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FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Tuesday, February 26, 2019  
12:30 p.m. to 5:00 p.m.

FDA White Oak Campus  
White Oak Conference Center  
Building 31, The Great Room  
Silver Spring, Maryland

1 **Meeting Roster**

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3 **Lauren Tesh, PharmD, BCPS**

4 Division of Advisory Committee and Consultant

5 Management

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16 Professor of Biostatistics and Bioinformatics

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15    Jay and Lori Eisenberg Distinguished Professor  
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17    Professor of Medicine, Department of  
18    Thoracic Head & Neck Medical Oncology  
19    The University of Texas MD Anderson Cancer Center  
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1     **Alice T. Shaw, MD, PhD**

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3     Massachusetts General Hospital

4     Paula O’Keeffe Endowed Chair in Thoracic Oncology

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9     **Brian I. Rini, MD, FACP**

10    *(Chairperson)*

11    Professor of Medicine, Lerner College of Medicine

12    Leader, GU Program

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10 **ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBER (Non-**  
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12 **Phuong Khanh (P.K.) Morrow, MD, FACP**

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1     **Clifton C. Mo, MD**

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1       **FDA PARTICIPANTS (Non-Voting)**

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3       Director, Oncology Center of Excellence, FDA

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13      **Nicole Gormley, MD**

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17      **Andrea C. Baines, MD, PhD**

18      Clinical Reviewer

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P R O C E E D I N G S

(12:30 p.m.)

**Call to Order**

**Introduction of Committee**

1 DR. RINI: Good afternoon, everyone. We're  
2 going to go ahead and get started. I'd first like  
3 to remind everyone to silence your cell phones or  
4 other devices if you've not already done so. I  
5 would also like to identify the FDA press contact,  
6 Amanda Turney.  
7

8 Amanda, if you're present, if you could  
9 please stand and give us a wave. Thank you.  
10

11 The first thing we'll do is go around the  
12 table and have everyone introduce themselves and  
13 their affiliation, and we'll start with P.K.  
14

15 DR. MORROW: Good afternoon. P.K. Morrow.  
16 I'm a medical oncologist, and I'm employed by  
17 Amgen.  
18

19 DR. MO: Good afternoon. Clifton Mo. I'm a  
20 staff hematologist and a stem cell transplant  
21 director at Walter Reed Military Medical Center in  
22 Bethesda, Maryland.

1 DR. HARRINGTON: Dave Harrington,  
2 biostatistician, Dana Farber Cancer Institute,  
3 Harvard School of Public Health.

4 DR. THANARAJASINGAM: Gita Thanarajasingam.  
5 I'm a staff hematologist and health outcomes  
6 researcher at the Mayo Clinic in Rochester,  
7 Minnesota.

8 DR. COMPAGNI PORTIS: Natalie Compagni  
9 Portis. I'm the patient representative on the  
10 meeting today.

11 DR. HAWKINS: Good afternoon. Randy  
12 Hawkins, private practice, Englewood, California,  
13 consumer representative.

14 DR. SHAW: Alice Shaw, medical oncology,  
15 Mass General Hospital in Boston.

16 DR. ULDRICK: Thomas Uldrick, medical  
17 oncologist, Fred Hutchinson Cancer Research Center,  
18 Seattle.

19 DR. HINRICHS: Christian Hinrichs, medical  
20 oncologist, National Cancer Institute in Bethesda.

21 DR. RINI: I'm Brian Rini. I'm a GU medical  
22 oncologist at Cleveland Clinic.

1 DR. TESH: Lauren Tesh, designated federal  
2 officer.

3 DR. KLEPIN: Heidi Klepin. I'm a geriatric  
4 oncologist at Wake Forest School of Medicine.

5 DR. CRISTOFANILLI: Massimo Cristofanilli,  
6 medical oncologists at Northwest University in  
7 Chicago.

8 DR. HALABI: Susan Halabi, biostatistician,  
9 Duke University.

10 DR. PAPADIMITRAKOPOULOU: Vali  
11 Papadimitrakopoulou, medical oncology at MD  
12 Anderson Cancer Center.

13 DR. BAINES: Andrea Baines, hematologist  
14 with the Division of Hematology Products at FDA.

15 DR. GORMLEY: Nicole Gormley, hematologist  
16 with the FDA, division of Hematology Products.

17 DR. FARRELL: Ann Farrell,  
18 hematologist/oncologist, Division of Hematology  
19 Products.

20 DR. PAZDUR: Richard Pazdur, FDA.

21 DR. RINI: For topics such as those being  
22 discussed at today's meeting, there are often a

1 wide variety of opinions, some of which are quite  
2 strongly held. Our goal is that today's meeting  
3 will be a fair and open forum for discussion of  
4 these issues and that individuals can express their  
5 views without interruption. As a gentle reminder,  
6 individuals will be allowed to speak into the  
7 record only if recognized by the chairperson. We  
8 look forward to a productive meeting.

9 In the spirit of the Federal Advisory  
10 Committee Act and the Government in the Sunshine  
11 Act, we ask that advisory committee members take  
12 that their conversations about the topic at hand  
13 take place in the open forum of the meeting. We  
14 are aware that members of the media are anxious to  
15 speak with FDA about these proceedings, however,  
16 FDA will refrain from discussing the details of  
17 this meeting with the media until its conclusion.  
18 Also, the committee is reminded to please refrain  
19 from discussing the meeting topic during the break.  
20 Thank you.

21 Now, I'll pass it to Lauren Tesh, who will  
22 read the Conflict of Interest Statement.

### **Conflict of Interest Statement**

1  
2 DR. TESH: The Food and Drug Administration  
3 is convening today's meeting of the Oncologic Drugs  
4 Advisory Committee under the authority of the  
5 Federal Advisory Committee Act of 1972. With the  
6 exception of the industry representative, all  
7 members and temporary voting members of the  
8 committee are special government employees or  
9 regular federal employees from other agencies and  
10 are subject to federal conflict of interest laws  
11 and regulations.

12 The following information on the status of  
13 this committee's compliance with federal ethics and  
14 conflict of interest laws, covered by but not  
15 limited to those found at 18 U.S.C. Section 208, is  
16 being provided to participants in today's meeting  
17 and to the public.

18 FDA has determined that members and  
19 temporary voting members of this committee are in  
20 compliance with federal ethics and conflict of  
21 interest laws. Under 18 U.S.C. Section 208,  
22 Congress has authorized FDA to grant waivers to

1 special government employees and regular federal  
2 employees who have potential financial conflicts  
3 when it is determined that the agency's need for a  
4 special government employee's service outweighs his  
5 or her potential financial conflict of interest or  
6 when the interest of a regular federal employee is  
7 not so substantial as to be deemed likely to affect  
8 the integrity of the services which the government  
9 may expect from the employee.

10 Related to the discussion of today's  
11 meeting, members and temporary voting members of  
12 this committee have been screened for potential  
13 financial conflicts of interest of their own, as  
14 well as those imputed to them, including those of  
15 their spouses or minor children, and for purposes  
16 of 18 U.S.C. Section 208, their employers. These  
17 interests may include investments; consulting;  
18 expert witness testimony; contracts, grants,  
19 CRADAs; teaching, speaking, writing; patents and  
20 royalties; and primary employment.

21 Today's agenda involves discussion of new  
22 drug application 212306 for selinexor tablets,

1 application submitted by Karyopharm Therapeutics,  
2 Inc. The proposed indication used for this product  
3 is in combination with dexamethasone for the  
4 treatment of patients with relapsed refractory  
5 multiple myeloma, who have received at least  
6 three prior therapies and whose disease is  
7 refractory to at least one proteasome inhibitor, at  
8 least one immunomodulatory agent, and one anti-CD38  
9 monoclonal antibody.

10 This is a particular matters meeting during  
11 which specific matters related to Karyopharm's NDA  
12 will be discussed. Based on the agenda for today's  
13 meeting and all financial interests reported by the  
14 committee members and temporary voting members, no  
15 conflict of interest waivers have been issued in  
16 connection with this meeting. To ensure  
17 transparency, we encourage all standing committee  
18 members and temporary voting members to disclose  
19 any public statements that they may have made  
20 concerning the product at issue.

21 With respect to FDA's invited industry  
22 representative, we would like to disclose that

1 Dr. P.K. Morrow is participating in the meeting as  
2 a nonvoting industry representative acting on  
3 behalf of regulated industry. Dr. Morrow's role at  
4 this meeting is to represent industry in general  
5 and not any particular company. Dr. Morrow is  
6 employed by Amgen.

7 We would like to remind members and  
8 temporary voting members that if the discussions  
9 involve any other products or firms not already on  
10 the agenda for which an FDA participant has a  
11 personal or imputed financial interest, the  
12 participants need to exclude themselves from such  
13 involvement, and their exclusion will be noted for  
14 the record. FDA encourages all other participants  
15 to advise the committee of any financial  
16 relationships that they may have with the firm at  
17 issue. Thank you.

18 DR. RINI: Thank you, Lauren.

19 We'll now proceed with FDA's introductory  
20 comments from Dr. Nicole Gormley.

21 **FDA Introductory Comments - Nicole Gormley**

22 DR. GORMLEY: Good afternoon. I'm Nicole

1 Gormley, a hematologist with the FDA's Division of  
2 Hematology Products. I'm the cross-discipline team  
3 leader for this application and will present a  
4 brief introduction to the selinexor application and  
5 the issues this application presents.

6 There are 9 drugs currently approved for the  
7 treatment of relapsed or refractory multiple  
8 myeloma. Four new drugs or biologics have been  
9 approved since 2015, including an HDAC inhibitor,  
10 an oral proteasome inhibitor, and two monoclonal  
11 antibodies.

12 These tables show the drug and biologic  
13 regimens approved for the treatment of relapsed  
14 refractory multiple myeloma with the approvals  
15 after 2015 shown in the right table. Unlike solid  
16 tumors, in some cases, patients with multiple  
17 myeloma may be retreated with the same agent or  
18 with the same agent combined with different  
19 combination partners.

20 The proposed indication, selinexor, an oral  
21 XPO inhibitor, is indicated in combination with  
22 dexamethasone for the treatment of patients with

1 relapsed refractory multiple myeloma who've  
2 received at least 3 prior therapies and whose  
3 disease is refractory to at least one proteasome  
4 inhibitor, at least one immunomodulatory agent, and  
5 an anti-CD38 monoclonal antibody.

6           The pivotal studies supporting the  
7 application is KCP-330-012, which I will  
8 subsequently refer to as STORM. STORM was a  
9 single-arm trial of the combination of selinexor  
10 and dexamethasone. Eligible patients were those  
11 with multiple myeloma who had received at least  
12 3 prior therapies, were refractory to a  
13 glucocorticoid proteasome inhibitor, IMiD and  
14 daratumumab, and were refractory to their most  
15 recent anti-myeloma therapy.

