Randomized, placebo-controlled, phase 3 study of perifosine combined with bortezomib and dexamethasone in patients with relapsed, refractory multiple myeloma previously treated with bortezomib

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Abstract
Perifosine, an investigational, oral, synthetic alkylphospholipid, inhibits signal transduction pathways of relevance in multiple myeloma (MM) including PI3K/Akt. Perifosine demonstrated anti-MM activity in preclinical studies and encouraging early-phase clinical activity in combination with bortezomib. A randomized, double-blind,
placebo-controlled phase 3 study was conducted to evaluate addition of perifosine to bortezomib-dexamethasone in MM patients with one to four prior therapies who had relapsed following previous bortezomib-based therapy. The primary endpoint was progression-free survival (PFS). The study was discontinued at planned interim analysis, with 135 patients enrolled. Median PFS was 22.7 weeks (95% confidence interval 16.0–45.4) in the perifosine arm and 39.0 weeks (18.3–50.1) in the placebo arm (hazard ratio 1.269 [0.817–1.969]; \( P = .287 \)); overall response rates were 20% and 27%, respectively. Conversely, median overall survival (OS) was 141.9 weeks and 83.3 weeks (hazard ratio 0.734 [0.380–1.419]; \( P = .356 \)). Overall, 61% and 55% of patients in the perifosine and placebo arms reported grade 3/4 adverse events, including thrombocytopenia (26% vs 14%), anemia (7% vs 8%), hyponatremia (6% vs 8%), and pneumonia (9% vs 3%). These findings demonstrate no PFS benefit from the addition of perifosine to bortezomib-dexamethasone in this study of relapsed/refractory MM, but comparable safety and OS.

**KEYWORDS**
Akt inhibition, bortezomib, multiple myeloma, perifosine, proteasome inhibition

## 1 INTRODUCTION

The treatment of multiple myeloma (MM) has been transformed over the past two decades with the introduction of novel targeted agents, such as proteasome inhibitors, immunomodulatory drugs, and monoclonal antibodies, and as a result of our increasing understanding of the complex disease biology of MM and the signaling pathways of importance [1–5]. Proteasome inhibitors and immunomodulatory drugs have emerged as backbone therapeutics for MM treatment as a result of the substantial efficacy demonstrated alone and in combination in different disease settings [6]. This activity arises due to these mechanisms of action affecting multiple critical signaling pathways of importance [7,8]. However, as MM progresses, patients can develop resistance to these and other commonly used agents. Therefore, an ongoing unmet need for patients with relapsed and/or refractory MM (RRMM) is for novel targeted agents that inhibit specific pathways of relevance and potentially synergize with or overcome resistance to the mechanisms of action of the proteasome inhibitors and the immunomodulatory drugs [9–11].

One of the pathways of interest for targeting in the treatment of MM has been the phosphoinositide-3-kinase (PI3K)/Akt signaling cascade, the activation of which is induced by interactions between MM cells and bone marrow stromal cells within the bone marrow microenvironment [12,13]. The induction of this and other signaling pathways results in MM proliferation, survival, and drug resistance [13], making it a rational therapeutic target in MM. Perifosine is an investigational, oral, synthetic alkylphospholipid that inhibits or modifies signal transduction pathways of relevance in MM including PI3K/Akt, nuclear factor-\( \kappa \)B, and c-Jun N-terminal kinase (JNK) cascades [13]. Perifosine demonstrated potent anti-MM activity in preclinical studies [14–18], including enhanced cytotoxicity in combination with bortezomib based on synergism between mechanisms of action [19]. Consequently, perifosine was investigated clinically in MM and demonstrated encouraging activity in patients with MM when combined with bortezomib and lenalidomide [20,21]. In a phase 1/2 study in 73 patients with RRMM, perifosine in combination with bortezomib, with or without added dexamethasone, resulted in a rate of minimal response or better of 41%, including rates of 65% in patients who had relapsed following prior bortezomib treatment and 32% in bortezomib-refractory patients [21]. Based on these promising early-phase study results, we conducted a randomized, double-blind, placebo-controlled phase 3 study to evaluate the benefit of adding perifosine to bortezomib-dexamethasone in MM patients who had previously relapsed after a bortezomib-based regimen.

