Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate that targets aminopeptidases and rapidly and selectively releases alkylating agents into tumor cells. The phase II HORIZON trial evaluated the efficacy of melflufen plus dexamethasone in relapsed and refractory multiple myeloma (RRMM), a population with an important unmet medical need.

PATIENTS AND METHODS Patients with RRMM refractory to pomalidomide and/or an anti-CD38 monoclonal antibody received melflufen 40 mg intravenously on day 1 of each 28-day cycle plus once weekly oral dexamethasone at a dose of 40 mg (20 mg in patients older than 75 years). The primary end point was overall response rate (partial response or better) assessed by the investigator and confirmed by independent review. Secondary end points included duration of response, progression-free survival, overall survival, and safety. The primary analysis is complete with long-term follow-up ongoing.

RESULTS Of 157 patients (median age 65 years; median five prior lines of therapy) enrolled and treated, 119 patients (76%) had triple-class–refractory disease, 55 (35%) had extramedullary disease, and 92 (59%) were refractory to previous alkylator therapy. The overall response rate was 29% in the all-treated population, with 26% in the triple-class–refractory population. In the all-treated population, median duration of response was 5.5 months, median progression-free survival was 4.2 months, and median overall survival was 11.6 months at a median follow-up of 14 months. Grade ≥ 3 treatment-emergent adverse events occurred in 96% of patients, most commonly neutropenia (79%), thrombocytopenia (76%), and anemia (43%). Pneumonia (10%) was the most common grade 3/4 nonhematologic event. Thrombocytopenia and bleeding (both grade 3/4 but fully reversible) occurred concomitantly in four patients. GI events, reported in 97 patients (62%), were predominantly grade 1/2 (93%); none were grade 4.

CONCLUSION Melflufen plus dexamethasone showed clinically meaningful efficacy and a manageable safety profile in patients with heavily pretreated RRMM, including those with triple-class–refractory and extramedullary disease.
Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate that targets aminopeptidases and rapidly and selectively releases alkylating agents into tumor cells.\(^7\)\(^-\)\(^12\) Melflufen is rapidly and passively taken up by cells because of its high lipophilicity, thereby circumventing the development of transporter-associated resistance.\(^8\)\(^-\)\(^11\) Intracellular aminopeptidases hydrolyze melflufen to release hydrophilic alkylating moieties.\(^11\) Melflufen and its metabolites melphalan and desethyl-melflufen have equipotent alkylating potential.\(^11\) Unlike previous aminopeptidase-targeting therapies that directly inhibit aminopeptidase activity, melflufen takes a novel approach by leveraging increased aminopeptidase activity to selectively direct potent cytotoxic agents into tumor cells.\(^11\)\(^-\)\(^15\) Melflufen and its metabolites trigger robust and irreversible DNA damage, have antiangiogenic effects, induce apoptosis—resulting in potent antitumor activity in myeloma cells, including those with resistance to melphalan, bortezomib, and dexamethasone—and, importantly, retain activity in myeloma cells with absent or impaired p53 function.\(^8\)\(^\text{–}\)\(^10\)\(^\text{,}\)\(^16\) Melflufen may also have activity in other hematologic malignancies (including immunoglobulin light chain amyloidosis and leukemia) and solid tumors (including breast cancer and ovarian cancer).\(^11\)

The phase I/II, multicenter O-12-M1 trial established the dosage of melflufen plus dexamethasone in patients who had RRMM, received a median of four previous lines of therapy (including lenalidomide and bortezomib), and had disease refractory to their last line of therapy.\(^17\) In 45 patients treated with infusional melflufen 40 mg administered on day 1 of each 28-day cycle and once weekly dexamethasone dosed at 40 mg, the overall response rate (ORR) was 31%, the median duration of response (DOR) was 8.4 months, the median progression-free survival (PFS) was 5.7 months, and the median overall survival (OS) was encouraging at 20.7 months. The safety profile of melflufen was characterized primarily by hematologic toxicities that were clinically manageable with appropriate dose delays, dose reductions, and supportive care. Based on these results, the efficacy and safety of melflufen plus dexamethasone were therefore evaluated in the current study in a larger population with heavily pretreated, resistant, and poor-risk RRMM, including those with triple-class–refractory disease, for whom few effective treatment options exist.\(^3\)
Melflufen and Dexamethasone in Relapsed and Refractory Myeloma

