

ORIGINAL ARTICLE

Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma

A. Chari, D.T. Vogl, M. Gavriatopoulou, A.K. Nooka, A.J. Yee, C.A. Huff, P. Moreau, D. Dingli, C. Cole, S. Lonial, M. Dimopoulos, A.K. Stewart, J. Richter, R. Vij, S. Tuchman, M.S. Raab, K.C. Weisel, M. Delforge, R.F. Cornell, D. Kaminetzky, J.E. Hoffman, L.J. Costa, T.L. Parker, M. Levy, M. Schreder, N. Meuleman, L. Frenzel, M. Mohty, S. Choquet, G. Schiller, R.L. Comenzo, M. Engelhardt, T. Illmer, P. Vlummens, C. Doyen, T. Facon, L. Karlin, A. Perrot, K. Podar, M.G. Kauffman, S. Shacham, L. Li, S. Tang, C. Picklesimer, J.-R. Saint-Martin, M. Crochiere, H. Chang, S. Parekh, Y. Landesman, J. Shah, P.G. Richardson, and S. Jagannath

ABSTRACT

BACKGROUND

Selinexor, a selective inhibitor of nuclear export compound that blocks exportin 1 (XPO1) and forces nuclear accumulation and activation of tumor suppressor proteins, inhibits nuclear factor κ B, and reduces oncoprotein messenger RNA translation, is a potential novel treatment for myeloma that is refractory to current therapeutic options.

METHODS

We administered oral selinexor (80 mg) plus dexamethasone (20 mg) twice weekly to patients with myeloma who had previous exposure to bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, and an alkylating agent and had disease refractory to at least one proteasome inhibitor, one immunomodulatory agent, and daratumumab (triple-class refractory). The primary end point was overall response, defined as a partial response or better, with response assessed by an independent review committee. Clinical benefit, defined as a minimal response or better, was a secondary end point.

RESULTS

A total of 122 patients in the United States and Europe were included in the modified intention-to-treat population (primary analysis), and 123 were included in the safety population. The median age was 65 years, and the median number of previous regimens was 7; a total of 53% of the patients had high-risk cytogenetic abnormalities. A partial response or better was observed in 26% of patients (95% confidence interval, 19 to 35), including two stringent complete responses; 39% of patients had a minimal response or better. The median duration of response was 4.4 months, median progression-free survival was 3.7 months, and median overall survival was 8.6 months. Fatigue, nausea, and decreased appetite were common and were typically grade 1 or 2 (grade 3 events were noted in up to 25% of patients, and no grade 4 events were reported). Thrombocytopenia occurred in 73% of the patients (grade 3 in 25% and grade 4 in 33%). Thrombocytopenia led to bleeding events of grade 3 or higher in 6 patients.

CONCLUSIONS

Selinexor–dexamethasone resulted in objective treatment responses in patients with myeloma refractory to currently available therapies. (Funded by Karyopharm Therapeutics; STORM ClinicalTrials.gov number, NCT02336815.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Jagannath at the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, 1470 Madison Ave., 3rd Fl., New York, NY 10029, or at sundar.jagannath@mountsinai.org.

Drs. Richardson and Jagannath contributed equally to this article.

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DESPITE THE AVAILABILITY OF PROTEASOME inhibitors, immunomodulatory agents, and monoclonal antibodies for multiple myeloma, most patients will have a relapse and refractory disease will develop. An increasing number of patients have triple-class refractory myeloma, defined as disease refractory to proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies, with most patients being treated with all five agents currently in use (carfilzomib, bortezomib, lenalidomide, pomalidomide, and daratumumab; i.e., penta-exposed). Overall survival in patients with myeloma refractory to these classes is short; patients with daratumumab-refractory myeloma have a median overall survival of 1.7 to 3.0 months.¹⁻⁴ Currently, these patients have no treatment options with proven clinical benefit.^{4,5}

Exportin 1 (XPO1) — the sole known nuclear exporter of tumor suppressor proteins, the glucocorticoid receptor, and oncoprotein messenger RNAs (mRNAs) — is overexpressed in myeloma and correlates with increased bone disease and shorter survival.⁶⁻¹¹ Selinexor, which was recently approved by the Food and Drug Administration, is a potent, oral, selective inhibitor of nuclear export that binds to Cys528 in the cargo-binding pocket of XPO1,¹²⁻¹⁴ forcing the nuclear localization and functional activation of tumor-suppressor proteins, trapping $\kappa B\alpha$ in the nucleus to suppress nuclear factor κB activity, and preventing oncoprotein mRNA translation.^{9,10,15} Selective induction of apoptosis in malignant hematologic and solid tumor cells is a result.⁹ Preclinical studies have shown that selinexor with or without dexamethasone induces apoptosis in a number of myeloma cell lines and has antitumor activity in animal models.^{3,8,9,16,17}

Administration of selinexor (80 mg) with dexamethasone (20 mg) according to two dosing schedules had been evaluated among patients with myeloma refractory to either four or five drugs in Part 1 of the phase 2 STORM (Selinexor Treatment of Refractory Myeloma) study.¹⁸ In that heterogeneous population, 21% of patients had a partial response or better. On the basis of those findings, the activity of selinexor at a dose of 80 mg twice weekly was examined in a more uniform population in the pivotal STORM Part 2 study.