16           The STORM trial has design elements that  
17 impact the interpretability of the results. First,  
18 this is a single-arm trial of a combination  
19 regimen. Because two agents are combined in this  
20 setting, it is difficult to isolate the activity of  
21 selinexor. The agency has issued guidance on the  
22 development of combination therapies. While the

1 guidance describes the combination of two or more  
2 new investigational drugs, the principles espoused  
3 in the guidance are applicable to this situation as  
4 well.

5 In general, when considering development of  
6 a combination regimen, there should be a strong  
7 biological rationale for the use of the  
8 combination. For example, each agent might inhibit  
9 a different target in the same pathway. There  
10 should also be demonstration of the contribution of  
11 each individual drug to the combination. This can  
12 be accomplished through the use of factorial  
13 designs. An example is a trial that evaluates drug  
14 A combined with drug B, versus drug A, versus drug  
15 B, versus standard of care.

16 The STORM trial was a single-arm trial of a  
17 combination regimen. Eligible patients were those  
18 with relapsed refractory multiple myeloma who had  
19 received at least 3 prior lines of therapy.  
20 Patients received selinexor in combination with  
21 dexamethasone until disease progression,  
22 unacceptable toxicity, or death. The primary

1 endpoint of the trial was overall response rate.

2           The overall response rate observed in the  
3 STORM trial was 25 percent with a duration of  
4 response of only 4.4 months. Historical trials of  
5 high-dose dexamethasone have demonstrated response  
6 rates between 18 and 27 percent in patients with  
7 relapsed or refractory multiple myeloma, but these  
8 trials evaluated higher doses of dexamethasone, and  
9 it is difficult to extrapolate these results to the  
10 current era of novel agents when patients may  
11 receive more lines of therapy and are exposed to  
12 more dexamethasone because it is a backbone of  
13 standard therapies.

14           A more recent trial, which used a  
15 dexamethasone-alone backbone was the MM-003 trial  
16 conducted to support the approval of pomalidomide.  
17 Patients were enrolled between 2011 and 2012. The  
18 trial compared pomalidomide in combination with  
19 low-dose dexamethasone to high-dose dexamethasone  
20 in patients with relapsed multiple myeloma.

21           All patients had received prior  
22 dexamethasone but were not refractory to

1 dexamethasone in their most recent treatment  
2 regimen. Patients had received a median of 5 prior  
3 lines, and their response rate with dexamethasone  
4 alone was 4 percent based on IRC assessment and was  
5 10 percent based on investigator assessment. These  
6 response rates are more likely to resemble what  
7 could be expected in the current era.

8 I will now discuss what is known about the  
9 single agent activity of selinexor. In the phase 1  
10 trial of selinexor conducted in patients with  
11 advanced hematologic malignancies, there were  
12 81 patients with multiple myeloma. The trial  
13 evaluated dosing with selinexor alone and selinexor  
14 in combination with dexamethasone. There was one  
15 response among the 56 patients who received  
16 selinexor alone, and in fact, this patient received  
17 dexamethasone as a concomitant medication, so  
18 ultimately there were no patients with multiple  
19 myeloma who responded to selinexor alone.

20 There were 6 responses among 25 patients who  
21 received selinexor in combination with  
22 dexamethasone. This data suggest that

1 dexamethasone may potentiate the activity of  
2 selinexor, but again, it is difficult to know the  
3 contribution of selinexor. Most importantly, this  
4 study highlights that there was no single-agent  
5 activity with selinexor alone, even at doses higher  
6 than what is currently proposed. This study will  
7 be further discussed during the FDA clinical  
8 presentation.

9           The other aspect to consider is that  
10 single-arm trials can be challenging to interpret.  
11 Without a control arm, it can be challenging to put  
12 the results of a single-arm trial in context. This  
13 is especially true for interpretation of safety  
14 results. To illustrate this further, I am showing  
15 you the results of a trial conducted in patients  
16 with relapsed refractory AML with selinexor,  
17 study KCP-330-008. The selinexor arm had a CR/CRI  
18 rate of 12 percent; 77 percent of patients  
19 experienced an SAE; and there were 85 deaths amount  
20 118 patients. The median overall survival was 94  
21 days.

22           The results may seem expected and even

1 reasonable for this disease, however, this was a  
2 randomized trial comparing selinexor to physician's  
3 choice. Physician's choice included best  
4 supportive care, low-dose AraC, and hypomethylating  
5 agents. The trial showed a worse overall survival  
6 trend for the selinexor arm. It is only because we  
7 have comparative data that we are able to fully  
8 interpret the safety and efficacy of selinexor in  
9 this patient population. This study of selinexor  
10 in patients with relapsed refractory AML will also  
11 be further discussed during the FDA clinical  
12 presentation.

13 I will now discuss the top level efficacy  
14 and safety results observed in a STORM trial. The  
15 primary endpoint was overall response rate assessed  
16 by IRC based on IMWG criteria. The evaluable  
17 patient population consisted of 122 patients. The  
18 overall response rate was 25 percent and the median  
19 duration of response was only 4.4 months.

20 With regards to safety, all patients  
21 enrolled experienced a treatment-emergent adverse  
22 event or TEAE. The most frequent TEAEs are listed

1 here. Severe, debilitating, or life-threatening  
2 TEAEs occurred in 95 percent of patients. Serious  
3 adverse events occurred in 60 percent of patients.  
4 TEAEs leading to dose modification or permanent  
5 discontinuation occurred in 89 percent of patients.  
6 The median duration on treatment at the proposed  
7 dose of 80 milligrams twice weekly was only 3 and a  
8 half weeks.

9           There were 23 deaths, 13 due to disease  
10 progression and 10 due to TEAEs. To put this  
11 information in further context, this table contains  
12 the incidence of SAEs, TEAEs resulting in treatment  
13 interruption, dose reduction, discontinuation and  
14 death in the initial trials of 3 recently approved  
15 multiple myeloma drugs compared to that observed  
16 with selinexor. Notably, the rates of TEAEs  
17 resulting in dose interruption, dose reduction,  
18 discontinuation, and death are higher with  
19 selinexor.

20           In summary, the issues presented by this  
21 application are, one, this is a single-arm trial of  
22 a combination regimen. There is no single-agent

1 activity of selinexor alone in patients with  
2 relapsed refractory multiple myeloma, while the  
3 trial design of STORM, we cannot isolate the  
4 treatment effect of selinexor, and it can be  
5 challenging to interpret single-arm trial data,  
6 especially when the product is associated with  
7 significant toxicity.

8           Second, selinexor was associated with  
9 significant toxicity in a phase 2, single-arm  
10 trial. There was a high rate of severe TEAEs,  
11 SAEs, and death. A randomized-controlled trial in  
12 relapsed refractory AML demonstrated a worse  
13 overall survival trend. For products that have  
14 significant toxicity, randomized controlled trials  
15 can provide additional information and allow for  
16 more accurate risk-benefit assessment.

17           Lastly, there were high rates of dose  
18 modifications and discontinuations; 89 percent of  
19 patients had a dose reduction, interruption, or  
20 discontinuation due to an adverse event. Patients  
21 remained on the proposed dose for only 3 and a half  
22 weeks. This high rate suggests that the optimal

1 dose has not been identified.

2 To further evaluate the activity of  
3 selinexor in patients with relapsed refractory  
4 multiple myeloma, the applicant has conducted the  
5 BOSTON trial. This is a randomized phase 3 trial  
6 of selinexor in combination with bortezomib and  
7 dexamethasone compared to bortezomib and  
8 dexamethasone alone. Eligible patients are those  
9 with relapsed refractory multiple myeloma who  
10 received 1 to 3 prior lines of therapy. The  
11 primary endpoint is progression-free survival as  
12 assessed by an IRC. Accrual is complete to this  
13 trial. Based on communication from the applicant,  
14 top-line data is expected later this year with a  
15 target regulatory submission in 2020.

16 Of note, if selinexor is not approved at  
17 this time, there are several expanded access or  
18 compassionate use mechanisms through which  
19 selinexor could be made available to patients.  
20 These include individual patient INDs, including  
21 for emergency use; intermediate-sized patient  
22 population INDs or protocols; and treatment INDs or

1 protocols.

2 I'd like to briefly review the evidentiary  
3 criteria for approval. It is important to note the  
4 drugs granted accelerated approval or traditional  
5 approval must meet the same statutory requirements  
6 for safety and effectiveness. For effectiveness,  
7 there must be substantial evidence of effectiveness  
8 based on adequate and well-controlled clinical  
9 investigations. For safety, there must be  
10 sufficient information to determine whether the  
11 drug is safe for use under the conditions  
12 prescribed, recommended, or suggested in the  
13 proposed labeling.

14 We would like for the committee to discuss  
15 whether the STORM data are conclusive to allow for  
16 an adequate assessment of the safety and efficacy  
17 in the proposed patient population and whether  
18 selinexor provides a benefit that outweighs the  
19 risk. The voting question is should the approval  
20 of selinexor be delayed until results of the  
21 randomized phase 3 trial, BOSTON, are available.  
22 Thank you very much.

1 DR. RINI: Thank you.

2 Both FDA and the public believe in a  
3 transparent process for information gathering and  
4 decision making. To ensure such transparency at  
5 the advisory committee meeting, FDA believes that  
6 it is important to understand the context of an  
7 individual's presentation. For this reason, FDA  
8 encourages all participants, including the  
9 sponsor's nonemployee presenters, to advise the  
10 committee of any financial relationships that they  
11 have with the firm at issue such as consulting  
12 fees, travel expenses, honoraria, and interest in  
13 the sponsor, including equity interest and those  
14 based on the outcome of this meeting.

15 Likewise, FDA encourages you at the  
16 beginning of your presentation to advise the  
17 committee if you do not have such financial  
18 relationships. If you choose not to address this  
19 issue of financial relationships at the beginning  
20 of your presentation, it will not preclude you from  
21 speaking, and we'll now proceed with the  
22 applicant's presentations.

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**Applicant Presentation - Tanya Lewis**

MS. LEWIS: Good afternoon. My name is Tanya Lewis, senior vice president of regulatory affairs at Karyopharm Therapeutics. We're pleased to present data supporting accelerated approval of selinexor for patients with triple-class refractory multiple myeloma. Here's the agenda for our presentation. Following my introduction, our speakers will review the unmet need, selinexor efficacy and safety, clinical perspective, and provide a conclusion. Additional experts shown here have been reimbursed for their time and expenses.

Now turning to our discussion for the day, selinexor is an oral, novel, anti-multiple myeloma agent that offers patients with triple-class refractory myeloma a new pathway to treat their cancer by selectively inhibiting as exportin 1 or XPO1. The proposed indication is as follows.

Selinexor, an oral XPO1 inhibitor is indicated in combination with dexamethasone for the treatment of patients with relapsed refractory

1 multiple myeloma who have received at least three  
2 prior therapies and whose disease is refractory to  
3 at least one proteasome inhibitor, at least one  
4 immunomodulatory agent, and an anti-CD38 monoclonal  
5 antibody.

6           These patients with triple-class refractory  
7 disease have exhausted all other treatment options  
8 with demonstrated efficacy. This means that their  
9 myeloma has become refractory to the three most  
10 effective classes of anti-myeloma therapies. It is  
11 also refractory to glucocorticoids such as  
12 dexamethasone, and these patients rapidly succumb  
13 to myeloma in 3.5 to 5.6 months.