age ≥ 75 years) once-weekly administered on days 1, 8, 15, and 22 of each 28-day cycle until disease progression, unacceptable toxicity, or the patient or treating physician determined it was not in the patient’s best interest to continue. Melflufen dose reduction for drug-related toxicities was allowed in 10 mg increments each cycle from 40 mg down to 30 mg and from 30 mg down to 20 mg (see the Data Supplement).

This study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines for Good Clinical Practice. The protocol was reviewed and approved by national regulatory authorities and an independent ethics committee or institutional review board at each study center. Each patient provided written informed consent.

Outcomes

The primary end point was ORR, defined as the proportion of patients achieving a confirmed response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as their best response per International Myeloma Working Group (IMWG) uniform response criteria, as assessed by the investigator. Response, confirmed response, and confirmed progression were subsequently verified by an independent review committee. Secondary end points included DOR, PFS, OS, clinical benefit rate (CBR), best response, time to response, time to progression, time to next treatment, and safety (defined in the Data Supplement). All response categories required confirmation with two consecutive assessments (see the Data Supplement). Adverse events (AEs) were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. AE frequency and relationship to study treatment were summarized.

Statistical Analysis

Planned enrollment was 150 patients. ORR and associated two-sided exact 95% CI19 were estimated for all patients treated (all-treated population). With a sample size of 150 patients and an assumed ORR of 30%, the exact 95% CI was estimated to range between 23% and 38%. CBR and disease stabilization were also summarized. Time-to-event end points were summarized using the Kaplan-Meier method in the all-treated population. Median and estimated 95% CIs were constructed using the methods of Brookmeyer and Crowley20; duration of follow-up was estimated by the reverse Kaplan-Meier methods of Schumacher and Smith.21 See the Data Supplement for patient censoring and handling of missing data.

A preplanned subgroup analysis was performed in patients with triple-class–refractory MM (refractory to or intolerant of at least one immunomodulatory drug, at least one proteasome inhibitor, and at least one anti-CD38 monoclonal antibody). With a sample size of 150 patients, 104-120 patients with triple-class–refractory disease were expected; the primary end point was considered met if the lower bound of the 95% CI for the ORR was higher than 15%. Additional subgroup analyses, including extramedullary disease, are described in the Data Supplement. Extramedullary disease was assessed at baseline for patients with known or suspected extramedullary disease and to confirm a response achieved by M-protein or for suspected progression per IMWG uniform response criteria.18