METHODS

TRIAL DESIGN AND OVERSIGHT

The STORM study was a phase 2b, multicenter, open-label study involving patients enrolled from May 2015 through March 2018 at 60 sites in the United States and Europe. The institutional review board or independent ethics committee at each study center approved the protocol (available with the full text of this article at NEJM.org), and the study was performed in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. The study was designed by the sponsor (Karyopharm Therapeutics). Disease response was adjudicated by an independent review committee of four physicians. The sponsor collected the data and analyzed them in conjunction with the authors. A professional medical writer, funded by the sponsor, wrote the first draft of the manuscript under close direction of the authors. The authors reviewed and revised the manuscript, had access to all data, and vouch for the completeness and accuracy of the data and for the adherence of the study to the protocol.

PATIENTS

Eligible patients had measurable myeloma according to International Myeloma Working Group (IMWG) criteria^{19,20} (see the Supplementary Appendix, available at NEJM.org); had previously received treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids, and an alkylating agent; and had disease refractory to at least one immunomodulatory drug, one proteasome inhibitor, daratumumab, glucocorticoids, and their most recent regimen. Refractory disease was defined as progression during treatment or within 60 days after completion of therapy, or less than 25% response to therapy.^{19,20} An Eastern Cooperative Oncology Group performance-status score of 0 to 2 (scores range from 0 to 5, with higher scores reflecting greater disability) and adequate hepatic function, renal function, and hematopoietic function were required. Systemic light-chain amyloidosis, active central nervous system involvement, peripheral neuropathy of grade 3 or higher, or painful neuropathy of grade 2 or

higher were exclusion criteria. A full list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix. Written informed consent was obtained from all patients before enrollment.

TREATMENT

Oral selinexor (80 mg) in combination with dexamethasone (20 mg) was administered on days 1 and 3, weekly, in 4-week cycles until disease progression, death, or discontinuation. A dose-modification protocol was used for the management of adverse events (Tables S2 and S3 in the Supplementary Appendix). All patients were required to receive 8 mg of ondansetron (or equivalent) before the first dose of study drug and two or three times daily as needed. Other antiemetics (olanzapine and neurokinin-1 receptor antagonists) were permitted for patients with unacceptable side effects to ondansetron (or its equivalent) or with persistent nausea. Supportive measures were provided at the discretion of the investigator and may have included intravenous fluids, hematopoietic growth factors, transfusions, appetite stimulants (olanzapine and megestrol acetate), or a combination of these.

END POINTS AND ASSESSMENTS

The primary end point was overall response, defined as a confirmed partial response ($\geq 50\%$ reduction in the serum level of myeloma protein) or better, with response adjudicated by the independent review committee.²¹ Secondary end points included response duration; clinical benefit, defined as a confirmed minimal response (≥ 25 to $< 50\%$ reduction in the serum level of myeloma protein) or better; progression-free survival; and overall survival. (Definitions of end points are provided in the Supplementary Appendix.) Disease-specific assessments were conducted at baseline, day 1 of each treatment cycle, and at the time of disease progression or suspected response. High-risk cytogenetic abnormalities included del(17p), t(4;14), t(14;16), and gain(1q) chromosomal abnormalities on fluorescence in situ hybridization.²² Quality of life was assessed with the Functional Assessment of Cancer Therapy–Multiple Myeloma questionnaire (see the protocol). Safety and side-effect profile were assessed through history taking, physical examination, laboratory assessments,

and 12-lead electrocardiography. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.²³

PHARMACODYNAMICS AND RESPONSE PREDICTOR

Methods regarding measurement of XPO1 mRNA induction and immunohistochemical analysis of glucocorticoid receptor induction are included in the Supplementary Appendix. A predictive biomarker of response to selinexor was sought in patients with myeloma with the use of the VIPER (Virtual Inference of Protein-activity by Enriched Regulon analysis) algorithm, which can transform gene-expression profiles from tumor samples into accurate predictions of protein activity for approximately 6000 regulatory proteins (DarwinHealth) (see the Supplementary Appendix).²⁴ RNA levels in CD138+ cells that were isolated from the pretreatment bone marrow aspirate of patients enrolled in the STORM Part 2 study were used for this analysis.