14           Our application is supported by STORM part  
15 2. In this study, selinexor met its prespecified  
16 primary endpoint of overall response rate. The  
17 rate and depth of response is comparable to recent  
18 anti-myeloma therapies, which also received  
19 accelerated approvals in patients with markedly  
20 less refractory disease.

21           Additionally, selinexor has a  
22 well-characterized safety profile. The common AEs

1 include thrombocytopenia, nausea and vomiting,  
2 fatigue, and decreased appetite. Physicians can  
3 prevent, monitor, and manage adverse events with  
4 supportive care and dose modifications, and we have  
5 prepared educational programs and materials for  
6 physicians and patients about potential adverse  
7 events.

8 Selinexor provides a positive benefit to  
9 risk profile for patients with triple-class  
10 refractory myeloma and fulfills the three criteria  
11 necessary for accelerated approval. First,  
12 refractory myeloma is an incurable, serious, and  
13 life-threatening disease. Survival in these  
14 patients is very short.

15 Second, there are no available therapies  
16 with demonstrated efficacy for these patients. It  
17 is in this setting, STORM part 2 showed a response  
18 rate of 25.4 percent, and this increased to  
19 26.2 percent as of the last update.

20 Third, in myeloma, the overall response rate  
21 is known to predict for longer overall survival.  
22 This response rate in triple-class refractory

1 myeloma is similar to that of other products that  
2 received accelerated approval in myeloma. This  
3 includes carfilzomib, pomalidomide plus low-dose  
4 dexamethasone, and daratumumab, each of which had a  
5 response rate ranging between 22.9 and 29.2 percent  
6 in patients with single or double-class refractory  
7 myeloma.

8 This study design, number of patients, and  
9 endpoints were all similar to STORM, but none of  
10 these studies were in patients with triple-class  
11 refractory disease. Each accelerated approval was  
12 subsequently confirmed in a randomized study and  
13 granted regular approval.

14 Moving to the confirmatory study, BOSTON,  
15 the BOSTON phase 3 randomized-controlled trial is  
16 fully enrolled, but approval will not occur for at  
17 least another 2 years based on NDA submission in  
18 late 2020. BOSTON is designed to confirm the  
19 clinical benefit of selinexor in combination with  
20 bortezomib and low-dose dexamethasone against  
21 bortezomib and low-dose dexamethasone alone. The  
22 study was based on positive phase 1 results, and

1 the design has been agreed upon with the FDA. FDA  
2 has asked you to vote on whether selinexor approval  
3 should be delayed at least 2 years until approval  
4 based on BOSTON. The patients with triple-class  
5 refractory myeloma cannot wait and need urgent  
6 access to selinexor.

7 Thank you. I now invite Dr. Richardson to  
8 discuss the serious unmet need.

9 **Applicant Presentation - Paul Richardson**

10 DR. RICHARDSON: Thank you, and good  
11 afternoon. My name is Dr. Paul Richardson. I am  
12 the RJ Corman Professor of Medicine at Harvard  
13 Medical School, and I serve as clinical program  
14 leader and director of clinical research at the  
15 Jerome Lipper Multiple Myeloma Center. It was my  
16 privilege to be involved as the principal  
17 investigator in numerous studies evaluating new  
18 myeloma therapies in the United States over the  
19 last 15 years, and I'm here today to describe the  
20 urgent need for novel therapies to improve outcomes  
21 for all patients with triple-class refractory  
22 myeloma.

1           It's important to note that multiple myeloma  
2           is the second most common hematologic cancer and  
3           remains incurable despite recent progress.  
4           Unfortunately, more than 12,900 patients in the  
5           U.S. alone are expected to die from myeloma this  
6           year. Patients with relapsed refractory myeloma  
7           have a seven-fold higher risk of developing  
8           infections, which are a major cause of death.  
9           Profound immunosuppression is characteristic of  
10          advanced disease, and multisystem organ  
11          dysfunction, including renal failure, is typical.

12           Mortality increases with each relapse as  
13          myeloma becomes more refractory to treatment and  
14          patients develop complex mechanisms of resistance.  
15          There are 5 drugs and 3 classes of anti-myeloma  
16          therapy that have shown single-agent efficacy used  
17          with or without steroids. These include  
18          immunomodulatory agents, proteasome inhibitors, and  
19          the anti-CD38 monoclonal antibody, daratumumab.  
20          Several additional drugs, which have no single  
21          agent activity, have been approved but only in  
22          combination with one of these three classes.

1       Essentially, all patients will ultimately relapse  
2       and develop disease that is refractory to currently  
3       available therapy.

4               Against this background, it's key to know  
5       that dexamethasone is ineffective in triple-class  
6       refractory myeloma, whether used at high dose or  
7       low dose. The lack of low-dose efficacy is  
8       supported by a consensus paper from experts in  
9       relapsed refractory myeloma acknowledging that  
10      low-dose dexamethasone has no significant activity  
11      in patients with triple-class refractory disease  
12      and should not be therefore used alone.

13              To clarify information presented in the FDA  
14      briefing book regarding high-dose dexamethasone,  
15      the 27 and 18 percent response rates come from  
16      studies, first in 1986 in the pre-novel therapy  
17      era, and second, in 2005 amongst patients who had  
18      not received lenalidomide or pomalidomide, nor any  
19      of the proteasome inhibitors, or daratumumab.  
20      These results therefore do not reflect today's  
21      standard of care. The only recent study from 2013  
22      of high-dose dexamethasone in relapsed refractory

1 myeloma demonstrated an IRC adjudicated response  
2 rate of 4 percent, which is negligible.

3 Patients with the most refractory myeloma,  
4 those who have exhausted the three major classes of  
5 therapeutic options, have so-called triple-class  
6 refractory disease. This is based first on the  
7 accepted definitions of relapsed and refractory  
8 disease, which is no response to a therapy or  
9 progression while on or within 60 days following  
10 treatment; and second, does not reflect the lines  
11 of prior treatment nor number of agents, but rather  
12 entire classes of therapy. In this case,  
13 proteasome inhibitors, IMiDs, and CD38 targeted  
14 monoclonal antibodies. Thus, we can define  
15 single-, double-, and triple-class refractory  
16 myeloma.

17 By the time a person's disease becomes  
18 triple-class refractory, almost all have received  
19 the 5 major drugs as well as alkylating agents and  
20 glucocorticoids. These patients have no other  
21 options with known clinical benefit.

22 Response rates correlate with clinical

1 benefit and improved outcomes for our patients with  
2 myeloma. The International Myeloma Working Group  
3 has established well-accepted and uniform  
4 myeloma-specific response criteria. An objective  
5 response is important for patients; first because  
6 we have reversed or minimized end-organ damage;  
7 second, responses have been validated to  
8 consistently correlate with improvements in  
9 survival. And finally, it's important to note that  
10 minimal response or better matters.

11 As we have shown in randomized phase 3  
12 clinical trials of relapsed refractory disease,  
13 minimal response clearly translates into meaningful  
14 clinical benefit. In contrast, the correlation  
15 between responses and survival in relapsed  
16 refractory AML, for example, is inconsistent and  
17 not what we see in myeloma.

18 The life expectancy for heavily pretreated  
19 patients with relapsed and refractory myeloma is  
20 tragically short. We consistently find median  
21 survival ranging from 3.5 to 5.6 months in patients  
22 with triple-class refractory myeloma, which is

1 distinguished in the MAMMOTH study from 3 drug  
2 resistance disease as shown. As a point of  
3 reference, this population best aligns with those  
4 patients treated in STORM.

5           Importantly, the two sources of clinical  
6 trial data shown here reflect current practice and  
7 are highly consistent. It's also a key point of  
8 emphasis that myeloma rapidly accelerates following  
9 multiple relapses and the development of  
10 increasingly refractory disease. The patient's  
11 prognosis becomes very poor as time between  
12 subsequent relapses gets shorter and the burden of  
13 disease magnifies. Therefore, efficacy is our  
14 number one goal and why we must consider adverse  
15 events in this context.

16           We know that serious adverse events are  
17 common with small-molecule based anti-myeloma  
18 therapies in patients with heavily pretreated and  
19 advanced disease, and this truly reflects the  
20 vulnerability of this population.

21           In a study with pomalidomide alone and  
22 pomalidomide plus low-dose dexamethasone, serious

1 adverse events occurred in 62 to 67 percent of  
2 patients, and adverse events lead to mortality in 5  
3 to 7 percent of patients. Similarly, in studies of  
4 carfilzomib, serious adverse events occurred in 47  
5 to 59 percent of patients, and adverse events led  
6 to death in 4 to 10 percent of patients.

7 In summary, there is an urgent need for new  
8 and novel therapies for patients with triple-class  
9 refractory disease. Despite recent approvals of  
10 several anti-myeloma agents, there are no approved  
11 treatments with demonstrated benefit for these  
12 patients; instead, we're often left with best  
13 supportive care. In this advanced stage of  
14 myeloma, the primary goal is to rapidly control the  
15 disease and reduce tumor burden to improve outcome.

16 I believe selinexor is a key new option and  
17 could provide clinical benefit for patients with  
18 triple-class refractory myeloma, who in my opinion  
19 constitutes a patient population with an exquisite  
20 unmet medical need. Thank you, and I will now  
21 invite Dr. Shah to discuss the STORM part 2 trial  
22 results.

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**Applicant Presentation - Jatin Shah**

DR. SHAH: Thank you, Dr. Richardson.

My name is Jatin Shah, and I lead a clinical development program at Karyopharm. Previously, I spent nine years at MD Anderson Cancer Center in the Department of Lymphoma and Myeloma, seeing patients and conducting clinical research. Today, I will review the selinexor mechanism of action and efficacy data. Let's first start with the mechanism of action.

There are 8 major exportins. Exportin 1, or XPO1, is responsible for inactivating tumor suppressor protein function by transporting them from the nucleus to the cytoplasm. By overexpressing XPO1, malignant cells will bypass the regulatory function of tumor suppressor proteins, permitting uncontrolled growth. XPO1 is known to be overexpressed in multiple myeloma and correlates with a poor prognosis.

Inhibition of XPO1 forces the nuclear retention of active tumor suppressor proteins such as p53, FOXO, and I-kappa-B. Selinexor

1 specifically inhibits XPO1 and subsequently leads  
2 to the accumulation of these active tumor  
3 suppressor proteins in the nucleus. This allows  
4 apoptosis to occur in malignant cells while sparing  
5 normal cells and leading to broad anticancer  
6 activity in both hematologic and solid tumors.  
7 Selinexor also demonstrates synergy with  
8 dexamethasone by up regulating glucocorticoid  
9 receptor expression and its activity.