FIG 1. Trial profile. OS, overall survival; PFS, progression-free survival.
Table 1. Baseline Demographics and Clinical Characteristics in the Overall Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All-Treated Population (N = 157)</th>
<th>Triple-Class Refractory (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (range), years</td>
<td>65 (35–86)</td>
<td>65 (35–86)</td>
</tr>
<tr>
<td>Male</td>
<td>89 (57)</td>
<td>70 (59)</td>
</tr>
<tr>
<td>ECOG performance status score&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
</tr>
<tr>
<td>0</td>
<td>39 (25)</td>
<td>26 (22)</td>
</tr>
<tr>
<td>1</td>
<td>93 (59)</td>
<td>75 (63)</td>
</tr>
<tr>
<td>2</td>
<td>25 (16)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>High-risk cytogenetics&lt;sup&gt;c,d&lt;/sup&gt;</td>
<td>59 (38)</td>
<td>41 (34)</td>
</tr>
<tr>
<td>≥2 high-risk abnormalities</td>
<td>21 (13)</td>
<td>14 (12)</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>18 (11)</td>
<td>10 (8)</td>
</tr>
<tr>
<td>International Staging System stage&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>63 (40)</td>
<td>41 (34)</td>
</tr>
<tr>
<td>II</td>
<td>49 (31)</td>
<td>36 (30)</td>
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<tr>
<td>III</td>
<td>39 (25)</td>
<td>36 (30)</td>
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<tr>
<td>Unknown</td>
<td>4 (3)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>Missing</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Extramedullary disease&lt;sup&gt;f,i&lt;/sup&gt;</td>
<td>55 (35)</td>
<td>50 (42)</td>
</tr>
<tr>
<td>Median time since initial diagnosis (range), years&lt;sup&gt;g&lt;/sup&gt;</td>
<td>6.5 (0.7-24.6)</td>
<td>6.2 (0.7-24.6)</td>
</tr>
<tr>
<td>Median no. of prior lines of therapy (range)</td>
<td>5 (2-12)</td>
<td>5 (2-12)</td>
</tr>
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<td>Previous anti-CD38 monoclonal antibody</td>
<td>125 (80)</td>
<td>119 (100)</td>
</tr>
<tr>
<td>Refractory (any)</td>
<td>125 (80)</td>
<td>119 (100)</td>
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<tr>
<td>Refractory to daratumumab</td>
<td>117 (75)</td>
<td>112 (94)</td>
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<td>Previous immunomodulatory drug</td>
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<td>119 (100)</td>
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<tr>
<td>Refractory (any)</td>
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<td>140 (89)</td>
<td>104 (87)</td>
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<td>Previous proteasome inhibitor</td>
<td>157 (100)</td>
<td>119 (100)</td>
</tr>
<tr>
<td>Refractory (any)</td>
<td>145 (92)</td>
<td>115 (97)</td>
</tr>
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<td>Refractory to bortezomib</td>
<td>101 (64)</td>
<td>80 (67)</td>
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<td>Previous alkylator therapy</td>
<td>138 (88)</td>
<td>105 (88)</td>
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<tr>
<td>Refractory (any)</td>
<td>92 (59)</td>
<td>76 (64)</td>
</tr>
<tr>
<td>Refractory to cyclophosphamide</td>
<td>80 (51)</td>
<td>65 (55)</td>
</tr>
<tr>
<td>Refractory to melphalan</td>
<td>21 (13)</td>
<td>19 (16)</td>
</tr>
<tr>
<td>Refractory to bendamustine</td>
<td>14 (9)</td>
<td>13 (11)</td>
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<tr>
<td>Refractory to other&lt;sup&gt;h&lt;/sup&gt;</td>
<td>10 (6)</td>
<td>7 (8)</td>
</tr>
<tr>
<td>Triple-class refractory&lt;sup&gt;i&lt;/sup&gt;</td>
<td>119 (76)</td>
<td>119 (100)</td>
</tr>
</tbody>
</table>

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Table 1. Baseline Demographics and Clinical Characteristics in the Overall Population (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All-Treated Population (N = 157)</th>
<th>Triple-Class Refractory (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Re refractory to the last line of therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥1</td>
<td>108 (69)</td>
<td>81 (68)</td>
</tr>
<tr>
<td>≥2</td>
<td>33 (21)</td>
<td>24 (20)</td>
</tr>
</tbody>
</table>

NOTE. Data are expressed as no. (%) unless otherwise indicated. Abbreviation: ECOG, Eastern Cooperative Oncology Group. 
<sup>a</sup>Baseline is defined as the most recent assessment before administration of the first dose of study drug.
<sup>b</sup>ECOG performance status scores range from 0 to 5, with 0 indicating no symptoms and higher scores indicating increasing disability, and were established at baseline (most recent assessment before administration of the first dose of study drug).
<sup>c</sup>High-risk cytogenetics at study entry was based on fluorescence in situ hybridization defined as t(4; 14), del(17/17p), and t(14; 16) per Sonneveld et al<sup>22</sup>; 31 patients (20%) had unknown cytogenetics. Cytogenetic assessments were not centralized.
<sup>d</sup>At study entry.
<sup>e</sup>International Staging System stages were defined as follows: stages I, II, not stage I or stage II; stage III, serum B2-microglobulin ≥ 5.5 mg/L. Patients with unknown status were coded as unknown; patients without an entry into the case report form were coded as missing.
<sup>f</sup>Extramedullary disease was defined as a multiple myeloma disease originating either in, but extending beyond, the cortical bone or as a separate soft tissue mass.
<sup>g</sup>Time since initial diagnosis is calculated relative to the first dose of study drug.
<sup>h</sup>Includes patients refractory to carmustine (6 [7%] in the all-treated population; 6 [5%] in the triple-class–refractory population), refractory to high-dose melphalan (3 [3%] in the all-treated population; 2 [2%] in the triple-class–refractory population), and refractory to busulfan (1 [1%] in the all-treated and triple-class–refractory population).
<sup>i</sup>Defined as refractory to or intolerant of ≥ 1 proteasome inhibitor, ≥ 1 immunomodulatory drug, and ≥ 1 anti-CD38 monoclonal antibody.