STATISTICAL ANALYSIS

The sample size was based on assumptions for penta-exposed, triple-class refractory myeloma with a minimal threshold of 10% of patients with a partial response or better.¹⁹ For the primary efficacy analysis, a sample of 122 patients allowed for a one-sided test at an alpha level of 0.025 to detect a minimum of 20% of patients with a partial response or better against a value of 10% under the null hypothesis with 90% power. The modified intention-to-treat population was used for the primary efficacy analysis; this population comprised all enrolled patients who met all eligibility criteria or received a waiver to enroll from the sponsor (12 patients; waivers were granted only in situations in which patient safety was not compromised and the scientific integrity of the study was not affected) and who received at least one dose of selinexor plus dexamethasone. The safety population included all patients who received at least one dose of study drug. The primary analysis used a two-sided, exact 95% confidence interval, calculated for the percentage of patients with a partial response or better in the modified intention-to-treat population, with statistical significance declared if the lower boundary of this interval

was more than 10%. Summary statistics were computed and displayed for each of the defined analysis populations and according to each assessment time point. Summary statistics for continuous variables minimally included number, mean, standard deviation, minimum, median, and maximum. For categorical variables, frequencies and percentages are presented. For time-to-event variables, the Kaplan–Meier method was used for descriptive summaries.

RESULTS

PATIENTS

A total of 123 patients were enrolled, all of whom were included in the safety population (Fig. S1 in the Supplementary Appendix). One patient did not meet full eligibility criteria (no previous carfilzomib); therefore, 122 patients were included in the modified intention-to-treat population. The median age was 65.2 years, and the median duration of myeloma was 6.6 years; 53% of the patients had high-risk cytogenetic abnormalities (Table 1, and Table S4 in the Supplementary Appendix). All patients had progressive myeloma at the time of enrollment, and the disease was typically rapidly progressive: 107 patients (88%) with available data on myeloma protein levels at both screening and the first day of therapy (median, 12 days) had a median increase in disease burden of 22%. Creatinine clearance was less than 60 ml per minute in 39 patients (32%) and less than 40 ml per minute in 14 patients (11%). The median number of previous therapies was 7 (range, 3 to 18); 86 patients (70%) had previously received daratumumab in combination with other agents, 102 (84%) had previously undergone stem-cell transplantation, and 2 (2%) had previously received chimeric antigen receptor T-cell (CAR-T) therapy. In the modified intention-to-treat population, all patients had penta-exposed myeloma that was refractory to at least one proteasome inhibitor, one immunomodulatory drug, and daratumumab, as required by the protocol. A total of 83 patients (68%) were documented to have penta-refractory myeloma. It is notable that 96% of the patients had myeloma that was refractory to the most potent agent of each class: carfilzomib, pomalidomide, and daratumumab (Table 1).

TREATMENT DURATION AND DOSES

Of the 123 patients enrolled, 118 (96%) discontinued treatment, with disease progression and adverse events the most common reasons (Table S1 in the Supplementary Appendix). At the last date of follow-up (August 17, 2018), 5 patients (4%) continued to receive treatment; 34 (28%) had discontinued treatment and remained in follow-up for long-term survival. The median duration of treatment with selinexor plus dexamethasone was 9.0 weeks (range, 1 to 60).

EFFICACY

A partial response or better was observed in 26% of patients (95% confidence interval [CI], 19 to 35), including 2 stringent complete responses (in 2% of the patients), 6 very good partial responses (in 5%), and 24 partial responses (in 20%) (Table 2); because the lower boundary of the confidence interval was more than 10%, the trial met its primary end point. Both patients with relapse after CAR-T therapy had a partial response. Minimal response according to IMWG criteria was observed in 16 patients (13%), and 48 patients (39%) had stable disease, whereas 26 (21%) had progressive disease or disease that could not be evaluated for response. The median time to a partial response or better was 4.1 weeks (range, 1 to 14). A minimal response or better was observed in 39% of patients (95% CI, 31 to 49). Additional response analyses are shown in Table 2. The median duration of response was 4.4 months (95% CI, 3.7 to 10.8) (Fig. 1). The median progression-free survival was 3.7 months (95% CI, 3.0 to 5.3), and the median overall survival was 8.6 months (95% CI, 6.2 to 11.3) (Fig. 2A and 2B). In patients who had a partial response or better or a minimal response or better, the median overall survival was 15.6 months (Fig. 2C).