10 Now, turning to an overview of clinical data  
11 for selinexor, study 001 demonstrated that  
12 selinexor monotherapy induced stable disease and  
13 minimal responses, and dexamethasone further  
14 increased deepened responses. This dose-finding  
15 study enrolled patients with heavily pretreated  
16 disease refractory myeloma and progressive disease  
17 at baseline. Selinexor monotherapy was evaluated  
18 in 35 patients, and across all of those ranges  
19 57 percent achieved a stable disease or a minimal  
20 response. These results support further evaluation  
21 in combination with dexamethasone.

22 The recommended dose for patients with

1 triple-class refractory myeloma is selinexor 80  
2 milligrams administered twice weekly with  
3 dexamethasone 20 milligrams. 80 milligrams had a  
4 better response rate than 60 milligrams with a  
5 50 percent overall response rate. This recommended  
6 dose was confirmed in STORM part 1.

7 Now, I will review the study design of the  
8 pivotal study. STORM part 2 was a phase 2b  
9 open-labeled, single-arm study of selinexor in  
10 combination with low-dose dexamethasone in patients  
11 with triple-class refractory myeloma. Patients  
12 were permitted to enter the study as early as  
13 2 weeks following their last therapy. Responses  
14 were determined by an independent review committee  
15 and assessments were made according to the  
16 International Myeloma Working Group response  
17 criteria.

18 The primary endpoint was overall response  
19 rate, and secondary endpoints included duration of  
20 response, clinical benefit rate, which is defined  
21 as patients with greater than or equal to a  
22 25 percent reduction in their disease burden, as

1 well as overall survival.

2           STORM part 2's inclusion criteria were broad  
3 and representative of typical patients, allowing  
4 patients to enroll who are often excluded from  
5 other studies. There was no upper age limit in  
6 patients older than 75 who were enrolled. Patients  
7 with moderate to severe renal dysfunction were  
8 permitted, as were patients with grade 2 cytopenias  
9 with neutrophils of at least 1,000 and platelets as  
10 low as 50,000. The study also permitted patients  
11 with prior infections, thromboembolic disease, and  
12 heart disease, and allowed any concomitant  
13 medication.

14           Moving to demographics, 123 patients were  
15 enrolled. One patient was excluded who had not  
16 received prior carfilzomib, and therefore 122  
17 patients were included in the efficacy analysis.  
18 The median age was 65, and note that 15 percent of  
19 patients were above the age of 75. This was a  
20 global trial, and 69 percent of patients were  
21 enrolled in the U.S.

22           All patients had documented triple-class

1 refractory multiple myeloma, and all patients had  
2 documented disease refractory to glucocorticoids,  
3 and in fact had a meeting of 6 prior  
4 glucocorticoid-containing regimens. Overall,  
5 patients had been treated with a median of 7 prior  
6 treatment regimens, and remember in myeloma, each  
7 regimen usually consist of 2 to 4 drugs in  
8 combination. Fifty-three percent of patients had  
9 high risk disease, and therefore, patients enrolled  
10 in STORM part 2 had the most refractory disease  
11 included in any myeloma trial to date.

12 I do want to note patients entering the  
13 study had rapidly progressive disease with a median  
14 increase in their disease burden of 22 percent in  
15 just the 12 days from screening to the first dose  
16 of selinexor. This highlights the urgent need for  
17 rapid disease control in this patient population in  
18 order to prevent further complications and  
19 associated morbidity and mortality.

20 Now turning to efficacy, 25.4 percent of  
21 patients achieve a partial response or better as  
22 defined by the IMWG and assessed by an IRC, and

1 therefore the study met the primary endpoint.  
2 Importantly, selinexor was able to achieve a  
3 significant depth of response with 2 patients  
4 achieving a stringent complete response, and both  
5 were MRD negative. Another six patients achieved a  
6 very good partial remission, which is a 90 percent  
7 reduction in their disease burden.

8 We see further evidence of clinical benefit  
9 as 39.3 percent of patients achieved at least a 25  
10 percent reduction in their disease burden. In  
11 addition, both patients who entered the study after  
12 relapsing, after experimental CAR T-cell therapy,  
13 both achieved a partial response.

14 Next, we look at dose response, and we found  
15 that patients who received the recommended dose of  
16 80 milligrams twice weekly in cycle 1 had the best  
17 response at 32.1 percent. In contrast, patients  
18 who received less than or equal to 60 milligrams  
19 twice weekly saw their overall response rates drop  
20 by half.

21 We also look at other factors that they may  
22 affect response rate, and we found that selinexor

1 was effective across subgroups, including  
2 demographics and regardless of prior therapy. This  
3 supports a lack of cross-resistance and is  
4 consistent with a novel mechanism of action.

5 In addition, when looking at the maximum  
6 reduction in the M protein markers depicted in this  
7 waterfall plot, 71 percent of patients had a  
8 reduction in their disease burden. And remember,  
9 these patients entering the study had rapidly  
10 progressive disease with a 22 percent increase in  
11 their disease burden in those 12 days between  
12 screening and cycle 1/day 1.

13 Now moving to our secondary endpoints, the  
14 median duration of response was 4.4 months, and  
15 importantly, the median time to response was less  
16 than 1 month, which is relevant and meaningful in  
17 these patients who had their rapid disease  
18 progression at study entry.

19 Now looking at overall survival, the median  
20 overall survival was 8 months. In a patient  
21 population with an expected median survival of 3 to  
22 5 months, this result is clinically meaningful.

1           Presented here is the overall survival based  
2 on the type of response attained, and for the 40  
3 percent of patients who achieved a minimum of a 25  
4 percent reduction in their disease burden, the  
5 median overall survival was 15.6 months and  
6 identical to those patients who achieved at least a  
7 partial response.

8           With continued follow-up, we have additional  
9 data available as part of a 90-day update. As seen  
10 here, the overall response rate has increased to  
11 26.2 percent, as one more patient achieved a  
12 response, and the overall survival has now matured  
13 from 8 months to 8.6 months.

14           The depth of response observed with  
15 selinexor is similar to the prior accelerated  
16 approvals. Carfilzomib demonstrated a response  
17 rate of 22.9 percent, and both pomalidomide with  
18 low-dose dexamethasone and daratumumab both  
19 demonstrated an overall response rate of 29.2  
20 percent. The overall response rate for selinexor  
21 in the most refractory disease was 26.2 percent.  
22 As highlighted, selinexor also demonstrated a CR

1 and a VGPR rates similar to these other drugs.

2 In conclusion, results from the phase 2  
3 study demonstrate clear efficacy of selinexor in  
4 patients with triple-class refractory myeloma who  
5 have exhausted all other effective options. For  
6 patients who entered the study with rapidly  
7 progressive disease and an expected overall  
8 survival of 3 to 5 months, these responses are  
9 clinically meaningful.

10 Thank you. I'd now like to turn the lectern  
11 over to Dr. Kauffman to review the safety data.

12 **Applicant Presentation - Michael Kauffman**

13 DR. KAUFFMAN: Thank you.

14 I'm Michael Kaufman, CEO and chief medical  
15 officer at Karyopharm Therapeutics. Selinexor has  
16 a well-characterized safety profile with more than  
17 1,000 patients treated, and based on our learnings,  
18 physicians will be able to prevent, monitor, and  
19 manage side effects through dose modifications and  
20 standard supportive care. We have created a robust  
21 multifaceted program to help caregivers optimize  
22 each patient's experience on selinexor.

1           While patients will experience an adverse  
2 event, these events were generally reversible and  
3 major organ toxicities were not prominent.  
4 Selinexor has been evaluated in 1116 patients with  
5 advanced heavily pretreated hematologic  
6 malignancies, including myeloma, lymphoma, and AML.  
7 The safety profile across the 214 patients with  
8 myeloma treated with selinexor 80 milligrams and  
9 dexamethasone 20 milligrams was similar to the  
10 patients treated in the pivotal STORM part 2 study,  
11 and therefore we'll review the STORM results.

12           Before turning to Myeloma, though, it's  
13 important to note that the AML study is not  
14 informative to the approval of selinexor in  
15 triple-class refractory myeloma. First, study 008  
16 was an exploratory phase 2 study in a very  
17 different tumor type. Second, the study compared  
18 single-agent selinexor against active standards of  
19 care anti-AML therapies. And finally, there were  
20 no significant differences between the arms in  
21 infection rate or adverse events leading to death,  
22 as verified by an independent review.

1           Now, I'll review the characteristics of the  
2 patients with myeloma in the STORM clinical  
3 studies. Patients who entered the STORM part 2  
4 trial had a median of 10 unique ongoing  
5 comorbidities when they began treatment. As  
6 expected, the most common baseline hematologic  
7 comorbidities included anemia and thrombocytopenia.  
8 Patients also had many non-hematologic  
9 comorbidities. Accompanying this, we also saw high  
10 concomitant medication use. The most common  
11 medications being used at baseline were antivirals,  
12 antibacterials, and antithrombotic agents.

13           Turning now to an overview of adverse events  
14 observed in STORM part 2, the majority of patients  
15 had an adverse event of grade 3 or higher, and  
16 these were typically reversible. Twenty-seven  
17 percent of patients discontinued due to an adverse  
18 event, and 60 percent of patients had at least one  
19 serious adverse event. Eight percent of the  
20 patients in STORM died due to an adverse event.

21           To give context, the rate of SAEs and AEs  
22 leading to death in STORM part 2 are similar to

1 what's been observed with other drugs that were  
2 granted accelerated approval in patients with less  
3 heavily pretreated myeloma. Amongst these studies,  
4 the rates of SAEs ranged between 47 percent to 67  
5 percent as compared to 60 percent with selinexor,  
6 and similarly, AEs leading to death ranged between  
7 4 percent and 10 percent as compared with 8 percent  
8 with selinexor.

9           The most commonly reported hematologic  
10 adverse events were thrombocytopenia and anemia.  
11 Grade 4 neutropenia was low at 3 percent, and there  
12 were 2 cases of febrile neutropenia, both grade 3  
13 and reversible. Thrombocytopenia was the most  
14 common hematologic side effect. This was  
15 reversible and typically not associated with  
16 significant bleeding even though about half the  
17 patients were also taking antithrombotic agents.

18           The most common non-hematologic adverse  
19 events were nausea, fatigue, and decreased  
20 appetite. The majority of these events were grade  
21 1 or 2, and they were transient and reversible.  
22 The most common grade 3 events were fatigue and

1 hyponatremia, and the hyponatremia was not usually  
2 associated with symptoms.

3           Importantly, selinexor offers a different  
4 safety profile than other anti-myeloma therapies.  
5 For example, rates of cardiac dysfunction,  
6 peripheral neuropathy, and thromboembolic disease  
7 are low. Dose modifications to address adverse  
8 events were effective for improving symptoms and  
9 reducing discontinuations.

10           For example, 44 percent of patients had a  
11 dose modification to address thrombocytopenia while  
12 3 percent discontinued treatment due to the adverse  
13 event. Furthermore, the reasons for  
14 discontinuation across the entire study were  
15 variable and consistent with this medically complex  
16 population. Discontinuations due to major organ  
17 toxicity, neuropathy, or infection were infrequent.