## 2 METHODS

### 2.1 Patients

Between March 2010 and March 2013, relapsed and/or refractory patients aged \( \geq 18 \) years with a confirmed diagnosis of MM, who had measurable disease (serum M-protein > 0.5 g/dL and/or > 200 mg/24-h urinary M-protein excretion) and an Eastern Cooperative Oncology Group performance status of 0–2, were enrolled at 48 study sites in the United States, Israel, Spain, South Korea, Canada, Russia, the Czech Republic, France, Ireland, and Slovakia. Patients were required to have received 1–4 prior anti-myeloma therapies, including at least two 21-day cycles of either single-agent bortezomib or bortezomib in combination with other agents, and patients had to have relapsed following
their prior bortezomib-based therapy, with progression occurring >60 days after last dose (ie, patients could not be refractory to prior bortezomib-containing regimens). Patients could have relapsed following or have been refractory to other non-bortezomib-based therapies. Patients also required adequate hematological (platelets ≥75 x 10⁹/L, absolute neutrophil count ≥0.5 x 10⁹/L, hemoglobin ≥8.0 g/dL), renal (creatinine ≤3.0 mg/dL), and hepatic (total bilirubin ≤1.5 x upper limit of normal) function. Patients were excluded if they had previously received treatment with perifosine or an experimental proteasome inhibitor.

2.2 Study design

This was a double-blind, placebo-controlled, randomized phase 3 study (NCT01002248). Patients were randomized in a 1:1 ratio to receive perifosine 50 mg orally, once-daily, or matching placebo, plus intravenous or subcutaneous bortezomib 1.3 mg/m² on days 1, 4, 8, and 11 and oral dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, and 12, in 21-day treatment cycles until disease progression. Randomization was stratified according to number of prior lines of therapy (1 vs > 1) and disease status after last prior therapy (refractory or relapsed with a treatment-free interval [TFI] of <6 vs ≥6 months). Dose reductions and delays were permitted for the management of toxicity.

The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall response rate, overall survival (OS), and safety. Tertiary endpoints included perifosine population pharmacokinetics and evaluation of treatment effects on electrocardiogram (ECG) parameters. Serum and urine protein electrophoresis were performed by a central laboratory at the start of each 21-day treatment cycle to assess disease status until confirmed disease progression. Response or progression determined according to parameters other than serum and urine M-protein or determined by local laboratory readings were adjudicated by an independent reviewer blinded to treatment arms. All responses were assessed using modified European Group for Blood and Marrow Transplantation criteria [22] and International Myeloma Working Group Uniform Criteria [23]. Survival status was assessed every 3 months. Toxicity was recorded throughout the study across both arms and through 30 days following the last dose of treatment; severity of adverse events (AEs) was assessed using the National Cancer Institute’s Common Terminology Criteria for AEs version 3.0, with attribution assessed locally and centrally as part of standard monitoring practice for safety.

2.3 Statistical analyses

Enrolment of 450 patients was planned in order to provide 265 events of disease progression or death for the final statistical analysis of the primary endpoint, PFS. Two formal nonbinding interim analyses were planned by the independent Data and Safety Monitoring Board (DSMB) to assess efficacy at the time of approximately 30% and 60% of the total PFS events having occurred, respectively, that is when approximately 80 and 160 PFS events had been observed. The results of the first planned interim analysis are reported herein, which was performed when 80 PFS events had been observed across the two arms. Following the recommendation of the DSMB, the study was discontinued at this interim analysis (March 12, 2013) due to absence of benefit in the primary endpoint, limited study logistics, and enrolment challenges, which had resulted in very slow patient accrual and thereby limited the sample size.

The primary analysis was performed using the intent-to-treat population and included only those progression events defined by a computer algorithm and, when required, an independent reviewer. Progression determined by the investigator alone was not considered a progression event. Hypothesis testing between the two treatment arms was performed using a log-rank test with an overall two-sided .05 level of significance via a model including treatment effects. For each treatment arm, the median duration of PFS and the proportion of patients alive and progression-free at 6 and 12 months were estimated using the Kaplan–Meier method. For each estimate, a 95% confidence interval (CI) was reported. The hazard ratio (HR) and its 95% CI were also reported. The secondary endpoint of OS was analyzed similarly to PFS. Other data were summarized using descriptive statistics.

3 RESULTS

3.1 Patients

At the data cut-off for the first interim analysis (March 12, 2013), a total of 135 patients had been enrolled and randomized – 69 to the perifosine arm and 66 to the placebo arm (Figure 1). Patient demographics and disease characteristics at randomization were similar between treatment arms (Table 1), except for a numerically higher proportion of patients aged <65 years in the perifosine arm versus the placebo arm (61% vs 42%). Prior treatment exposure and relapsed/refractory status were balanced between arms.