SAFETY PROFILE

The most common adverse events that emerged during treatment were thrombocytopenia (in 73% of the patients), fatigue (in 73%), nausea (in 72%), and anemia (in 67%) (Table 3). The most common grade 3 or 4 adverse events were thrombocytopenia (in 59% of the patients), anemia (in 44%), hyponatremia (in 22%), and neutropenia (in 21%). Thrombocytopenia occurred

Table 1. Baseline Demographic and Clinical Characteristics in the Modified Intention-to-Treat Population.*

Characteristic	Value (N=122)
Age	
Median (range) — yr	65.2 (40–86)
Distribution — no. (%)	
18–50 yr	8 (7)
51–64 yr	52 (43)
65–75 yr	44 (36)
>75 yr	18 (15)
Male sex — no. (%)	71 (58)
ECOG performance-status score — no. (%)†	
0	36 (30)
1	71 (58)
2	11 (9)
Missing data	4 (3)
Chromosomal abnormality — no. (%)	
High risk overall‡	65 (53)
del(17p)/p53	32 (26)
t(4;14)	17 (14)
t(14;16)	5 (4)
gain(1q)	40 (33)
Median time since initial diagnosis (range) — yr	6.6 (1.1–23.4)
Median no. of previous treatment regimens (range)	7 (3–18)
Previous therapies to which the disease was refractory — no. (%)§	
≥1 Immunomodulatory drug, ≥1 proteasome inhibitor, and daratumumab	122 (100)
Carfilzomib, pomalidomide, and daratumumab	117 (96)
Carfilzomib, lenalidomide, pomalidomide, and daratumumab	101 (83)
Bortezomib, carfilzomib, pomalidomide, and daratumumab	94 (77)
Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab¶	83 (68)

* A total of 123 patients were enrolled; 1 patient did not meet eligibility criteria, so 122 patients were included in the modified intention-to-treat population. Percentages may not total 100 because of rounding.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores reflecting greater disability.

‡ This category includes any of del(17p)/p53, t(14;16), t(4;14), or 1q21 (1q gain >2).

§ The disease was defined as refractory to an antimyeloma therapy if the best response to the therapy was stable disease or worse or if the patient had progression or a relapse either during treatment or within 60 days after discontinuing the therapy.

¶ Myeloma that was refractory to these five agents was considered to be penta-refractory.

more frequently in patients who had thrombocytopenia at baseline than in those who did not (Fig. S2 in the Supplementary Appendix), and six patients with thrombocytopenia of grade 3 or higher had a concurrent bleeding event of grade 3 or higher. Most nonhematologic adverse events

were limited in severity to grades 1 or 2, with only 10% of patients having grade 3 nausea and 3% having grade 3 vomiting.

In all, 18% of the patients discontinued study treatment because of an adverse event considered by the investigator to be related to selinexor or

Variable	Patients Included in Analysis	Patients with Partial Response or Better	Patients with Minimal Response or Better
	number	number (percent)	
Total	122	32 (26)	48 (39)
Previous therapies to which the disease was refractory			
Bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab	83	21 (25)	31 (37)
Carfilzomib, lenalidomide, pomalidomide, and daratumumab	101	26 (26)	37 (37)
Bortezomib, carfilzomib, pomalidomide, and daratumumab	94	25 (27)	36 (38)
Carfilzomib, pomalidomide, and daratumumab	117	31 (26)	45 (38)
R-ISS disease stage			
I	20	7 (35)	10 (50)
II	78	21 (27)	32 (41)
III	23	4 (17)	6 (26)
Measurable free light chains			
Yes	35	15 (43)	19 (54)
No	87	17 (20)	29 (33)
High-risk cytogenetic abnormality†	65	12 (18)	24 (37)

* Overall response was defined as a partial response ($\geq 50\%$ reduction in the serum level of myeloma protein) or better, and clinical benefit was defined as a minimal response ($\geq 25\%$ to $< 50\%$ reduction in the serum level of myeloma protein) or better. Among the 122 patients, the best response to therapy was a stringent complete response in 2 (2%), a very good partial response in 6 (5%), a partial response in 24 (20%), a minimal response in 16 (13%), stable disease in 48 (39%), and progressive disease or disease that could not be evaluated for response in 32 (26%). R-ISS denotes Revised International Staging System.

† This category included any of del(17p)/p53, t(14;16), t(4;14), or 1q21 (1q gain > 2).

dexamethasone, although such determinations for a new agent are imprecise (Table S5 in the Supplementary Appendix). Adverse events leading to dose modification or interruption occurred in 80% of the patients, with the majority of events occurring in the first two cycles. The most common adverse events leading to dose reduction or interruption were thrombocytopenia (in 43% of the patients), fatigue (in 16%), and neutropenia (in 11%). Supportive care — including granulocyte colony-stimulating factors, thrombopoietin-receptor agonists, appropriate fluid and caloric intake, appetite stimulants, psychostimulants, and additional antiemetic agents — usually reduced the intensity or duration of adverse events. Side effects were reversible without evidence of toxic effects in major organs (treatment-related cardiac, pulmonary, hepatic, or renal dysfunction of grade 3 or higher) or cumulative toxic effects, with irreversible acute kidney injury reported in one patient (1%).