18           The types of serious adverse events were  
19 consistent with what would be expected in patients  
20 with triple-class refractory myeloma who have been  
21 heavily pretreated and have many underlying  
22 comorbidities, including prior infections. The

1 most commonly reported serious adverse events were  
2 pneumonia and sepsis, which are unfortunately  
3 common in patients with heavily pretreated myeloma.

4           Amongst the 23 patients who died within 30  
5 days of last dose of study drug, 13 were due to  
6 progressive disease; 10 were due to an adverse  
7 event; 4 of these 10 also had disease progression.  
8 Similar to other studies in patients with heavily  
9 pretreated refractory myeloma, infection was a  
10 common cause of death.

11           Next, let me review actions to manage the  
12 common adverse events. Across the entire myeloma  
13 clinical program, prophylactic olanzapine and/or  
14 megesterol reduce the incidence of common  
15 symptomatic side effects, and these agents will be  
16 recommended to treating physicians and caregivers.  
17 In particular, patients who receive prophylactic  
18 supportive care with these agents had a lower  
19 incidence of nausea, vomiting, fatigue, or  
20 anorexia.

21           Monitoring will play an important role to  
22 prevent and manage selinexor side effects.

1 Monitoring is recommended every week for the first  
2 8 weeks of therapy with routine complete blood  
3 count, basic serum chemistry, and body weight  
4 assessment. After the first 8 weeks, monitoring is  
5 recommended at least monthly based on the  
6 individual clinical situation.

7           Next, we'll turn to specific dose  
8 modifications and supportive care for addressing  
9 the common adverse events if they do occur. If  
10 thrombocytopenia develops, platelet transfusions  
11 are used to supportive care and thrombopoietin  
12 agonists can be considered. For grade 3 or 4  
13 thrombocytopenia, selinexor dosing should be  
14 reduced to 100 milligrams once weekly while  
15 supportive care is instituted. For persistent  
16 thrombocytopenia, dose is further reduced by  
17 20-milligram increments until platelet counts  
18 improve.

19           Nausea, fatigue, and decreased appetite can  
20 be managed with olanzapine, megesterol, and/or  
21 hydration. These supportive care strategies  
22 diminish the rates and duration of these side

1 effects. Grade 2 events were managed by  
2 withholding one dose of selinexor and then  
3 restarting at a reduced dose while supportive care  
4 was implemented.

5 We are committed to educating and supporting  
6 patients and their caregivers and have developed  
7 five key initiatives that will be implemented to  
8 support selinexor use. First, we will educate  
9 prescribers and their staff. A team of trained  
10 nurse liaisons will provide guidelines about the  
11 management of selinexor adverse events, including  
12 peer-reviewed publications.

13 Healthcare professionals will discuss the  
14 benefits and risks of treatments with patients  
15 along with advice on the management of expected  
16 side effects. A limited network of specialty  
17 pharmacy staffed with oncology trained nurses are  
18 available 24-7, as well as the myeloma advocacy  
19 groups will also support patients to optimize their  
20 treatment. Next, we recommend regular monitoring  
21 of CBC, basic serum chemistry, and body weight.  
22 This should occur weekly during the first 8 weeks,

1 and then at least monthly thereafter.

2 We will communicate the management of common  
3 AEs with clear guidance on dose modifications and  
4 supportive care delivered prophylactically or as  
5 needed. We will communicate clear stopping  
6 criteria for disease progression in the first 1 to  
7 2 months of therapy or for significant side effects  
8 despite dose modifications and supportive care.

9 In conclusion, selinexor has a well-defined  
10 safety profile with most events reversible and  
11 manageable. The common adverse events are  
12 thrombocytopenia, nausea, vomiting, fatigue, and  
13 decreased appetite. High-grade thrombocytopenia  
14 was typically reversible and generally not  
15 associated with bleeding. The common  
16 non-hematologic adverse events, mainly grade 1 or 2  
17 in intensity, were reversible and generally  
18 manageable with dose modification and/or standard  
19 prophylactic or supportive care.

20 Selinexor does not appear to aggravate organ  
21 function even in patients with baseline organ  
22 impairment. The safety profile supports the use of

1 this oral agent in patients with multiple comorbid  
2 conditions and heavily pretreated myeloma, and  
3 these risks and mitigations will be communicated.

4 Thank you. I'd now like to turn the lectern  
5 over to Dr. Jagannath to provide his clinical  
6 perspective of selinexor and the benefit-risk.

7 **Applicant Presentation - Sundar Jagannath**

8 DR. JAGANNATH: Thank you.

9 I am Sundar Jagannath, and I was the  
10 principal investigator in the pivotal trial  
11 studying selinexor. I am pleased to provide my  
12 clinical perspective on selinexor as a novel  
13 treatment for patients suffering from this  
14 progressive, incurable disease. It is my  
15 conclusion that the benefits of selinexor clearly  
16 outweigh the risks for patients with triple-class  
17 refractory multiple myeloma.

18 When I meet these patients in the clinic, we  
19 are at a very serious and critical juncture. The  
20 disease has become refractory to the anti-myeloma  
21 treatments known to be effective, and there are  
22 simply no approved drugs to try. We often start

1 recycling therapies using the same drugs in  
2 different combinations.

3 Like those in the selinexor pivotal study,  
4 the patients in my clinic with relapse and  
5 refractory myeloma are generally older with  
6 multiple comorbidities and are on many concomitant  
7 medications. They are vulnerable following the  
8 cumulative effects from prior therapies, their  
9 myeloma, and other medical problems. Many have  
10 developed peripheral neuropathy, renal, and liver  
11 function decline or cardiac compromise from the  
12 disease or prior therapies. In my experience,  
13 these medically complex patients have a very poor  
14 prognosis, and we have a small window of  
15 opportunity to achieve disease control. This  
16 underscores the urgent need for novel therapies  
17 like selinexor.

18 Although selinexor is a new drug from a new  
19 therapeutic class with a novel mechanism of action,  
20 selinexor is the first agent specifically evaluated  
21 in patients with triple-class refractory myeloma,  
22 and it has a different side effect profile than

1 available therapies. It has a low risk for  
2 peripheral neuropathy, renal, hepatic toxicity, and  
3 cardiovascular side effects.

4 In addition, the rate of infections is  
5 consistent with other studies in heavily pretreated  
6 multiple myeloma. The median overall survival of  
7 15.6 months in 40 percent of patients with a  
8 minimal response or better highlights the favorable  
9 benefit-risk ratio. The pivotal study results were  
10 meaningful, particularly for a group of patients in  
11 dire need of an effective fast-acting treatment.

12 The 26.2 percent response rate and the duration of  
13 response observed is clinically meaningful and  
14 included patients who achieved both stringent  
15 complete responses and very good partial responses.

16 Let me share two examples of patients from  
17 our clinic, both whom experienced substantial  
18 benefits from the treatment. The first is a  
19 65-year-old woman with a complicated medical  
20 history that included 8 prior treatment regimens.  
21 She had received all the commonly use anti-myeloma  
22 drugs like the proteasome inhibitors, the

1 immunomodulatory molecules, and daratumumab, as  
2 well as 2 transplants. Most recently, she received  
3 a multi-agent cytotoxic regimen and experienced  
4 progression within a month.

5 After trying all prior therapies, her  
6 disease relapsed and became triple-class  
7 refractory. She enrolled in STORM part 2. After  
8 receiving selinexor, she had a rapid response and  
9 achieved a very good partial remission on day 15.  
10 By 4 months, she achieved a stringent complete  
11 remission and became MRD negative in the bone  
12 marrow. She's still on therapy.

13 The second patient is a 58-year-old man with  
14 6 prior regimens and importantly a baseline  
15 creatinine of 3.94, limiting his eligibility for  
16 most other clinical trials. He started with a bone  
17 marrow containing 70 to 80 percent plasma cells and  
18 a free light chain of 12,000 milligrams per liter.  
19 On selinexor, he achieved a very good partial  
20 remission and his kidney function improved. While  
21 his myeloma progressed after several months on  
22 selinexor, the improvements in his renal function

1 allowed him to participate in another clinical  
2 trial.

3 By the way, this renal function improvement  
4 is not unique. Among pertinent [indiscernible]  
5 patients with renal dysfunction at baseline, 21  
6 showed improvement at the end of the study. This  
7 leads me to a final point on efficacy with this  
8 agent. At the end of the trial, patients are often  
9 left with a lower burden of disease or fewer  
10 clinical complications, and this can then allow  
11 them to try other therapies for which they were  
12 previously ineligible.

13 Patients with triple-class refractory  
14 myeloma have many medical complications as well as  
15 a rapidly growing cancer. Therefore, we initiate  
16 selinexor at the recommended dose to rapidly halt  
17 their disease and then expect that most patients  
18 will need dose modifications. This is an  
19 anticipated normal part of clinical practice.

20 Treating physicians should expect the  
21 adverse events described earlier and implement the  
22 supportive care that we now know can be effective

1 for patients. The clinical experience gained in  
2 managing adverse events will be shared to keep  
3 patients on therapy to improve patient outcomes.

4 As our experience grew, we were better able  
5 to manage the side effects and support our  
6 patients, which leads to longer treatment duration  
7 and improved response rates. The algorithms  
8 developed to manage side effects, which have been  
9 described previously, will be communicated to  
10 treating physicians and their staffs in order to  
11 optimize each patient's experience on selinexor.

12 As I conclude, I want to impress upon the  
13 committee the urgency of making this novel active  
14 therapy available to patients as soon as possible.  
15 Today, when patients with this very late stage of  
16 myeloma walk into our clinic, we have no effective  
17 options left to offer. We are often left with best  
18 supportive care or hospice. We feel helpless and  
19 the patients leave with little hope. Looking at  
20 the benefits and the ability to manage adverse  
21 events, I can conclude that we should not wait to  
22 act. In short, we know enough today to provide

1 patients and physicians with the opportunity to try  
2 this novel effective therapy.

3 Thank you. Dr. Shacham will now provide  
4 concluding remarks.

5 **Applicant Presentation - Sharon Shacham**

6 DR. SHACHAM: Thank you, Dr. Jagannath.

7 I'm Sharon Shacham, president and chief  
8 scientific officer at Karyopharm. I'll begin with  
9 a big thank you to our investigators and the many  
10 brave patients who made the courageous decision to  
11 enroll in a clinical trial with selinexor and take  
12 what might have been the one last chance at  
13 controlling their disease.

14 Selinexor provides a positive benefit-risk  
15 profile for a group of heavily pretreated patients  
16 who have no effective options available. These  
17 patients have rapidly progressing disease at study  
18 entry, and the priority is to halt the disease and  
19 reduce tumor burden.

20 In order to change the course of the  
21 disease, all patients are started at selinexor 80  
22 mg plus dexamethasone, and as shown in this graph,

1 the majority of patients did in fact have a  
2 reduction in their disease burden within 4 weeks on  
3 therapy. Reduced doses of selinexor at this point  
4 are able to maintain efficacy with an improved  
5 durability profile. With weekly monitoring and  
6 using the dose modification and supportive care  
7 algorithms, side effects of selinexor can be  
8 managed effectively while preventing disease  
9 progression.