RESULTS

Patients

In total, 157 patients were enrolled in the study, received at least one dose of study medication, and were included in the all-treated population. At the data cutoff date (January 14, 2020), 131 patients (83%) had discontinued treatment—the most common primary reasons for discontinuation were disease progression (n = 88; 56%) and AEs (n = 26; 17%)—and 26 patients (17%) remained on treatment (Fig 1). The median duration of treatment with melflufen plus dexamethasone was 3.8 months (range, 0.9–22.7 months). At baseline, the median age was 65 years, patients had received a median of five prior lines of therapy, 154 patients (98%) had disease that was...
refractory to the last line of therapy received, 119 (76%) had triple-class–refractory disease, and 92 (59%) had MM that was refractory to prior alkylator therapy (Table 1). Overall, 59 patients (38%) had high-risk cytogenetics, 39 (25%) had International Staging System stage III disease, and 55 (35%) had extramedullary disease.

### Efficacy

The ORR per investigator assessment was 29% (95% CI, 22% to 37%), with one patient achieving an sCR, 17 a VGPR, and 28 a PR (Table 2). An additional 25 patients achieved a minimal response for a CBR of 45% (95% CI, 37% to 53%). In the triple-class–refractory population, the ORR was 26% (95% CI, 18% to 35%), with 13 patients achieving a VGPR and 18 a PR. The ORR per independent review committee was 30% (95% CI, 23% to 38%) overall and 26% (95% CI, 18% to 35%) in the triple-class–refractory population (Data Supplement).

Reduction in M-protein was observed in 118 of the 145 patients (81.4%) (Data Supplement). In the all-treated and triple-class–refractory populations, the median time to PR or better was 1.9 months (range, 1.0-7.4 months) and 1.9 months (range, 1.0-6.1 months), respectively, and the median duration of PR or better was 5.5 months.

### Table 2: Overall Response and Clinical Benefit Rate

<table>
<thead>
<tr>
<th>Response Category</th>
<th>All-Treated Population (N = 157)</th>
<th>Triple-Class Refractory (n = 119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>VGPR</td>
<td>17 (11)</td>
<td>13 (11)</td>
</tr>
<tr>
<td>PR</td>
<td>28 (18)</td>
<td>18 (15)</td>
</tr>
<tr>
<td>Minimal response</td>
<td>25 (16)</td>
<td>16 (13)</td>
</tr>
<tr>
<td>ORR</td>
<td>46 (29) [22 to 37]</td>
<td>31 (26) [18 to 35]</td>
</tr>
<tr>
<td>CBR</td>
<td>71 (45) [37 to 53]</td>
<td>47 (39) [31 to 49]</td>
</tr>
</tbody>
</table>

NOTE. Data are expressed as no. (%) [95% CI].

Abbreviations: CBR, clinical benefit rate; CR, complete response; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

*Investigator assessed per the International Myeloma Working Group uniform response criteria.18

*Defined as the proportion of patients with a PR or better.

*Defined as the proportion of patients with a minimal response or better.
(95% CI, 3.9 to 7.6 months) and 4.4 months (95% CI, 3.4 to 7.6 months), respectively (Fig 2 and Data Supplement).