Serious adverse events occurred in 63% of the patients, with pneumonia (in 11%) and sepsis (in 9%) being the most common (Table S6 in the Supplementary Appendix). A total of 28 patients died during the study — 16 from disease progression and 12 from an adverse event. In the 12 patients with these adverse events, 2 events were assessed by the investigator as being related to treatment (pneumonia with concurrent disease progression [in 1 patient] and sepsis [in 1]).

BIOMARKERS OF SELINEXOR RESPONSE IN MULTIPLE MYELOMA

The binding of selinexor to XPO1 leads to rapid inactivation of nuclear export, XPO1 protein degradation, and induction of XPO1 mRNA transcription (without new protein production).⁹ XPO1 mRNA induction is one pharmacodynamic marker in selinexor-treated patients, as observed from blood samples obtained before and after selinexor administration, as well as enhanced glucocorti-

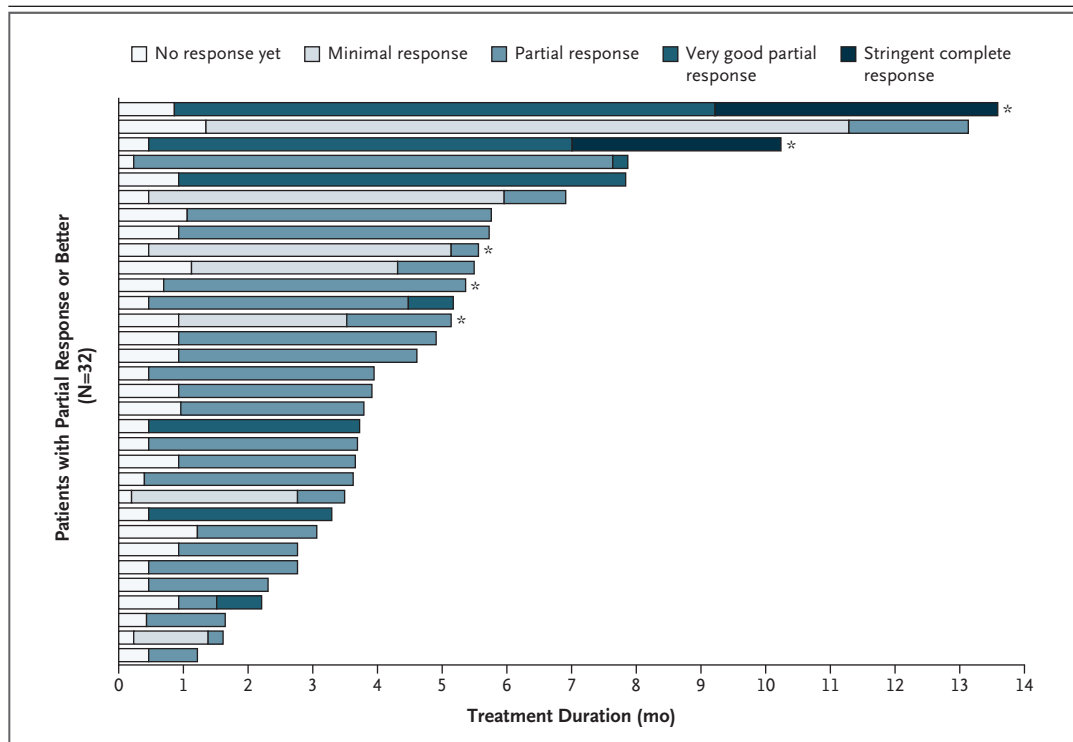


Figure 1. Duration of Response to Treatment.
 An asterisk indicates that the patient was still receiving treatment at the date of data cutoff.

coid receptor nuclear localization (Fig. S5 in the Supplementary Appendix).^{25,26} A model based on a linear discriminant analysis classifier that was trained on 35 pretreatment patient samples, including 16 obtained from patients who had a response and 19 from patients who did not have a response, identified four master regulators: IRF3, ARL2BP, ZBTB17, and ATRX (Fig. S7 in the Supplementary Appendix). The four-protein classifier had a high predictive performance according to leave-one-out cross-validation (area under the receiver-operating-characteristic curve [AUC], 0.862; 95% CI, 0.741 to 0.982). The four-protein classifier was then validated in an independent, blinded analysis of 12 samples obtained from patients with myeloma who were enrolled in Parts 1 and 2 of the STORM study (AUC, 0.770; 95% CI, 0.456 to 1.000). Specifically, four of five patients who had a response and six of seven who did not have a response to selinexor were correctly identified by the marker, yielding a prediction accuracy of 83% (95% CI, 55 to 95). Training the classifier with the use of differential gene-expression data alone produced no effective classification.

