up take were consequently selected for biopsy site and as the reference standard? We can clearly state in our paper, remains only speculate.

We acknowledge the risk of missing DLBCL and discordant indolent histology in the NCCN-IPI in contrast to BMB-ascertained bone marrow disease supports independent prognostic value of PET/CT-ascertained bone marrow involvement in multivariate analysis, while Cerci et al. (not cited in our article) reported adverse outcome in patients with PET/CT-ascertained bone marrow involvement only when BMB was concordantly positive, and vice versa [13,14]. The results of Cerci et al. clearly question the prognostic relevance of searching for bone marrow involvement in PET/CT negative cases [13]. In a retrospective cohort study by Adams’ own group, focally increased FDG uptake in the bone marrow was not prognostic for PFS or OS. However, because of the small number of patients the analysis is likely underpowered and 34/78 (44%) of patients had PET/CT-detected bone marrow involvement, which is higher than usually reported [1,10,13–16]. Our study supports an independent prognostic value of PET/CT-ascertained bone marrow involvement, but we do not “claim” prognostic irrelevance of BMB, as accused by Adams et al. The fact that positive BMB was more frequent in patients with PET/CT-detected bone marrow involvement only reflects the interplay with other important prognostic factors. As in a previous letter, Adams et al. indicate that failure to include imaging-detected bone marrow disease in the NCCN-IPI in contrast to BMB-ascertained bone marrow disease supports prognostic irrelevance of imaging-detected bone marrow disease [3,5]. However, it is worth noting that PET/CT staging was not mandatory in the cohorts that gave rise to the NCCN-IPI [3,17]. At present, we are evaluating the prognostic role of focal PET/CT in further analyses to add further clarity to this ambiguity of PET/CT-ascertained bone marrow lesions in DLBCL.

In our discussion, we state that our data may suggest that BMB is not necessary in PET/CT-staged patients, but conclude that more comprehensive exploration is needed. This evokes the third objection by Adams et al. We are aware that some previous studies, including large series and our own data, have shown minimal sensitivity of PET/CT to detect bone marrow involvement by BMB [13,16,18]. The Lugano classification recommends BMB in patients without evidence of bone marrow involvement by PET/CT and only if finding of a discordant histology is relevant for patient management [19]. We acknowledge the risk of missing DLBCL and discordant indolent histology in the bone marrow if routine BMB is not performed as part of the routine staging work-up [14,18,20]. However, the guidelines apply a critical view on the added diagnostic value of an invasive diagnostic procedure like BMB. For many patients BMBs are associated with anxiety and pain [21]. Thus, the discussion of PET/CT versus BMB in DLBCL should not be a discussion of sensitivities alone, but need to include all aspects [5]. Staging does not serve its own purpose, but guides treatment decisions and provides baseline information for treatment response assessment. In the current landscape of R-CHOP (like) therapy for DLBCL it seems unlikely that indiscriminate use of BMB will alter treatment in a relevant number of patients. Last but not least, future treatment decisions will hopefully be guided by the biological heterogeneity of DLBCL rather than by bone marrow disease detected by BMB (or PET/CT) [22].

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Safety and efficacy of ferumoxyl for the episodic treatment of iron deficiency anemia in patients with a history of unsatisfactory oral iron therapy: Results of a phase III, open-label, 6-month extension study To the Editor: Although oral iron supplementation is recommended as first-line treatment for iron deficiency anemia (IDA), many patients are intolerant of oral iron due to gastrointestinal side effects or do not achieve adequate replenishment of iron stores [1,2]. For such patients, administration of iron intravenously (IV) may be the preferred alternative [1,3,4]; however, there are limited data evaluating repeat IV iron dosing over an extended period of time in patients intolerant to oral iron and without concurrent advanced renal dysfunction. Ferumoxyl is a colloidal iron oxide product approved in the United States for the treatment of IDA in adults with chronic kidney disease. The results of a phase III, 5-week, double-blind, placebo-controlled study (ClinicalTrials.gov identifier: NCT01114139) showed that ferumoxyl was effective and well tolerated in patients with IDA of any underlying cause in whom oral iron was ineffective or could not be used [5]. Patients who completed the primary phase III study with eligible to enter an open-label extension study (see Supporting Information Fig. 1 study design). The objective of this extension study was to assess the safety and efficacy of ferumoxyl for the episodic treatment of IDA over a 6-month period (NCT01114217). The extension study included a 14-day screening period followed by 6 months of observation during which patients were evaluated for IDA monthly. Those with persistent or recurrent IDA (hemoglobin [Hgb] <11.0 g/dl and transferrin saturation [Tsat] <20%) at any evaluation visit began a 5-week treatment period (TP), in which patients received two 510-mg doses of ferumoxyl.
administered 2–8 days apart, then resumed monthly monitoring for IDA; patients were retreated if criteria for IDA were met again. The first ferumoxytol treatment (2 × 510 mg) for patients who previously received placebo in the primary study was Treatment Course 1; subsequent treatment courses were serially numbered. For patients who previously received ferumoxytol in the primary study, their first ferumoxytol treatment in the extension study was Treatment Course 2; subsequent courses were serially numbered.