3.2 Efficacy

The primary endpoint of PFS was assessed in the intent-to-treat population, with the exception of one patient in the placebo arm. This patient was not evaluable for time-to-event outcomes; subsequent to randomization, the patient was found not to meet eligibility criteria based on M-protein levels required by the protocol, and so they were excluded from the analyses of PFS and OS. At the time of data cutoff for this first planned interim analysis, a total of 42 patients in the perifosine arm and 38 patients in the placebo arm had progressed or died, with 27 patients in each arm remaining alive and progression-free after a median follow-up of approximately 28 and 31 weeks, respectively. The median PFS was 22.7 weeks (95% CI 16.0–45.4) in the perifosine arm and 39.0 weeks (18.3–50.1) in the placebo arm; the HR for PFS in the perifosine arm relative to the placebo arm was 1.269 (0.817–
The overall response rates were 20% (14 patients) and 27% (18 patients) in the perifosine and placebo arms, respectively (Table 2). An additional 18 and 11 patients, respectively, achieved a minimal response or stable disease, giving clinical benefit rates (stable disease or better) of 46% and 44%.

At the time of data cut-off, a total of 17 patients in the perifosine arm and 19 patients in the placebo arm had died, with 52 and 46 patients in the respective arms remaining alive after a median follow-up of approximately 48 and 40 weeks, respectively. The median OS was 141.9 weeks (95% CI 72.6–not estimable) in the perifosine arm and 83.3 weeks (51.1–not estimable) in the placebo arm; the HR for OS in the perifosine arm relative to the placebo arm was 0.734 (0.380–1.419; \( P = .356 \)). The Kaplan–Meier distributions for OS are shown in Figure 2B.

### 3.3 Safety

All 135 patients were evaluable for safety. In total, 60 (87%) of patients in the perifosine arm and 50 (75.8%) of patients in the placebo arm reported at least one AE; the most common events are summarized in Table 3. Among these patients, 43 (62%) and 38 (58%) reported at least one grade \( \geq 3 \) AE; the most common individual grade 3/4 AE events in the perifosine versus placebo arms included thrombocytopenia (26% vs 14%), anemia (7% vs 8%), hyponatremia (6% vs 8%), and pneumonia (9% vs 3%; Table 3). Rates of grade 3 neuropathy AEs were limited, including two patients (3%) on each arm with peripheral neuropathy and only one patient (2%) on the placebo arm having a grade 3 AE of peripheral sensory neuropathy; no grade 4 neuropathy AEs were reported. However, four patients (6%) on the perifosine arm and one patient (2%) on the placebo arm discontinued treatment due to an AE of neuropathy or neuralgia. Overall, 13 (19%) and 9 (14%) patients on the perifosine and placebo arms, respectively, discontinued treatment due to an AE. Other AEs resulting in treatment discontinuation on the perifosine arm were pneumonia (\( n = 2 \)), and thrombocytopenia, oral pain/toothache, meningioma, bronchitis, asthenia, diarrhea, and ocular hyperemia (each \( n = 1 \)), and on the placebo arm were respiratory failure/sepsis, nausea, congestive heart failure, fatigue, diarrhea/asthenia/thrombocytopenia, back pain, abdominal pain, and muscular weakness/pain in extremity (each \( n = 1 \)).

A total of four patients (6%) on the perifosine arm and three patients (5%) on the placebo arm died during the study reporting period due to reasons other than disease progression, including respiratory infection, suicide, sudden death (treatment-emergent grade 5 AE), and myocardial infarction (each \( n = 1 \)) on the perifosine arm, and respiratory failure/sepsis (treatment-emergent grade 5 AE) and respiratory failure/sepsis (treatment-emergent grade 5 AE), congestive heart failure, and pneumococcal sepsis (treatment-emergent grade 5 AE) (each \( n = 1 \)) on the placebo arm.