In the all-treated and triple-class–refractory populations, the median PFS was 4.2 months (95% CI, 3.4 to 4.9 months) and 3.9 months (95% CI, 3.0 to 4.6 months), respectively (Fig 3A). The median OS was 11.6 months (95% CI, 9.3 to 15.4 months) and 11.2 months (95% CI, 7.7 to 13.2 months), with an estimated 1-year event-free rate of 48.8% (95% CI, 39.6% to 57.4%) and 41.9% (95% CI, 31.6% to 51.8%), respectively (Fig 3B), at a median follow-up of 14 months (range, 10.8-18.7 months). Among responders, the median PFS was 8.5 months (95% CI, 5.4 to 13.4 months) and 8.5 months (95% CI, 5.3 to 13.4 months), and the median OS was 17.6 months (95% CI, 13.2 to 28.9 months) and 16.5 months (95% CI, 11.5 to 18.5 months) in the all-treated and triple-class–refractory populations, respectively (Data Supplement). Among patients in the all-treated population and the triple-class–refractory group (n = 70 and n = 52, respectively) who discontinued the study and initiated a new myeloma therapy, the median time to next therapy was 8.2 months (95% CI, 7.2 to 10.8 months) and 7.9 months (95% CI, 6.9 to 10.9 months), respectively. The median time to next therapy or death was 5.8 months (95% CI, 4.8 to 7.1 months) in the all-treated population and 5.3 months (95% CI, 4.5 to 6.3 months) in the triple-class–refractory group.

In a subgroup analysis, 19 of the 54 patients (35%) age 65-74 years and 8 of the 25 patients (32%) older than 75 years achieved a PR or better. In addition, a PR or better was achieved in 13 of the 55 patients (24%) with extramedullary

**FIG 3.** PFS and OS. Kaplan-Meier analysis of PFS (A) and OS (B) in the all-treated (N = 157) and triple-class–refractory (n = 119) populations. OS, overall survival; PFS, progression-free survival.
disease and 12 of the 59 patients (20%) with high-risk cytogenetics (Data Supplement). Among patients with MM refractory to previous alkylator therapy, the ORR was 21% (19 of the 92 patients achieved a PR or better, including one sCR, six VGPRs, and 12 PRs) and the CBR was 34% (Data Supplement). Among patients refractory to an alkylator in one previous line of therapy (n = 60), the ORR was 28% (CBR, 40%). In patients refractory to alkylators in multiple previous lines of therapy (n = 32), the ORR was 6% (CBR, 22%). Median PFS and OS in the subgroups analyzed were consistent with those of the all-treated population (Data Supplement).

Safety

Treatment-emergent AEs (TEAEs) were reported in all 157 patients (100%) in the all-treated population, with 149 (95%) reporting at least one melflufen-related TEAE (Table 3 and Data Supplement). Grade ≥ 3 TEAEs occurred in 150 patients (96%), most commonly neutropenia (124 [79%]), thrombocytopenia (120 [76%]), and anemia (67 [43%]). Any-grade and grade 3/4 bleeding events with concurrent grade 3/4 thrombocytopenia occurred in 25 patients (16%) and four patients (3%), respectively. The most common nonhematologic treatment-emergent grade 3/4 events included pneumonia (16 [10%]; grade 3, 14 [9%]; grade 4, two [1%]) and hypophosphatemia (eight [5%]; grade 3, eight [5%]; grade 4, 0). Grade 3/4 neutropenia with concurrent grade 3/4 infections occurred in 18 patients (11%); of these, 11 (7%) had pneumonia (Data Supplement). GI events occurred in 97 patients overall and were grade 1/2 in 90 of the 97 patients (93%) and grade 3 in seven of the 97 patients (7%). No grade 4 events were reported. The most common any-grade GI events included nausea (50 [32%]), diarrhea (42 [27%]), constipation (23 [15%]), and vomiting (21 [13%]). Mucositis occurred in one patient (1%; grade 1 event), and there were no reports of alopecia or neuropathy.