10 We are committed to educating and supporting  
11 patients and their caregivers to optimize the  
12 patient's outcomes. If we wait for the results  
13 from the confirmatory BOSTON study, patients will  
14 not have access to selinexor for at least two more  
15 years. As you have heard from Dr. Jagannath and  
16 Dr. Richardson, these patients, with no remaining  
17 effective options, urgently need access to new  
18 effective medications with novel mechanism of  
19 action.

20 The phase 2 results reviewed today are  
21 unprecedented. We have shown clear signs of  
22 efficacy from the largest clinical trial in

1 patients with the most refractory myeloma conducted  
2 to date. It is important to point out that  
3 expanded access was not designed to be a substitute  
4 for regulatory approval. Accelerated approval  
5 provides both access and will allow implementation  
6 of the planned education and support for  
7 physicians, caregivers, and patients. The totality  
8 of evidence presented today demonstrates selinexor  
9 benefits and supports accelerated approval. Thank  
10 you.

11 DR. RINI: Thank you for that nice  
12 presentation.

13 We'll now proceed with presentations from  
14 FDA.

15 **FDA Presentation - Andrea Baines**

16 DR. BAINES: Good afternoon. My name is  
17 Andrea Baines, and I'm a hematologist with the  
18 Division of Hematology Products at the FDA. I am  
19 the clinical reviewer for the new drug application  
20 for selinexor. Today, I will present some of the  
21 relevant findings from our review of this  
22 application that make the risk-benefit

1 determination for selinexor challenging.

2 We are seeking the committee's advice on  
3 whether the data from the pivotal trial  
4 KCP-330-012, referred to as STORM, are conclusive  
5 to allow for an adequate assessment of the safety  
6 and efficacy in the proposed patient population and  
7 whether selinexor provides a benefit that outweighs  
8 the risk, especially considering the limitations of  
9 the STORM trial that I will discuss. The voting  
10 question will be should be approval of selinexor be  
11 delayed until the results of the randomized phase 3  
12 BOSTON trial are available?

13 Our review and presentation is primarily  
14 based on part 2 of the pivotal trial STORM.  
15 Additional supportive data comes from part 1 of  
16 STORM, the phase 1 trial, KCP-330-001, in patients  
17 with advanced hematologic malignancies, and the  
18 phase 2 trial, KCP-330-008, in patients with  
19 relapsed refractory acute myeloid leukemia. The  
20 applicant also submitted a real-world data study,  
21 KS-50039.

22 The pivotal trial, part 2 of STORM, has

1 already been described in detail in the applicant's  
2 presentation. STORM was a single-arm trial of the  
3 combination of selinexor and dexamethasone in  
4 patients with relapsed or refractory multiple  
5 myeloma with a primary endpoint of overall response  
6 rate.

7           There are three key issues that we would  
8 like to discuss today. First, STORM was a  
9 single-arm trial evaluating the combination  
10 regimen. There is no single-agent activity of  
11 selinexor in patients with relapsed refractory  
12 multiple myeloma. With the STORM trial design, the  
13 treatment effect of selinexor cannot be isolated  
14 from that of dexamethasone. In addition, it is  
15 challenging to interpret single-arm trial data,  
16 especially when there is significant toxicity  
17 associated with the product.

18           Second, treatment with selinexor is  
19 associated with significant toxicity, and in the  
20 absence of a control arm, it is challenging to  
21 fully characterize the safety profile as it relates  
22 to the analysis of risk-benefit.

1 Third, dose finding was limited in the phase  
2 1 trial, and there was a high rate of dose  
3 modifications due to adverse events in STORM,  
4 suggesting that the optimal dose of selinexor has  
5 not been identified.

6 To further illustrate some of the issues  
7 with interpretation of single-arm trials of  
8 combination therapy, I will discuss the results of  
9 the phase 1 trial, which showed essentially no  
10 single-agent activity of selinexor in relapse  
11 refractory multiple myeloma along with historical  
12 data showing that dexamethasone does have  
13 single-agent activity in this disease setting. I  
14 will also discuss issues with the applicant's  
15 submitted real-world data study and the results of  
16 a randomized-controlled trial selinexor in patients  
17 with relapsed refractory acute myeloid leukemia,  
18 which demonstrated a worse overall survival trend  
19 in patients treated with selinexor.

20 Supportive data for the NDA includes results  
21 from trial KCP-330-001. This was a phase 1,  
22 open-label, dose escalation and expansion study to

1 evaluate the safety and tolerability of selinexor  
2 in patients with advanced hematologic malignancies.  
3 The study included 8 arms and 11 different dose  
4 schedules across arms. Arms 1, 6, and 8 included  
5 patients with multiple myeloma.

6 Eligible patients for the 3 multiple myeloma  
7 cohorts had at least 3 prior lines of therapy,  
8 including an alkylating agent, a proteasome  
9 inhibitor, an immunomodulatory agent, and steroids.  
10 Patients on arm 6 received selinexor in combination  
11 with dexamethasone. Patients on arms 1 and 8  
12 received single-agent selinexor. However, patients  
13 on schedules 3 and 11 were permitted to receive  
14 dexamethasone as a concomitant medication.

15 Of all 81 patients with relapsed refractory  
16 multiple myeloma treated across the dose regimens,  
17 ranges, and schedules on the phase 1 trial, there  
18 were only 7 responses corresponding to an overall  
19 response rate of 8.6 percent. Among the 25  
20 patients who received selinexor in combination with  
21 dexamethasone, the overall response rate was 24  
22 percent, which is similar to that observed in

1       STORM.

2               Among the 56 patients who received selinexor  
3 alone, only one patient responded. This was a  
4 partial response, and notably this patient received  
5 dexamethasone 12 milligrams twice weekly with  
6 selinexor as a concomitant medication. Therefore,  
7 no patients responded to single-agent selinexor  
8 alone, even at doses that were higher than the dose  
9 evaluated in STORM.

10              In contrast, single-agent selinexor did show  
11 some activity in patients with other advanced  
12 hematologic malignancies with the highest response  
13 rates in patients with non-Hodgkin's lymphoma and  
14 diffuse large B cell lymphoma. Although the data  
15 from the phase 1 trial suggest that dexamethasone  
16 may potentiate the activity of selinexor, given the  
17 lack of responses to selinexor monotherapy in  
18 patients with relapsed refractory multiple myeloma,  
19 it is difficult to determine the contribution of  
20 selinexor as compared to dexamethasone in the  
21 combination therapy.

22              In fact, historical trials have demonstrated

1 response rates between 18 and 27 percent with the  
2 use of single-agent high-dose dexamethasone in  
3 patients with relapsed refractory multiple myeloma  
4 and even higher response rates in patients with  
5 newly diagnosed myeloma. However, it is difficult  
6 to extrapolate these results to the current era of  
7 multiple myeloma therapy in which patients receive  
8 multiple lines of therapy, many of which include  
9 dexamethasone as a backbone of standard therapy.

10 The more recent MM-003 trial, conducted to  
11 support the approval of pomalidomide, compared  
12 pomalidomide in combination with low-dose  
13 dexamethasone to high-dose dexamethasone in  
14 patients with relapsed refractory multiple myeloma.  
15 The response rate to high-dose dexamethasone in  
16 this trial was 10 percent based on investigator  
17 assessment and 4 percent by IRC assessment.

18 Overall, the literature demonstrates that  
19 dexamethasone has single-agent activity in relapsed  
20 refractory multiple myeloma, where selinexor  
21 failed to demonstrate single-agent activity in this  
22 disease in the phase 1 trial.

1           The primary efficacy results from part 1 of  
2 STORM are summarized here. The modified  
3 intent-to-treat population included 122 patients  
4 with triple-class refractory multiple myeloma  
5 enrolled in part 2 of STORM who met all eligibility  
6 criteria and received at least one dose of  
7 selinexor and dexamethasone. The overall response  
8 rate was 25.4 percent and the median duration of  
9 response was 4.4 months.

10           Two patients had a stringent complete  
11 response, but most of the responses were partial  
12 responses. Overall, the combination of selinexor  
13 and dexamethasone demonstrated limited efficacy in  
14 this population with a modest overall response rate  
15 and short duration of response. Importantly,  
16 because the response rate is confounded by the use  
17 of a combination regimen in a single-arm trial, it  
18 is unclear whether these results would translate  
19 into an improvement in progression-free survival or  
20 overall survival.

21           To provide some context for these results,  
22 here are the results from the initial approvals for

1 carfilzomib, pomalidomide with dexamethasone,  
2 daratumumab. Although, pomalidomide's initial  
3 approval was in combination with dexamethasone,  
4 this was a randomized trial that compared  
5 pomalidomide versus pomalidomide plus dexamethasone  
6 to isolate the treatment effect of pomalidomide.  
7 While the response rates are comparable, the  
8 duration of response with these approved agents was  
9 slightly longer than that of selinexor.

10 Some of the results I've just summarized are  
11 from single-arm trials, and in general, FDA  
12 routinely considers single-arm trials with an  
13 endpoint of disease response supported by duration  
14 of response. However, single-arm trials cannot  
15 adequately characterize time-to-event endpoints  
16 such as progression-free survival and overall  
17 survival.

18 In general, survival estimates are more  
19 complicated and depend on factors that cannot be  
20 addressed without a control arm. Overall, the  
21 assessment of risk-benefit in a single-arm trial  
22 can be challenging, especially when the agent has

1 significant toxicity, and even more so when the  
2 single-arm trial is evaluating a combination  
3 therapy.

4           Lastly, although the applicant derived a  
5 median overall survival of 8 months from part 2 of  
6 STORM, this is not interpretable in the absence of  
7 a control arm because of confounding factors. As  
8 one example, STORM excluded patients who had a life  
9 expectancy of less than 4 months. Therefore, this  
10 result is not interpretable and is not appropriate  
11 to compare the overall survival from STORM with  
12 survival data reported in the literature.

13           To illustrate this further, I'm showing you  
14 results from the MAMMOTH study put forth by the  
15 applicant. This was a retrospective study to  
16 evaluate the natural history of patients with  
17 multiple myeloma who became refractory to therapy  
18 with anti-CD38 monoclonal antibodies. In this  
19 study, refractory status was based on the  
20 individual treatment rather than to class as was  
21 done in STORM.

22           The inclusion criteria for STORM more

1 closely aligned with the triple-class refractory  
2 population, which actually had a median overall  
3 survival of 9.2 months. However, some of the  
4 patients in STORM would fall within the triple and  
5 quad-refractory category, and others would fall  
6 within the penta-refractory. Additionally, not all  
7 patients in the MAMMOTH cohort received treatment.  
8 This example underscores the challenges of  
9 comparisons across trials and the literature,  
10 further highlighting the limitations of  
11 interpreting data from single-arm trials.

12 In support of the selinexor NDA, the  
13 applicant also submitted an analysis of overall  
14 survival from real-world data in study KS-50039.  
15 The agency is committed to the use of real-world  
16 data analyses to support regulatory decision making  
17 and has recently published a framework that  
18 outlines considerations for the development of  
19 studies using real-world data.