### 4 DISCUSSION

The findings from the first planned interim analysis of this randomized, double-blind, placebo-controlled, phase 3 study demonstrated no benefit in terms of the primary endpoint, PFS, with the addition of perifosine to bortezomib-dexamethasone in patients with RRMM who had previously relapsed following bortezomib-based treatment. Based on these data and the recommendation of the DSMB, and associated with concerns regarding slow accrual resulting in a limited sample size and regarding resource constraints and study logistics, the study was
TABLE 1  Patient demographics and disease characteristics at randomization

|                          | Perifosine + Vd, n = 69 | Placebo + Vd, n = 66 |
|--------------------------|--------------------------|-----------------------|
| **Age <65/≥65 years, n (%)** | 41 (61)/26 (39)†         | 28 (42)/38 (58)‡      |
| **Male/Female, n (%)**   | 41 (60)/27 (40)†         | 37 (56)/29 (44)‡      |
| **Race, n (%)**          | 68                       | 66                    |
| **White**                | 58 (85)                  | 54 (82)               |
| **Asian**                | 6 (9)                    | 7 (11)                |
| **Black or African American** | 4 (6)                    | 5 (8)                 |
| **ECOG PS, n (%)**       | 56                       | 57                    |
| **0**                    | 32 (57)                  | 31 (54)               |
| **1**                    | 17 (30)                  | 24 (42)               |
| **2**                    | 7 (13)                   | 2 (4)                 |
| **Myeloma subtype, n (%)** | 65†                      | 66                    |
| **IgG**                  | 43 (66)                  | 45 (68)               |
| **IgA**                  | 10 (15)                  | 14 (21)               |
| **IgM**                  | 0                        | 2 (3)                 |
| **IgD**                  | 1 (2)                    | 0                     |
| **Other**                | 11 (17)                  | 5 (8)                 |
| **Prior therapy and disease status (stratification), n (%)** | n = 69                   | n = 66                  |
| **1 line, refractory**   | 2 (3)                    | 2 (3)                 |
| **>1 line, refractory**  | 15 (22)                  | 12 (18)               |
| **1 line, relapse, TFI < 6 months** | 3 (4)                   | 4 (6)                 |
| **>1 line, relapse, TFI < 6 months** | 16 (23)                  | 16 (24)               |
| **1 line, relapse, TFI ≥ 6 months** | 6 (9)                    | 7 (11)                |
| **>1 line, relapse, TFI ≥ 6 months** | 27 (39)                  | 25 (38)               |
| **Disease status at randomization, n (%)** | n = 67§                   | n = 66                  |
| **Relapsed**             | 55 (82)                  | 54 (82)               |
| **Refractory**           | 12 (18)                  | 12 (18)               |

†Data missing for two patients.
‡Data missing for one patient.
§Data missing for 13 and 9 patients in the perifosine and placebo arms, respectively.
¶Data missing for four patients.
§Patients not refractory to bortezomib-based component of prior line of therapy.

Abbreviations: ECOG PS, Eastern Cooperative Oncology performance status; Ig, immunoglobulin; TFI, treatment-free interval; Vd, bortezomib-dexamethasone.

The response rates reported in the present study appeared low compared to data from the previous phase 1/2 study of perifosine plus bortezomib-dexamethasone in RRMM [21]; in the previous study, an overall response rate of 45% was reported, compared to 20% in the present study, and all patients achieved stable disease or better, compared to 46%. However, these previous data were based on a cohort of only 20 bortezomib-relapsed patients who had received a median of 4 prior therapies, suggesting ongoing sensitivity to drug therapy in these patients. By contrast, the data from the present study suggest that the enrolled patients had relatively resistant disease, with almost a quarter stratified as refractory to other, non-bortezomib-based prior therapies. Additionally, the discrepancy between the phase 2 and phase 3 experiences may have been due to the small number of patients in the previous open-label phase 2 study; this may not have been optimal for subsequent phase 3 exploration – a larger, randomized phase 2 study or an adaptive study design may have been preferable and may potentially have provided response data more similar to those reported from the present study. It is also notable that the response rate in the placebo arm (27%) appeared lower compared to data from a phase 2 study of bortezomib + dexamethasone retreatment in patients with relapsed MM (40%) [24].

It is of interest to assess the overall response and clinical benefit rates in both arms in the context of the high proportion of unevaluable patients and patients missing response data (40.5% and 45.5% in the perifosine and placebo arms, respectively); if these patients were to be omitted from the calculations of overall response and clinical benefit rates, the rates would be similar to those previously reported for perifosine plus bortezomib-dexamethasone in bortezomib-relapsed RRMM patients and bortezomib + dexamethasone retreatment in patients with relapsed MM (overall response rate of 34.1% and 50.0%, and clinical benefit rate of 78.0% and 80.6%, in the perifosine and placebo arms, respectively). Nevertheless, these findings suggest the acute antitumor activity of the triplet combination in bortezomib-relapsed patients was primarily driven by bortezomib-dexamethasone, a hypothesis supported by data from a previous multicenter phase 2 study of perifosine + dexamethasone in RRMM patients after a median of 4 prior lines of therapy [25], in which single-agent perifosine had modest activity and perifosine + dexamethasone resulted in an overall response rate of 12.9% and a clinical benefit rate of 38.7%. While the prior phase 1/2 study of perifosine plus bortezomib-dexamethasone in RRMM suggested some antitumor activity or resensitizing effect of perifosine in bortezomib-refractory patients (with an overall response rate of 13.2% and a clinical benefit rate of 32.1%) [21], such patients were not included in the present study.