Serious TEAEs occurred in 77 patients (49%), most commonly pneumonia (14 [9%]) and febrile neutropenia (eight [5%]; Data Supplement). Second primary malignancies occurred in five patients; of these, four had malignancies with cutaneous manifestations (two patients with basal cell carcinoma, one patient with squamous cell carcinoma, and one patient with basal cell carcinoma, squamous cell carcinoma, and malignant melanoma; see the Data Supplement). One patient developed myelodysplasia after having received 17 cycles of study medication and in the context of multiple prior cycles of alkylator-based therapy, including stem-cell transplant prior to study entry. Moreover, the review of fluorescence in situ hybridization studies from the screening bone marrow confirmed pre-existing abnormalities supporting a subclinical myelodysplastic syndrome that was likely treatment-related and not otherwise apparent. No other cases of myelodysplastic syndromes were seen. Overall, 10 patients (6%) died from TEAEs. Most commonly, general physical health deterioration was associated with progressive disease (n = 3; 2%) and respiratory failure (n = 2; 1%; Data Supplement). None of the deaths were considered related to melflufen.

The average (standard deviation) monthly dose of melflufen received was 37.8 mg (± 4.0). TEAEs leading to melflufen dose reductions occurred in 42 patients (27%), most commonly thrombocytopenia (n = 22; 14%) and neutropenia (n = 5; 3%). While on study, 102 patients (65%) received concomitant RBC or platelet transfusion support, with 68 (43%) receiving platelet transfusion support only and 106 (68%) receiving concomitant growth factor support (Data Supplement). Overall, 34 patients (22%) had at least one TEAE leading to melflufen treatment discontinuation, most commonly thrombocytopenia (n = 16) and neutropenia (n = 5; Data Supplement). Overall, 95 patients (61%) experienced at least one dose delay, and the median number of treatment cycles with a dose delay was one (range, 0-9).

DISCUSSION

In this study, melflufen plus dexamethasone demonstrated meaningful efficacy and a manageable safety profile in patients with heavily pretreated RRMM. These findings build substantially on previously reported results but in a population that is more aligned with current treatment practice in the relapsed and refractory as well as highly resistant disease setting (ie, patients refractory to an anti-CD38 monoclonal antibody and/or pomalidomide, as well as exposed and refractory to prior lenalidomide, dexamethasone, and proteasome inhibitors). Durable responses were seen in this heavily pretreated population with a high proportion of extramedullary disease and high-risk cytogenetic features. Although the median DOR was 5.5 months, the median PFS among responders was encouragingly longer at 8.5 months. Furthermore, the median time to first response was 1.9 months, but many patients achieved their best response beyond 2 months of treatment. Altogether, these data support the notion that the clinical benefit of melflufen plus dexamethasone improves with longer treatment duration.

The ORR of 29% was consistent among high-risk patient subgroups, including those with triple-class–refractory disease (26%), those with extramedullary disease (24%), and patients age 75 years or older (32%), which is encouraging given the reported ORRs (10%-31%) in patients refractory to anti-CD38 monoclonal antibody therapy and/or with extramedullary disease at relapse. In fact, this is the largest population with extramedullary disease reported to date in a prospective study. Subgroup analyses showed sufficient efficacy in 60 patients refractory to an alkylator in one previous line of therapy with an ORR of 28%, while the ORR was only 6% in the 32 patients refractory to alkylators in two or more previous lines. Melflufen may have a mechanism of action that is different from that
of other alkylators. For example, melflufen induced cell death more effectively than melphalan in TP53-mutated cell lines and in cells from patients with TP53-mutated RRMM, suggesting that the mechanism of cytotoxicity of melflufen—but not that of other alkylators—is independent of p53 function. Unlike other newer agents that work via immune-based mechanisms (including chimeric antigen receptor T cell therapy, belantamab mafodotin, iberdomide, and isatuximab), melflufen adds a unique mechanism of action to the treatment landscape in