The primary efficacy endpoint was mean change in Hgb from TP baseline (defined as level immediately prior to ferumoxytol treatment course) to week 5 following the first ferumoxytol treatment course. Other efficacy and safety endpoints and statistical methods are shown in Supporting Information Table I.

Of the 808 patients from the original study, 634 enrolled in the present study. A total of 151 placebo- and 186 ferumoxytol-treated patients met the criteria for treatment during the 6-month extension and received ≥1 course of ferumoxytol (intent-to-treat population) (Supporting Information Fig. 2). Among the remaining 297 patients, mean monthly Hgb remained ≥12 g/dL without further treatment. For the 151 patients who received placebo during the primary study, their first course of ferumoxytol during the extension study was categorized as Treatment Course 1. Treatment Course 2 (n = 244) included 58 patients who received Treatment Course 1 in the extension study and 186 patients who previously received Treatment Course 1 of ferumoxytol in the primary study. Treatment Course 3 (n = 69) included 15 patients who received both Treatment Courses 1 and 2 of ferumoxytol in the extension study and 54 patients who received Treatment Course 1 in the primary study and Treatment Course 2 in the extension study. Baseline patient characteristics and demographics are summarized in Supporting Information Table II.

Baseline Hgb and TSAT values were lower for Treatment Course 1 (8.7 g/dL and 5.1%, respectively) than for Treatment Courses 2 (10.2 g/dL and 8.8%) and 3 (10.2 g/dL and 10.1%). For the primary efficacy analysis, there was a statistically significant increase in Hgb of 2.6 g/dL from TP baseline to week 5 (P < 0.0001) among the 151 patients who received their first course of ferumoxytol treatment during the extension study (Table I; Supporting Information Fig. 3). Patients also achieved statistically significant increases in Hgb from TP baseline to week 5 following the second and third ferumoxytol treatment courses (Table I; Supporting Information Fig. 3); however, since the TP baselines were higher, the mean Hgb increases were lower (1.5 g/dL and 1.1 g/dL for Treatment Courses 2 and 3, respectively; P < 0.0001 vs. TP baseline for each), as expected, than those after the first treatment course. Mean monthly Hgb values from baseline to the end of the study among patients who did and did not receive ferumoxytol are shown in Supporting Information Fig. 4. Among the 337 patients who received ferumoxytol, mean Hgb increased from 10.1 g/dL at baseline to 11.6–11.8 g/dL by months 2–5 and remained relatively stable for the duration of the extension study. Significantly more patients with baseline Hgb <8.5 g/dL required more than one course of treatment compared with patients who had baseline Hgb >8.5 g/dL (i.e., 50% vs. 33%, respectively; P < 0.0001). More specifically, patients with baseline Hgb <8.5 g/dL were twice as likely to require >1 dose of treatment compared with patients with baseline Hgb >8.5 g/dL (odds ratios: 2.0; 95% confidence interval, 1.4–2.9). Other efficacy endpoints are summarized in Supporting Information Table III.

Supporting Information Table IV summarizes treatment-emergent adverse events (TEAEs) occurring in ≥2% of patients in the treated safety population. The most common TEAEs were headache, urinary tract infection, and nausea. The overall incidence of TEAEs decreased with repeated treatment courses (Supporting Information Table V). Overall, 30 ferumoxytol-treated patients (8.9%) experienced an event that was considered by investigators to be related to study medication. Treatment-related adverse events that occurred in ≥1% were nausea (1.2%) and headache (1.2%). TEAEs by category are summarized in Supporting Information Table V. No serious TEAEs were considered by investigators to be drug related.

In summary, this extension study demonstrated ferumoxytol to be an effective treatment option for patients with persistent or recurrent IDA and a history of unsatisfactory oral iron therapy or in whom oral iron could not be used, producing durable responses in the majority of patients. Mean Hgb increased significantly following Treatment Course 1 with smaller increases after Treatment Courses 2 and 3 (P < 0.0001 for all). Overall, 61% of ferumoxytol-treated patients never required a second course of treatment. Ferumoxytol was well tolerated with no new safety signals identified among patients who received repeat dosing.