A limitation of the present study is that, due to the dates between which it was conducted, a number of now-commonly collected prognostic parameters were not recorded, including cytogenetics; thus, it is not possible to determine whether the patients in the study presented with an elevated rate of poor prognostic features, such as high-risk cytogenetic abnormalities, which could potentially explain the poor response rates and outcomes seen in both arms. Further, no correlative
studies related to the PI3K/Akt signaling cascade were prospectively planned; such analyses may have helped identify a patient population who did benefit from the combination [26].

Reflecting the previous phase 1/2 study of perifosine plus bortezomib-dexamethasone [21] the triplet regimen appeared tolerable at the selected dose of perifosine; indeed, it might be queried, given the limited activity seen with the triplet regimen, whether the perifosine dose was optimal in this study, given that no dose-limiting toxicities were reported using a 100 mg dose of perifosine in the previous phase 1/2 study [21]. However, as noted in that report, toxicity was generally greater in this higher-dose cohort, and this impacted the duration of treatment; thus, the 50 mg dose was selected for the phase 2 component of the previous study and for the present study [21]. In the present study, no specific safety concerns were observed...
TABLE 2  Best response to treatment

| Best response, n (%)               | Perifosine + Vd, n = 69 | Placebo + Vd, n = 66 |
|-----------------------------------|-------------------------|----------------------|
| Overall response rate             | 14 (20.3)               | 18 (27.3)            |
| Complete response                 | 2 (2.9)                 | 0                    |
| Very good partial response        | 4 (5.8)                 | 5 (7.6)              |
| Partial response                  | 8 (11.6)                | 13 (19.7)            |
| Clinical benefit rate             | 32 (46.4)               | 29 (43.9)            |
| Minimal response                  | 5 (7.2)                 | 6 (9.1)              |
| Stable disease                    | 13 (18.8)               | 5 (7.6)              |
| Progressive disease               | 9 (13.0)                | 7 (10.6)             |
| Unevaluable                       | 5 (7.2)                 | 4 (6.1)              |
| Missing                           | 23 (33.3)               | 26 (39.4)            |

in the perifosine arm compared with the placebo arm. Common grade 3/4 AEs included thrombocytopenia, pneumonia, and anemia, which were also among the most common grade 3/4 AEs in the previous study [21]. Overall, the low rates of treatment discontinuation and the convenience of the oral approach of the triplet supported the real-world strategy underlying the combination’s development [27], as well as the equipoise in the design, given the favorable performance of the control group and the OS data in the experimental arm subsequent to interim analysis.

Subsequent to the discontinuation of this study, perifosine is no longer being investigated as a potential novel targeted agent for patients with RRMM. Reflecting these findings, a similar lack of OS benefit was seen with the addition of perifosine to capcitabine in patients with metastatic colorectal cancer in the phase 3 X-PECT study [28]. Nevertheless, the PI3K/Akt signaling cascade remains a rational target of interest in MM [29–31] and multiple other cancers [32–35], with several Akt inhibitors in ongoing clinical development either alone or in combination regimens [32,36–39], and preclinical data demonstrating the validity of this mechanism of action with perifosine and other agents both in hematological malignancies and solid tumors [40–43]. Meanwhile, additional therapeutic approaches targeted at other signaling cascades of known importance are being explored in RRMM [9,44], warranting further evaluation.

In conclusion, perifosine at the dose tested did not improve response rates or outcomes in combination with bortezomib-dexamethasone in patients with RRMM who have relapsed following previous bortezomib-based treatment. Although the rational combination of Akt pathway inhibition with perifosine and proteasome inhibition with bortezomib demonstrated synergistic anti-MM activity in preclinical investigation [19], this was not reflected in the phase 3 clinical setting, despite earlier-phase clinical studies showing promise.