<table>
<thead>
<tr>
<th>TEAEa</th>
<th>Any-Gradeb</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
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<tr>
<td>Any,b,d</td>
<td>157 (100)</td>
<td>0</td>
<td>7 (4)</td>
<td>40 (25)</td>
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<td>Hematologic</td>
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<td>Neutropeniaa</td>
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<td>1 (&lt; 1)</td>
<td>4 (3)</td>
<td>50 (32)</td>
<td>74 (47)</td>
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<td>128 (82)</td>
<td>5 (3)</td>
<td>3 (2)</td>
<td>40 (25)</td>
<td>80 (51)</td>
</tr>
<tr>
<td>Anemiaa</td>
<td>111 (71)</td>
<td>3 (2)</td>
<td>41 (26)</td>
<td>66 (42)</td>
<td>1 (&lt; 1)</td>
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<td>Nonhematologic</td>
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<tr>
<td>Nausea</td>
<td>50 (32)</td>
<td>31 (20)</td>
<td>18 (11)</td>
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<td>17 (11)</td>
<td>25 (16)</td>
<td>4 (3)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
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<td>13 (8)</td>
<td>23 (15)</td>
<td>5 (3)</td>
<td>1 (&lt; 1)</td>
</tr>
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<td>Diarrhea</td>
<td>42 (27)</td>
<td>24 (15)</td>
<td>18 (11)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>38 (24)</td>
<td>24 (15)</td>
<td>11 (7)</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>26 (17)</td>
<td>16 (10)</td>
<td>10 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>25 (16)</td>
<td>3 (2)</td>
<td>19 (12)</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>23 (15)</td>
<td>18 (11)</td>
<td>4 (3)</td>
<td>1 (&lt; 1)</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>22 (14)</td>
<td>10 (6)</td>
<td>11 (7)</td>
<td>1 (&lt; 1)</td>
<td>0</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>22 (14)</td>
<td>14 (9)</td>
<td>6 (4)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>22 (14)</td>
<td>15 (10)</td>
<td>5 (3)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (13)</td>
<td>13 (8)</td>
<td>8 (5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>21 (13)</td>
<td>12 (8)</td>
<td>9 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>20 (13)</td>
<td>9 (6)</td>
<td>8 (5)</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>20 (13)</td>
<td>7 (4)</td>
<td>10 (6)</td>
<td>3 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20 (13c)</td>
<td>0</td>
<td>3 (2)</td>
<td>14 (9)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Back pain</td>
<td>19 (12)</td>
<td>9 (6)</td>
<td>9 (6)</td>
<td>1 (&lt; 1)</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>18 (11)</td>
<td>14 (9)</td>
<td>3 (2)</td>
<td>1 (&lt; 1)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17 (11)</td>
<td>14 (9)</td>
<td>3 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (11)</td>
<td>9 (6)</td>
<td>6 (4)</td>
<td>2 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>16 (10)</td>
<td>11 (7)</td>
<td>5 (3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Exertional dyspnea</td>
<td>16 (10)</td>
<td>13 (8)</td>
<td>3 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>16 (10)</td>
<td>9 (6)</td>
<td>6 (4)</td>
<td>1 (&lt; 1)</td>
<td>0</td>
</tr>
</tbody>
</table>

NOTE. Data are expressed as no. (%).
Abbreviation: TEAE, treatment-emergent adverse event.
aAdverse events are coded to the preferred term using MedDRA, version 19.1.
bAt each level of summarization (any event and preferred term), patients reporting more than one incidence of each adverse event are counted only once by maximum severity.
cTEAEs were defined as adverse events with onset date/time or increase in the severity level after the initial dose of study drug and within 30 days (unless considered related to study drug) after the last dose of study drug or initiation of new multiple myeloma therapy, whichever occurred sooner.
dIncludes 10 patients who experienced grade 5 TEAEs.
*Hematologic TEAEs of special interest were categorized by standardized MedDRA query. For anemia, the preferred terms under hematopoietic erythropenia were counted. For neutropenia, the preferred terms under hematopoietic leukopenia were combined. For thrombocytopenia, the preferred terms under hematopoietic thrombocytopenia were combined.
eIncludes one grade 5 event.
relapsed disease as a potent and novel cytotoxic agent targeting myeloma more broadly while providing meaningful clinical efficacy and a manageable safety profile for heavily pretreated RRMM.\textsuperscript{5,10,28-30}