20 Randomized trials are designed to control  
21 for unknown covariates and minimize bias through  
22 randomization. Real-world data sources may have

1 inherent bias that limit their value for drawing  
2 causal inferences. However, with careful protocol  
3 design, these biases can be addressed. Therefore,  
4 investigators should discuss their plan analyses  
5 with the agency and submit the proposed protocol  
6 before initiating a real-world data study.

7 The agency has concerns about the  
8 reliability and interpretability of study KS-50039,  
9 which was not prespecified or discussed with the  
10 agency in advance. I will now discuss a few  
11 examples that highlight our concerns with this  
12 study.

13 The analysis population for KS-50039 was  
14 selected using electronic health record data from  
15 the Flatiron Health Analytic database, abbreviated  
16 as FHAD. The applicant's criteria for selection of  
17 patients is outlined here. Certain aspects of the  
18 selection criteria are problematic. For example,  
19 patients who receive treatment in a clinical trial  
20 setting were excluded. Furthermore, the criteria  
21 required patients to have an ECOG performance  
22 status of 0 to 2, however, it did not exclude

1 patients with a missing ECOG status.

2 In addition, no selection criterion was  
3 applied to ensure that patients in the Flatiron  
4 population received subsequent anti-myeloma  
5 therapy. STORM also excluded patients with a life  
6 expectancy less than 4 months and had minimum  
7 requirements for platelet count, hemoglobin, and  
8 organ function. However, there were no similar  
9 criteria for the Flatiron population.

10 These issues, and other important  
11 differences between the selection criteria for  
12 Flatiron and the eligibility criteria for STORM,  
13 biased the survival results in favor of STORM. In  
14 addition, while one of the promises of real-world  
15 data is to provide big data, application of these  
16 limited selection criteria to over 38,000 records  
17 narrowed the population down to only 64 patients.

18 The importance of the differences in  
19 selection criteria are underscored by the  
20 differences we see in key baseline characteristics  
21 such as ECOG status, refractoriness to prior  
22 therapies, number of prior regimens, history of

1 stem cell transplantation, and other baseline  
2 characteristics such as hemoglobin and platelet  
3 count. Because of these differences in others,  
4 there's an overall lack of comparability between  
5 the  
6 Flatiron population and STORM.

7 In summary, due to critical differences  
8 between the Flatiron and STORM population  
9 summarized here, and other design issues with study  
10 KS-50039, the survival estimates from this study  
11 should be interpreted with caution. Given the lack  
12 of comparability between the Flatiron and STORM  
13 populations, comparison between these two  
14 populations of survival is not appropriate.

15 Again, the agency is committed to the use of  
16 real-world data, however, careful design is needed  
17 to ensure that the data are robust and is  
18 sufficient quality to inform regulatory decision  
19 making.

20 To further highlight some of the challenges  
21 with interpretation of single-arm trials,  
22 especially in the setting of a drug with

1 significant toxicity, I will discuss data from a  
2 randomized trial of selinexor in patients with  
3 acute myeloid leukemia, which showed a worse  
4 overall survival trend in the selinexor arm.

5 Study KCP-330-008 was a phase 2, randomized,  
6 open-label study of selinexor versus physician's  
7 choice in patients aged 60 or older with relapsed  
8 refractory acute myeloid leukemia. Eligible  
9 patients received at least 2 prior lines of  
10 therapy, including both and AraC-containing regimen  
11 and a hypomethylating agent containing regimen and  
12 were considered ineligible for intensive  
13 chemotherapy or stem cell transplantation.

14 The protocol had multiple amendments, which  
15 changed the patient population and the selinexor  
16 dose, so I will present the design results based on  
17 protocol version 5.1, which served as the  
18 intent-to-treat population. In total, 317 patients  
19 were enrolled, but the modified intent-to-treat  
20 population consisted of 175 patients.

21 These patients were randomized 2 to 2 to  
22 receive either selinexor or physician's choice.

1 Physician's choice was limited to 1 of 3 regimens,  
2 including best supportive care alone, or with AraC,  
3 or a hypomethylating agent. Note that these are  
4 agents that the patients would have already  
5 received per the eligibility criteria. Treatment  
6 continued until disease progression, unacceptable  
7 toxicity, or death. The primary endpoint was  
8 overall survival.

9           The median age in this trial was 74. The  
10 treatment arms were well balanced for the  
11 stratification factors, however, there were some  
12 important differences in baseline disease  
13 characteristics. Patients in the selinexor arm  
14 were more likely to have an ECOG performance status  
15 of 0 to 1 compared to the physician's choice arm.  
16 In addition, more patients in the selinexor arm had  
17 prior myelodysplastic syndrome, p53 mutations, and  
18 an ANC less than 500. There were also imbalances  
19 in the number of patients who were randomized but  
20 not treated.

21           The results showed a worse overall survival  
22 trend with selinexor compared to physician's

1 choice. The hazard ratio was 1.18 with a median  
2 overall survival of 94 days in the selinexor arm  
3 compared to 170 days in the physician's choice arm.  
4 The overall survival trend was slightly worse for  
5 the remaining 142 patients who were not included in  
6 the intent-to-treat population with a hazard ratio  
7 of 1.42.

8 The combined rate of complete remission and  
9 complete remission with incomplete recovery was 12  
10 percent in the selinexor arm compared with 4  
11 percent in the physician's choice arm. However, it  
12 should be noted that there was a lot of missing  
13 data due to dropouts in both arms.

14 The toxicity profile observed with selinexor  
15 in patients with relapsed refractory AML was  
16 similar to that observed in patients with relapsed  
17 refractory multiple myeloma in STORM. The most  
18 frequent treatment-emergent adverse events in  
19 patients with AML were anemia, thrombocytopenia,  
20 nausea, vomiting, diarrhea, decreased appetite,  
21 fatigue, and hyponatremia.

22 Of note, although selinexor resulted in

1 higher rates of remission than physician's choice,  
2 the overall survival trend was worse in the  
3 selinexor arm. Disparate response in survival  
4 trends can be observed with therapies that have  
5 significant toxicity. The results of this study of  
6 selinexor in patients with relapsed refractory AML  
7 underscore the importance of randomized-controlled  
8 trials to allow a full characterization of risk-  
9 benefit.

10 I will now discuss the safety profile of  
11 selinexor in patients with relapsed refractory  
12 multiple myeloma with a focus on the safety results  
13 from part 2 of STORM. Treatment with selinexor is  
14 associated with high rates of treatment-emergent  
15 adverse events and a unique toxicity profile  
16 compared to other approved therapies for relapsed  
17 refractory multiple myeloma.

18 All patients enrolled and treated on STORM  
19 experienced at least one treatment-emergent adverse  
20 events. Overall, there was a high frequency of  
21 severe treatment-emergent adverse events. In  
22 part 2 of STORM, 94 percent of patients experienced

1 at least one grade 3 or 4 adverse event and 60  
2 percent of patients experienced at least one  
3 serious adverse event; 27 percent of patients  
4 permanently discontinued selinexor due to an  
5 adverse event and 8 percent of patients had a fatal  
6 adverse event.

7           Again, all patients experienced at least one  
8 treatment-emergent adverse event. The most common  
9 adverse events are listed here. Grade 3 or 4  
10 adverse events are events that are severe,  
11 debilitating, or life threatening. Ninety-four  
12 percent of patients experienced at least one grade  
13 3 or grade 4 adverse event. The most common grade  
14 3 or grade 4 adverse events are listed here.

15           Serious adverse events include those adverse  
16 events that may result in death, be life  
17 threatening, or require hospitalization. Sixty  
18 percent of patients experienced at least one  
19 serious adverse event. Among these, the most  
20 frequent were pneumonia, sepsis, and mental status  
21 changes.

22           There were 23 deaths on or within 30 days of

1 study treatment. Of these, 13 were attributed to  
2 disease progression and 10 were due to a fatal  
3 adverse event. The causes of death in these 10  
4 patients are listed here. Given the difficulty in  
5 ascertaining the baseline incidence of adverse  
6 events in a population of patients with advanced  
7 multiple myeloma on a single-arm trial, the agency  
8 considers all deaths due to a treatment-emergent  
9 adverse event in this setting to be treatment  
10 related unless clearly related to other extraneous  
11 causes.

12 The third issue is the uncertainty whether  
13 the optimal dose of selinexor has been identified  
14 for patients with relapsed refractory multiple  
15 myeloma. First, dose finding was limited in the  
16 phase 1 trial. Specifically, no doses of selinexor  
17 lower than 45 milligrams per metered-squared in  
18 combination with dexamethasone 20 milligrams twice  
19 weekly were tested in patients with relapsed  
20 refractory multiple myeloma. Furthermore, I will  
21 show you data from STORM indicating that the  
22 proposed dose of selinexor is poorly tolerated in

1 this population as evidenced by the high rates of  
2 dose modifications and limited duration of  
3 treatment.

4 A substantial proportion of patients  
5 required dose modifications and permanent  
6 discontinuation of study treatment. Eighty-nine  
7 percent of patients required at least one dose  
8 modification, including either a dose reduction,  
9 dose interruption, or permanent discontinuation of  
10 selinexor due to a treatment-emergent adverse  
11 event, and the majority of patients required more  
12 than one dose modification. Twenty-nine percent of  
13 patients permanently discontinued selinexor due to  
14 a treatment-emergent adverse event.

15 In addition, the need for dose modifications  
16 arose early in the course of treatment as depicted  
17 in this stacked bar chart. The bar heights  
18 represent the fraction of patients on a particular  
19 dose at weekly intervals with each bar representing  
20 1 week in the trial. This plot excludes doses that  
21 were missed and dose modifications for disease  
22 progression. The blue regions represent the

1 fraction of patients receiving selinexor 80  
2 milligrams twice weekly. Over time, the fraction  
3 of patients on this dose decreases, and of note,  
4 the median duration on selinexor 80 milligrams  
5 twice weekly was only 3 and a half weeks,  
6 indicating that the 80-milligram dose is poorly  
7 tolerated.

8 In conclusion, the pivotal study STORM was a  
9 single-arm trial of the combination of selinexor  
10 plus dexamethasone. With this design, we cannot  
11 isolate the treatment effect of selinexor. It can  
12 be challenging to interpret single-arm trial data,  
13 especially when the product is associated with  
14 significant toxicity.

15 Selinexor demonstrated essentially no  
16 single-agent activity in the phase 1 trial and  
17 limited efficacy in the phase 2 trial. Selinexor  
18 was associated with significant toxicity with high  
19 rates of adverse events, including deaths and  
20 discontinuation of study treatment due to adverse  
21 events in STORM. Additionally, there was worse  
22 overall survival trend in patients with AML treated

1 with selinexor in a randomized-controlled trial.

2           Considering the high rates of dose  
3 modifications and short duration of treatment with  
4 selinexor, it is uncertain whether the optimal dose  
5 has been identified. Given the limited efficacy  
6 and significant toxicity of selinexor, combined  
7 with the challenges in determining the contribution  
8 of selinexor to the treatment effect, it is unclear  
9 whether the benefit of selinexor outweighs the  
10 risks.