TABLE 3  Summary of most frequently reported all-grade (reported in ≥ 10% of patients in either arm) and grade 3/4 adverse events (reported in ≥ 5% of patients in either arm)

|                      | Perifosine + Vd, n = 69 | Placebo + Vd, n = 66 |
|----------------------|-------------------------|----------------------|
| Any AE               | 60 (87)                 | 50 (76)              |
| Thrombocytopenia     | 24 (35)                 | 15 (23)              |
| Fatigue              | 19 (28)                 | 20 (30)              |
| Diarrhea             | 18 (26)                 | 19 (29)              |
| Anemia               | 15 (22)                 | 12 (18)              |
| Neuropathy peripheral| 14 (20)                 | 12 (18)              |
| Nausea               | 14 (20)                 | 8 (12)               |
| Insomnia             | 13 (19)                 | 8 (12)               |
| Asthenia             | 10 (14)                 | 11 (17)              |
| Hyperglycemia        | 9 (13)                  | 7 (11)               |
| Constipation         | 9 (13)                  | 18 (27)              |
| Upper respiratory tract infection | 9 (13) | 10 (15) |
| Pneumonia            | 8 (12)                  | 4 (6)                |
| Hyponatremia         | 7 (10)                  | 7 (11)               |
| Hypophosphatemia     | 6 (9)                   | 8 (12)               |
| Peripheral edema     | 6 (9)                   | 12 (18)              |
| Neutropenia          | 4 (6)                   | 7 (11)               |

Abbreviations: AE, adverse event; SOC, system organ class; Vd, bortezomib-dexamethasone.

*In addition, one patient on the perifosine arm and two patients on the placebo arm had grade 5 AEs, as described in the text.
Dana-Farber Cancer Institute and the RJ Corman Multiple Myeloma Research Fund, and Aeterna Zentaris GmbH. This study was supported by research funding from AOI Pharmaceuticals, Inc., a subsidiary of Keryx Biopharmaceuticals, Inc., and Aeterna Zentaris GmbH.

AUTHOR CONTRIBUTIONS
P.G.R. was the principal investigator and takes primary responsibility for the paper; P.G.R., A.N., D.B.-Y., A.B., P.N.H., R.H., I.S., H.K., R.L.B., S.-S.Y., K.K., J.M.-L., M.M., O.S., K.C., J.P.L., I.M.G., M.E.G., and K.C.A. collected data and/or recruited patients; P.G.R., A.N., P.B., T.H., P.S., and K.C.A. designed the study. P.S. and M.C. participated in the statistical analysis; P.G.R., P.S., and M.C. co-ordinated preparation and analysis of the dataset; P.G.R. and P.S. interpreted the data and prepared the manuscript. All authors reviewed and approved the manuscript.

CONFLICT OF INTEREST
P.G.R. received research support from Oncopeptides, Celgene, Takeda, and Bristol-Myers Squibb and served as advisory committee member for Karyopharm, Oncopeptides, Celgene, Takeda, Amgen, Janssen, and Sanofi. P.N.H. received research funding from Takeda and Celgene, and served as a consultant for Takeda, Celgene, Bristol-Myers Squibb, Janssen, Spectrum, Pharmacys, and Kite. R.H. received consulting fees, honoraria, and research funding from Amgen, Takeda, Celgene, Janssen, Abbvie, Novartis, PharmaMar, and BMS. H.K. served as a consultant and also served on a Speakers Bureau for Takeda. J.M.-L. received research funding from BMS, Janssen, Novartis, and Celgene, and served as a consultant for Janssen, Novartis, Celgene, and Roche. P.B. was an employee of Aeterna Zentaris. K.C. served as a consultant for Celgene. I.M.G. served as a consultant for GSK, Sanofi, Janssen, Takeda, Celgene, Karyopharm, AbbVie, GNS, Cellectar, Medscape, Genentech, Adaptive, BMS, Aptitude, Curio Science, and Oncopeptides, and served as an advisor for GSK, AbbVie, and BMS. P.S. was an employee and had equity interest in Keryx Biopharmaceuticals. M.C. served as a consultant for Keryx Biopharmaceuticals. K.C.A. served as a consultant for Celgene, Millennium Pharmaceuticals, Bristol Myers Squibb, Janssen, Gilead, and Sanofi, and was a scientific founder of Oncopep and C4 Therapeutics.

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How to cite this article: Richardson PG, Nagler A, Ben-Yehuda D, et al. Randomised, placebo-controlled, phase 3 study of perifosine combined with bortezomib and dexamethasone in patients with relapsed, refractory multiple myeloma previously treated with bortezomib. eJHaem. 2020;1:94–102. https://doi.org/10.1002/jha2.4