants	4 3 2 1	4 3 2 1
Management of bortezomib-associated neuropathy	4 3 2 1	4 3 2 1
Pivotal research supporting the use of triplet induction regimens in multiple myeloma	4 3 2 1	4 3 2 1
VERTICAL trial: Bortezomib, bendamustine and rituximab in FL	4 3 2 1	4 3 2 1
Maintenance rituximab after initial rituximab/chemotherapy induction therapy in FL	4 3 2 1	4 3 2 1
Recommendations for treating multiple myeloma and FL in elderly patients	4 3 2 1	4 3 2 1

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

☐ Yes ☐ No

If no, please explain: .....

.....

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 learning objectives (LOs) by circling the appropriate selection:

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

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

- Compare treatment strategies employed by community oncologists/hematologists, and apply this knowledge to the routine management of MM and FL. . . . . 4 3 2 1 N/M N/A
- Recognize clinical issues for which relative agreement or heterogeneity exists in MM and FL practice patterns, and use this information to refine or validate your existing treatment algorithms. . . . . 4 3 2 1 N/M N/A
- Communicate the benefits and risks of evidence-based triplet induction therapy to patients with MM who may or may not be eligible for transplant. . . . . 4 3 2 1 N/M N/A
- Critique the clinical evidence, and integrate maintenance rituximab, as appropriate, after initial immunotherapeutic management of newly diagnosed FL. . . . . 4 3 2 1 N/M N/A
- Individualize maintenance therapy recommendations for MM according to baseline prognostic and predictive molecular markers. . . . . 4 3 2 1 N/M N/A
- Counsel appropriately selected patients about the availability of ongoing clinical trial participation. . . . . 4 3 2 1 N/M N/A

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 faculty and editor for this educational activity

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

Faculty	Knowledge of subject matter	Effectiveness as an educator
Stephanie A Gregory, MD	4 3 2 1	4 3 2 1
Sagar Lonial, MD	4 3 2 1	4 3 2 1
Kenneth C Anderson, MD	4 3 2 1	4 3 2 1
Bruce D Cheson, MD	4 3 2 1	4 3 2 1
Myron S Czuczman, MD	4 3 2 1	4 3 2 1
Rafael Fonseca, MD	4 3 2 1	4 3 2 1
Editor	**Knowledge of subject matter**	**Effectiveness as an educator**
Neil Love, MD	4 3 2 1	4 3 2 1

Please recommend additional faculty for future activities:

.....

Other comments about the faculty and editor for this activity:

.....

REQUEST FOR CREDIT — Please print clearly

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

Professional Designation:

⬭ MD ⬭ DO ⬭ PharmD ⬭ NP ⬭ RN ⬭ PA ⬭ Other .....

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City, State, Zip: .....

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I certify my actual time spent to complete this educational activity to be _____ hour(s).

Signature: ..... Date: .....

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Hematologic Oncology™
UPDATE

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