DISCUSSION

In this trial, 26% of the patients with penta-exposed, triple-class refractory myeloma who received oral selinexor, a first-in-class XPO1 inhibitor, with dexamethasone twice weekly had a partial response or better. Two patients had stringent complete responses, and 6 had very good partial responses. Although all patients entered the study with progressive disease, 26 (21%) had persistent disease progression or their disease could not be evaluated for response. Among the patients who had a response, efficacy was consistent across subgroups, including patients with high-risk cytogenetic abnormalities (53% of the patients).

The results of this study are notable for several reasons. The trial was permissive, allowing patients with reduced renal function, thrombocytopenia, and neutropenia to enroll. These patients were heavily pretreated, with a median of 7 previous therapeutic regimens, including a median of 10 unique antimyeloma agents. Patients had rapidly progressing myeloma, with a 22%

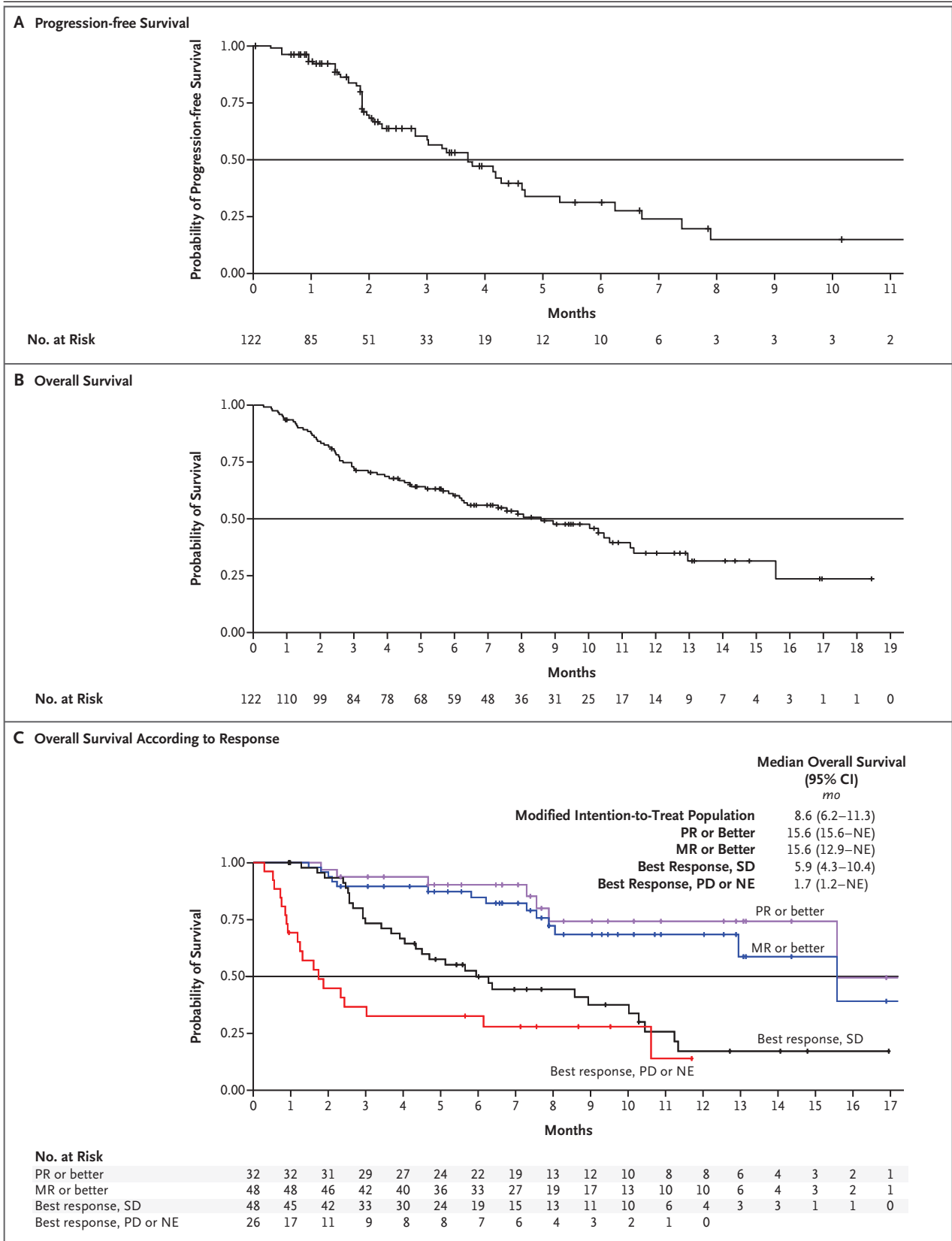


Table 3. Adverse Events That Emerged during Treatment.*

Event	Grade 1	Grade 2	Grade 3	Grade 4	Total (N = 123)
	<i>number (percent)</i>				
≥1 Adverse event					123 (100)
Hematologic adverse events					
Thrombocytopenia	12 (10)	6 (5)	31 (25)	41 (33)	90 (73)
Anemia	7 (6)	22 (18)	53 (43)	1 (1)	83 (67)
Neutropenia	7 (6)	16 (13)	22 (18)	4 (3)	49 (40)
Leukopenia	8 (7)	16 (13)	17 (14)	0	41 (33)
Lymphopenia	2 (2)	4 (3)	10 (8)	4 (3)	20 (16)
Nonhematologic adverse events					
Fatigue	16 (13)	43 (35)	31 (25)	0	90 (73)
Nausea	34 (28)	42 (34)	12 (10)	0	88 (72)
Decreased appetite	22 (18)	41 (33)	6 (5)	0	69 (56)
Decreased weight	34 (28)	27 (22)	1 (1)	0	62 (50)
Diarrhea	32 (26)	15 (12)	9 (7)	0	56 (46)
Vomiting	22 (18)	21 (17)	4 (3)	0	47 (38)
Hyponatremia	18 (15)	0	26 (21)	1 (1)	45 (37)
Upper respiratory tract infection	3 (2)	23 (19)	2 (2)	0	28 (23)
Constipation	16 (13)	9 (7)	2 (2)	0	27 (22)
Dyspnea	11 (9)	11 (9)	5 (4)	0	27 (22)
Cough	14 (11)	7 (6)	0	0	21 (17)
Hypokalemia	10 (8)	3 (2)	8 (7)	0	21 (17)
Insomnia	13 (11)	6 (5)	2 (2)	0	21 (17)
Mental status changes	7 (6)	7 (6)	7 (6)	0	21 (17)
Pneumonia	0	8 (7)	10 (8)	1 (1)	21 (17)†
Dizziness	14 (11)	5 (4)	0	0	19 (15)