### Table I. Efficacy Results (Intent-to-Treat Population)

| Outcome                                      | Ferumoxytol treatment course |
|----------------------------------------------|------------------------------|
|                                              | Course 1 (n = 151)           | Course 2 (n = 244)           | Course 3 (n = 69)           |
|                                              | Value                        | 95% CI; P-value              | Value                        | 95% CI; P-value              | Value                        | 95% CI; P-value              |
| Baseline Hgb, g/dL, mean (SD)                | 8.7 (1.02)                   |                              | 10.2 (0.89)                  |                              | 10.2 (0.93)                  |
| Change in Hgb between TP baseline and week 5, g/dL, mean (SD) | 2.6 (1.55)                  | 2.4–2.8; < 0.0001            | 1.5 (1.28)                  | 1.3–1.7; < 0.0001            | 1.1 (1.30)                  | 0.8–1.4; < 0.0001            |
| Achieved ≥2.0-g/dL increase in Hgb between TP baseline and week 5, n (%) | 119 (78.8)                   | 72.3–85.3                    | 107 (43.9)                  | 37.6–50.1                    | 26 (37.7)                   | 26.2–49.1                    |
| Achieved Hgb ≥12.0 g/dL between TP baseline and week 5, n (%) | 58 (38.4)                   | 30.7–46.2                    | 139 (67.0)                  | 50.8–63.2                    | 28 (40.6)                   | 29.0–52.2                    |
| Baseline TSAT, %, mean (SD)                 | 5.1 (4.63)                   |                              | 8.8 (8.16)                  |                              | 10.1 (6.59)                 |
| Change in TSAT between TP baseline and week 5, %, mean (SD) | 12.8 (10.19)                 | 11.2–14.5; < 0.0001          | 11.7 (12.47)                | 10.6–13.2; < 0.0001          | 7.5 (9.13)                  | 5.3–9.7; < 0.0001            |

CI: confidence interval; Hgb: hemoglobin; SD: standard deviation; TP: treatment period; TSAT: transferrin saturation.

### Authorship Contributions

S.V.-R.: contributed patients; performed the clinical trial; wrote, edited, and proofread the manuscript; provided input on the study; and agreed upon the data presented; D.C.F.: contributed patients; performed the clinical trial; wrote, edited, and proofread the manuscript; and agreed upon the data presented; N.V.D.: analyzed the data; wrote, edited, and proofread the manuscript; and agreed upon the data presented; K.B.: designed and oversaw the execution of the trial; analyzed the data; wrote, edited, and proofread the manuscript; and agreed upon the data presented; W.E.S.: designed and oversaw the execution of the trial; analyzed the data; wrote, edited, and proofread the manuscript; and agreed upon the data presented; Z.L.: designed and oversaw the execution of the trial; analyzed the data; performed statistical analysis; wrote, edited, and proofread the manuscript; and agreed upon the data presented; L.F.A.: designed and oversaw the execution of the trial; analyzed the data; wrote, edited, and proofread the manuscript; and agreed upon the data presented.

### Acknowledgment

The authors thank Maria McGill, RPh, CMPP, of inScience Communications and Brett Fulton, RPh, who provided medical writing support.

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Additional Supporting Information may be found in the online version of this article.

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Conflict of interest: S.V.-R. and D.C.F. received research funding to support the clinical trial. N.V.D. and K.B. were employees of AMAG Pharmaceuticals, Inc, at the time of the study and writing of the manuscript. L.F.A. was an employee of AMAG Pharmaceuticals, Inc, at the time of the study and writing of the manuscript. W.E.S. and Z.L. were employees of AMAG Pharmaceuticals, Inc, at the time of the study and writing of the manuscript. S.V.-R. and D.C.F. received research funding to support the clinical trial.

Contract grant sponsor: AMAG Pharmaceuticals, Inc.

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Received for publication: 4 November 2015; Accepted: 10 November 2015

Published online: 17 November 2015 in Wiley Online Library (wileyonlinelibrary.com)

DOI: 10.1002/ajh.24225
Effective use of panobinostat in combination with other active agents in myeloma in a novel five-drug combination: Case report and interesting observations

To the Editor: Multiple myeloma (MM) is a clonal plasma cell proliferative disorder characterized by hypercalcemia, anemia, renal dysfunction, and osteolytic bone lesions [1]. The treatment of MM is rapidly changing with the arrival of several active new agents [2]. New drugs that have entered the market in the last few years and have shown promise in various ongoing trials worldwide include carfilzomib, pomalidomide, and panobinostat. With the advent of these drugs, comes a multitude of new combinations that can be tailored to suit each individual patient’s needs whether they are newly diagnosed, eventually relapse, and drugs with new mechanisms of action, and combinations that utilize these drugs are needed.