The safety profile of melflufen primarily consisted of hematologic AEs, consistent with previous results.\textsuperscript{17} Despite cytopenias being common, the incidence of significant bleeding events or infections was low. Hematologic AEs were generally reversible and clinically manageable with dose adjustments, dose delays, growth factor use, platelet transfusions, and appropriate supportive care. Nonhematologic grade 3/4 AEs were infrequent, with infections being the most common. Moreover, the frequency of infections was generally consistent with the expected rates of infections in heavily pretreated patients.\textsuperscript{23,27,31} Specifically, the 10% rate of grade 3/4 pneumonia reported in HORIZON was similar to 9%-11% reported with pomalidomide plus dexamethasone, bortezomib plus dexamethasone, and selinexor plus dexamethasone in RRMM.\textsuperscript{23,27,31} GI toxicities, a common reason for treatment discontinuation with other agents,\textsuperscript{23} were infrequent, primarily grade 1/2, and did not lead to melflufen treatment cessation in HORIZON in any patient. Encouragingly, alopecia and treatment-emergent peripheral neuropathy were not reported. Patients were therefore able to tolerate treatment, with rates of discontinuation from AEs lower than or comparable with other studies (which range from 6% to 33%) in this patient population and with a prolonged median duration of treatment, together with the added convenience of monthly infusions, which is an especially important consideration in the current era of COVID-19.\textsuperscript{23,27,28}

In conclusion, the results from HORIZON suggest that melflufen has the potential to be an important therapeutic option in RRMM by providing a novel mechanism of action, clinically meaningful efficacy, and manageable safety when combined with dexamethasone in heavily pretreated patients.\textsuperscript{32} Based on these results, the efficacy and safety of melflufen plus dexamethasone versus pomalidomide plus dexamethasone are being further evaluated in OCEAN (OP-103), a randomized, global, phase III multicenter study (ClinicalTrials.gov identifier: NCT03151811) for patients in earlier relapse.\textsuperscript{33} Studies of melflufen plus dexamethasone in combination with bortezomib or daratumumab are also ongoing, with promising results to date.\textsuperscript{34}

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**PRIOR PRESENTATION**


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**CLINICAL TRIAL INFORMATION**

NCT02963493

**DATA SHARING STATEMENT**

Oncopeptides commits to share clinical study data with qualified researchers to enable enhancement of public health. As such, Oncopeptides will share anonymized patient-level data on request or if required by law or regulation. Qualified scientific and medical researchers can request patient-level data for studies of Oncopeptides pharmaceutical substances listed on ClinicalTrials.gov and approved by health authorities in the United States and the EU. Patient-level data for studies of newly approved pharmaceutical substances or indications can be requested 9 months after US Food and Drug Administration and European Medicines Agency approval. Such requests are assessed at Oncopeptides’ discretion, and the decisions depend on the scientific merit of the proposed request, data availability, and the purpose of the proposal. The applicants should be willing to submit both positive and negative findings to a scientific journal. If Oncopeptides agrees to share clinical data for research purposes, the applicant is required to sign an agreement for data sharing before data release, to ensure that the patient data are de-identified. In case of any risk of re-identification on anonymized data despite measures to protect patient confidentiality, the data will not be shared. The patients’ informed consent
REFERENCES

17. Richardson et al
AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Melffuflen and Dexamethasone in Heavily Pretreated Relapsed and Refractory Multiple Myeloma

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No other potential conflicts of interest were reported.

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**APPENDIX**

**TABLE A1. HORIZON (OP-106) Investigators and Recruitment Sites**

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<th>Principal Investigator</th>
<th>Recruitment Site</th>
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<tbody>
<tr>
<td>Paul Richardson</td>
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<td>Joan Bladé</td>
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<td>Ematologia “L. e A. Seragnoi”—PAD 8. Policlinico Sant’Orsola-Malpighi</td>
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<tr>
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<td>Memorial Sloan Kettering Cancer Center</td>
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<td><strong>John Hiemenz</strong></td>
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<tr>
<td>Maxim Norkin</td>
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<tr>
<td>Jan Moreb</td>
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<td>Hudson Valley Hematology and Oncology Associates</td>
</tr>
<tr>
<td>Amitabha Mazumder</td>
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*For institutions at which a principal investigator change occurred throughout the course of the study, the current principal investigator is listed in bold.*