Pyrexia	11 (9)	8 (7)	0	0	19 (15)
Epistaxis	11 (9)	3 (2)	1 (1)	0	15 (12)
Fall	9 (7)	4 (3)	2 (2)	0	15 (12)
Hyperglycemia	2 (2)	3 (2)	8 (7)	0	13 (11)
Peripheral edema	8 (7)	3 (2)	2 (2)	0	13 (11)
Blurred vision	8 (7)	3 (2)	2 (2)	0	13 (11)

* Shown are events that occurred in at least 10% of the patients. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.²³

† The total includes two events of grade 5.

Figure 2 (facing page). Kaplan–Meier Analysis of Progression-free Survival, Overall Survival, and Overall Survival According to Response.

CI denotes confidence interval, MR minimal response, NE not able to be evaluated, PD progressive disease, PR partial response, and SD stable disease. Tick marks indicate censored data.

increase in disease burden in the 12 days from screening to initial therapy. These characteristics are consistent with the growing population of patients who have exhausted available therapies but still desire to continue therapy.

Given the rapid progression of penta-exposed, triple-class refractory myeloma, the window of opportunity to prevent further illness and death is small. Therefore, the regimen that was used in the STORM study began with a high dose of selinexor to achieve rapid disease control. Because most patients involved in the study were older and frail, with limited end-organ reserve and an increased risk for adverse events, dose modifications were anticipated and were specified along with supportive care in the protocol. The adverse events that were observed in the study were a function of dose, schedule, and baseline clinical characteristics (e.g., cytopenias). Thrombocytopenia, which is due in part to inhibition by selinexor of thrombopoietin signaling in early megakaryopoiesis, was reversible and was managed with dose interruptions and thrombopoietin-receptor agonists.²⁷ Although this study establishes the activity of selinexor with dexamethasone, combination regimens are typically used in patients with myeloma. Preclinical studies of selinexor show enhancement of $\text{I}\kappa\text{B}$, which supports its synergy in combination with proteasome inhibitors, additivity with immunomodulatory drugs, and sensitization of myeloma cells to anti-CD38 monoclonal antibodies.²⁸⁻³⁰