Panobinostat is a new treatment option that has emerged for the treatment of relapsed and refractory MM. It was approved by the United States Food and Drug Administration (FDA) in 2015 for use in patients with MM who have received at least two previous treatments including bortezomib and an immunomodulatory agent. The FDA approval was based on improved progression-free survival (PFS) in the Panorama1 trial that compared panobinostat plus bortezomib/dexamethasone to placebo plus bortezomib/dexamethasone [3]. In this trial, the median PFS was significantly longer with the use of panobinostat, 12 months versus 8.1 months, P < 0.001, respectively. Panobinostat is a non-selective histone deacetylase (HDAC) inhibitor that results in increased acetylation of histone proteins thereby inducing cell cycle arrest and/or apoptosis of the tumor cells via multiple pathways. In addition, it has an inhibitory effect on the aggresome pathway which functions as an alternative protein degradation mechanism in the cell that may in part be responsible for the resistance to proteasome inhibitors. Although panobinostat has no significant single-agent activity, the Panorama trial demonstrates synergistic activity in combination with bortezomib in patients with relapsed refractory MM. It is therefore a novel agent with a unique mechanism of action that can be combined with other active drugs and incorporated into rational drug combinations.

Three major factors significantly curtail the use of panobinostat in MM. First is the risk of severe Grade 3 or higher diarrhea (seven or more loose stools or need for hospitalization) that occurred in ~26% of patients treated in the Panorama 1 trial [3]. Second, panobinostat is a drug that needs a partner drug for efficacy since it has minimal single-agent activity in MM. In the schedule used in combination with panobinostat, bortezomib has the unfortunate side effect of severe neuropathy; in the Panorama 1 trial Grade 3 or higher neuropathy was seen in 18% [3]. Third, the efficacy results in combination with bortezomib-dexamethasone are underwhelming. There was minimal improvement in response rates, only modest prolongation of PFS, and no improvement in overall survival. We report on a patient with relapsed and refractory MM treated with a novel five-drug regimen incorporating panobinostat that has the potential to overcome these three limitations of the drug.

The patient is a 56-year-old male who was diagnosed with IgG kappa (Durie-Salmon Stage 3A, International Staging System (ISS) Stage III MM in 2004. He presented with severe back pain. Plain radiographic imaging showed pathologic compressions fractures at T7, T8, T10, and T11. Initial workup showed hemoglobin 11.1 g/dL, serum calcium 9.2 mg/dL, serum creatinine 1.1 mg/dL, serum lactate dehydrogenase 141 U/L, beta-2 microglobulin 5.33 mcg/L, and serum albumin 4.3 g/dL. He had a serum monoclonal (M) protein spike of 5.5 g/dL (IgG kappa). Quantitative immunoglobulin levels were IgG 9.750 mg/dL, IgA 26 mg/dL, and IgM 6 mg/dL. The serum free light chain (FLC) assay showed kappa 48.7 mg/dL, lambda <0.04 mg/dL, and kappa/lambda ratio >1036.2. Urine M spike was 137 mg/24 hr. On further work up bone marrow biopsy showed 70–80% clonal plasma cells. Conventional metaphase cytogenetics revealed complex hyperdiploid karyotype with trisomy 3, 4, 5, 9, 11, 15, 21, and 19; in addition, there was an imbalanced rearrangement with breakpoints at 4p12 and 8q24.1. Fluorescent in situ hybridization (FISH) results were not available.

Details of therapy are listed chronologically in Supporting Information Table S1. One week after the diagnosis was confirmed, he was started on lenalidomide and dexamethasone (Rd) as initial therapy. Although the best response to Rd was a partial response (PR), his response was remarkably durable, and he took Rd for a total of 60 cycles. Early in the treatment course with Rd, autologous stem cells adequate for two transplants were collected and cryopreserved for future use. In July 2009, he had disease progression and underwent an autologous SCT with melphalan 200 mg/m2 using half of his previously collected stem cells. Day 100 evaluation post-transplant showed PR, and he opted not to receive maintenance therapy or a second autologous SCT. Subsequently he had multiple remissions and relapses (Supporting Information Table S1), and received a variety of treatment regimens, including a second autologous SCT in July 2013. As part of these regimens he received almost all known active drugs in MM including melphalan, cyclophosphamide, corticosteroids, doxorubicin, thalidomide, lenalidomide, bortezomib, and new active drugs carfilzomib, pomalidomide, and bendamustine. PFS with the second autologous ASCT was 15 months (with maintenance). Disease progression occurred within 1 month with the last four regimens prior to starting on panobinostat. In April 2015, he was started on a quintuplet regimen of thalidomide, cyclophosphamide, bortezomib, dexamethasone, and low-dose panobinostat (10 mg three times a week). Thalidomide was used instead of other more potent immunomodulators since it causes less cytopenias, and the patient was transfusion dependent for platelets and red cells at that point. In addition, it was felt that...