In conclusion, the results of the STORM Part 2 study showed that oral selinexor with low-dose dexamethasone induced responses in 26% of patients with refractory myeloma. The most common toxic effects of grade 3 or higher included thrombocytopenia without bleeding, anemia, neutropenia without fever, and hyponatremia.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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The authors' full names and academic degrees are as follows: Ajai Chari, M.D., Dan T. Vogl, M.D., Maria Gavriatopoulou, M.D., Ajay K. Nooka, M.D., Andrew J. Yee, M.D., Carol A. Huff, M.D., Philippe Moreau, M.D., David Dingli, M.D., Ph.D., Craig Cole, M.D., Sagar Lonial, M.D., Meletios Dimopoulos, M.D., A. Keith Stewart, M.B., Ch.B., Joshua Richter, M.D., Ravi Vij, M.D., Sascha Tuchman, M.D., Marc S. Raab, M.D., Katja C. Weisel, M.D., Michel Delforge, M.D., Ph.D., Robert F. Cornell, M.D., David Kaminetzky, M.D., James E. Hoffman, M.D., Luciano J. Costa, M.D., Ph.D., Terri L. Parker, M.D., Moshe Levy, M.D., Martin Schreder, M.D., Nathalie Meuleman, M.D., Ph.D., Laurent Frenzel, M.D., Ph.D., Mohamad Mohty, M.D., Ph.D., Sylvain Choquet, M.D., Gary Schiller, M.D., Raymond L. Comenzo, M.D., Monika Engelhardt, M.D., Thomas Illmer, M.D., Philip Vlummens, M.D., Chantal Doyen, M.D., Thierry Facon, M.D., Lionel Karlin, M.D., Aurore Perrot, M.D., Ph.D., Klaus Podar, M.D., Ph.D., Michael G. Kauffman, M.D., Ph.D., Sharon Shacham, Ph.D., Lingling Li, Ph.D., Shijie Tang, Ph.D., Carla Picklesimer, B.S., Jean-Richard Saint-Martin, B.S., Marsha Crochiere, Ph.D., Hua Chang, Ph.D., Samir Parekh, M.B., B.S., Yosef Landesman, Ph.D., Jatin Shah, M.D., Paul G. Richardson, M.D., and Sundar Jagannath, M.B., B.S.

The authors' affiliations are as follows: the Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai (A.C., S.P., S.J.), and New York University Langone Medical Center (D.K.) — both in New York; the Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia (D.T.V.); the School of Medicine, National and Kapodistrian University of Athens, Athens (M.G., M. Dimopoulos); the Winship Cancer Institute, Emory University, Atlanta (A.K.N., S.L.); Massachusetts General Hospital Cancer Center (A.J.Y.), Tufts Medical Center (R.L.C.), and the Dana-Farber Cancer Institute (P.G.R.), Boston, and Karyopharm Therapeutics, Newton (M.G.K., S.S., L.L., S. Tang, C.P., J.-R.S.-M., M.C., H.C., Y.L., J.S.) — all in Massachusetts; Johns Hopkins University, Baltimore (C.A.H.); the University of Nantes, Nantes (P.M.), Hôpital Necker (L.F.), Hôpital Saint-Antoine (M.M.), and La Pitié-Salpêtrière Hospital (S.C.), Paris, University Hospital, Lille (T.F.), Centre Hospitalier Lyon Sud, Pierre-Benite (L.K.), and Centre Hospitalo-Universitaire Vandoeuvre-lès-Nancy, Nancy (A.P.) — all in France; the Mayo Clinic, Rochester, MN (D.D.); the University of Michigan, Ann Arbor (C.C.); the Mayo Clinic of Arizona, Phoenix (A.K.S.); Hackensack University Medical Center, Hackensack, NJ (J.R.); Washington University School of Medicine, St. Louis (R.V.); Lineberger Comprehensive Cancer Center at University of North Carolina—Chapel Hill, Chapel Hill (S. Tuchman); the University of Heidelberg, Heidelberg (M.S.R.), University Medical Center Hamburg-Eppendorf, Hamburg (K.C.W.), the University of Tübingen, Tübingen (K.C.W.), University Hospital Würzburg, Würzburg (M.S.), the University of Freiburg, Freiburg (M.E.), and Gemeinschaftspraxis Hämatologie-Onkologie, Dresden (T.I.) — all in Germany; the University of Leuven, Leuven (M. Delforge), Institut Jules Bordet, Université Libre de Bruxelles, Brussels (N.M.), University Hospital Ghent, Ghent (P.V.), and Centre Hospitalier Universitaire Université Catholique de Louvain Namur, Yvoir (C.D.) — all in Belgium; Vanderbilt University Medical Center, Nashville (R.F.C.); Sylvester Cancer Center, University of Miami, Miami (J.E.H.); the University of Alabama at Birmingham, Birmingham (L.J.C.); Yale School of Medicine, New Haven, CT (T.L.P.); Baylor University Medical Center, Dallas (M.L.); the David Geffen School of Medicine at the University of California, Los Angeles, Los Angeles (G.S.); and University Hospital Krems, Karl Landsteiner University of Health Sciences, Krems an der Donau, Austria (K.P.).

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