11           Before we proceed with the discussion topic  
12 and voting question, I would like to remind you  
13 that the phase 3 randomized trial comparing  
14 selinexor in combination with bortezomib and  
15 dexamethasone versus bortezomib and dexamethasone  
16 is ongoing and has completed accrual. Based on the  
17 applicant's communication with us, top-line results  
18 of the BOSTON study are expected at the end of this  
19 year.

20           Should selinexor remain investigational,  
21 there are mechanisms by which patients in need  
22 could receive treatment with selinexor outside of a

1 clinical trial. FDA has a long history of  
2 facilitating access to investigational drugs for  
3 patients with serious or immediately  
4 life-threatening diseases or conditions who do not  
5 have alternative therapies available to them.  
6 These expanded access programs, often referred to  
7 as compassionate-use programs, could provide a  
8 mechanism by which patients could receive selinexor  
9 if the approval decision were delayed until the  
10 results of the BOSTON are available.

11 We'd like for you to discuss whether the  
12 data from STORM are conclusive to allow for an  
13 adequate assessment of safety and efficacy in the  
14 proposed patient population and whether selinexor  
15 provides a benefit that outweighs the risk.

16 The voting question will be should the  
17 approval selinexor be delayed until results of the  
18 randomized phase 3 BOSTON trial are available. A  
19 vote of yes means that an approval decision should  
20 be delayed until the results of a randomized phase  
21 3 trial are available and we have more information.  
22 A vote of no means that benefit-risk has already

1       been demonstrated such that approval can be  
2       considered without further data from the randomized  
3       trial.

4               Thank you. This concludes the FDA clinical  
5       presentation.

6                               **Clarifying Questions**

7               DR. RINI: Thank you.

8               We're now going to take clarifying questions  
9       from the committee to the presenters. If you'd  
10       like to speak, and I encourage everyone to do so,  
11       just state your name for the record. And if you  
12       want to speak, just give Lauren a wave, and she'll  
13       write your name down in order, and then we'll call  
14       you out in turn.

15               I'll go ahead and start while people are  
16       thinking. I think it was Dr. Jagannath who  
17       mentioned that a large proportion of patients had  
18       improvement in their renal function from baseline  
19       till on therapy or end of therapy, and I think  
20       implied that maybe there were improvements in other  
21       end-organ function as well.

22               You guys have characterized this population,

1 I think rightfully so, as was one with obviously  
2 refractory disease, high-tumor burden rapidly  
3 progressive disease, so I'm wondering if there's  
4 been other analyses of the renal function  
5 improvement or other end-organ improvement for  
6 patients on trial.

7 DR. SHACHAM: I'm going to ask  
8 Dr. Jagannath to answer the question.

9 DR. JAGANNATH: As you correctly pointed  
10 out, these are advance and refractory myeloma, and  
11 this particular trial allowed us to enroll patients  
12 with severe renal impairment with an eGFR of  
13 20 milliliter and above. It allowed us -- with  
14 patients with hematologic compromised, already with  
15 grade 2 hematologic toxicity with platelet count as  
16 low as 50,000 or about, and anemia, a hemoglobin  
17 grader than 8, which normally does not use the  
18 criteria. But this was very advanced refractory  
19 myeloma, and their disease was progressing rapidly.

20 The second point, also these  
21 patients -- this was an oral agent -- from the time  
22 they enrolled to their first dosing, within that 2

1 weeks time, you saw 22 percent increase in their  
2 paraprotein going up. So we have a need to have a  
3 drug that not only is effective but brings the  
4 myeloma down rather quickly. So we feel that it is  
5 important to use this dose recommended at full dose  
6 to bring the disease under control within the first  
7 month.

8           The second thing is most of the adverse  
9 events, which are attributed to this particular  
10 medicine, are all familiar to the oncologists.  
11 They are hematologic, which are thrombocytopenia,  
12 and the hematologists are very comfortable. And in  
13 terms of the non-hematologic toxicity, it is more  
14 in terms of nausea, vomiting, low sodium, or  
15 fatigue, and this could all be managed with NCCN  
16 guidelines with the use of the appropriate  
17 anti-nausea medication, et cetera.

18           That's where we noted that not one isolated  
19 case had presented, but 29 other patients with  
20 renal impairment got better. But I do not  
21 personally know all the hematologic patients who  
22 came under grade 2 toxicity.

1 DR. SHACHAM: Dr. Jagannath, do you want to  
2 also discuss pain, plasma cytomas, and other  
3 aspects of tumor burden?

4 DR. JAGANNATH: Rapid tumor control in  
5 advanced myeloma, as my colleague Doc Chari would  
6 say, advanced myeloma itself gives rise to a lot of  
7 adverse events: pain, plasma cytomas, fractures,  
8 and infection and complications like that. Under  
9 those circumstances, having a drug which brings the  
10 myeloma down and rapidly controls it also helps in  
11 the mitigation of the pain, avoidance of fracture,  
12 so it improves the patient's quality of life there,  
13 too.

14 DR. RINI: I agree with you. My question is  
15 do you have quantification of all those things you  
16 just said, about improvement in renal function,  
17 reduction of pain, reduction of fractures? I  
18 totally believe what you said. I'm just wondering  
19 if there's quantification of that.

20 DR. SHACHAM: I can add to that. If the  
21 team can provide the data on -- we had 29 patients  
22 that started the study with moderate to severe

1 renal impairment. The response rate in this  
2 patient population was similar to the overall  
3 populations. The exposure in these patients was  
4 similar, and we didn't require different doses for  
5 this patient population.

6 The AE profile in this population was  
7 similar, and more than half of them actually had  
8 improvement, including dose with severe renal  
9 impairment. We show improvement in their renal  
10 function. In addition, when we looked at the  
11 quality-of-life data, we show improvement in pain  
12 score with the limitation of using quality-of-life  
13 data in a single-arm study.

14 DR. RINI: Dr. Harrington?

15 DR. HARRINGTON: Thank you; a question for  
16 the sponsor. A drug, which at least in combination  
17 with dexamethasone, has side effects. I would  
18 assume as a trialist that the trial was done in a  
19 limited number of expert investigators who would  
20 have had rapid communication from managing the side  
21 effects.

22 So should we expect that your algorithms for

1 managing treatments -- once the drug, if it's  
2 approved -- will show fewer side effects than  
3 you've seen in your trial or no worse than you've  
4 seen in your trial? Are you essentially trying to  
5 prevent things from being more dangerous?

6 DR. SHACHAM: This study was conducted in  
7 over 30 sites across the U.S. and Europe. The  
8 learning from there is being summarized as we  
9 are -- and I will ask Dr. Jagannath and  
10 Dr. Richardson to speak about the learning and the  
11 ability to implement this from patient number 1 if  
12 the drug is approved.

13 DR. JAGANNATH: Yes. When we participated  
14 in the clinical trial, it was our first experience.  
15 It took us about 2 to 3 patients before we realized  
16 the side effect profile of this particular drug.  
17 What is unique is the side effect profile of this  
18 drug is quite different from the other myeloma  
19 drugs. Its major side effects, hematologic, is  
20 thrombocytopenia, but that we anticipated because  
21 we enrolled patients with grade 2 thrombocytopenia,  
22 about 60 patients with platelet counts which were

1 on the lower side below 100. So thrombocytopenia  
2 we anticipated.

3           What was somewhat different in this  
4 particular one was the nausea, vomiting, anorexia,  
5 and hyponatremia. So once we started realizing  
6 that there was nausea, vomiting, and anorexia in  
7 this particular patient population, then we started  
8 using the commonly used NCCN guideline. While the  
9 solid tumor oncologists are very familiar with it,  
10 in myeloma, we had the luxury of going through a  
11 series of novel agents without nausea and vomiting.  
12 So we were able to implement the NCCN guidelines,  
13 including using the olanzapine and using meges [ph]  
14 for these patients as an appetite stimulant.  
15 Monitoring the sodium, the hyponatremia turned out  
16 it was not related to SIADH; it was due to poor  
17 oral intake or avoiding dehydration. We were able  
18 to give them salt tablets at home or to give them  
19 IV fluid hydration.

20           All of this, now that we know, we are able  
21 to start them, and monitor them weekly, and  
22 anticipate them, so we are able to manage better.

1 Thank you.

2 DR. HARRINGTON: Do you have data, then,  
3 from this trial showing that the incidence of those  
4 side effects, or the seriousness, or the  
5 reversibility decreased over time as you learned  
6 from the patients on the trial? We see just the  
7 aggregated data. Are there time trends?

8 DR. SHACHAM: Yes. We have looked at the  
9 number of days that patients experienced an AE in  
10 the different cycles. In many of the side effects,  
11 as we mentioned, including anorexia, vomiting,  
12 nausea, and fatigue, we see that the number of  
13 days, which if you'll take the cumulative of all  
14 grades, around 7 days out of the 28-day cycle, in  
15 all of these, it's not getting worse. And in some  
16 cases, like nausea and vomiting, it is getting  
17 better with time. We can provide these results, if  
18 needed, after the break.

19 DR. HARRINGTON: Thanks. It's not quite my  
20 question. My question is, over time, over the  
21 course of the 123 patients, do you see either a  
22 decrease in the side effects or an increase in the

1 manageability of those side effects so that if this  
2 is approved and your algorithms are made public, we  
3 can expect that oncologists can use this drug in  
4 this very difficult population acceptably well?

5 DR. SHACHAM: I'll ask to put the slide  
6 about high-enrolling sites. Dr. Richardson?

7 DR. RICHARDSON: I would just add to that,  
8 the sites that enrolled more patients, we saw a  
9 higher response rate reflecting the greater  
10 experience with the drug. And speaking for  
11 ourselves, we had a very similar learning curve to  
12 what Dr. Jagannath alluded to. And I think over  
13 time, certainly, we'd anticipate that these side  
14 effect management profiles would have a positive  
15 impact.

16 To your question, Dr. Harrington, about the  
17 effects over time, perhaps, Sharon, if the team has  
18 it on one of these slides, that might be useful to  
19 show.

20 DR. SHACHAM: For both cycles?

21 DR. RICHARDSON: Yes, exactly; this one  
22 here.

1 DR. HARRINGTON: I'm sorry [inaudible - off  
2 mic].

3 DR. RINI: Dr. Thanarajasingham?

4 DR. THANARAJASINGAM: I'm a practicing  
5 hematologist, a clinical investigator, and a  
6 researcher that's focused on adverse events in the  
7 evaluation of tolerability, which by necessity  
8 involves the perspective of the patient. I know in  
9 this study -- and neither group discussed it -- you  
10 did employ the FACT multiple myeloma, which is a  
11 static instrument that gets at some aspects of  
12 tolerability, so I have a few questions related to  
13 that.

14 Number one, of the 122 patients, baseline  
15 and 4-week post-FACT myeloma scores were available  
16 only in 83, so I wonder if you looked at what the  
17 reasons for data missingness from the data that was  
18 collected from patients was. Then additionally,  
19 looking at some of the impact on patients, we talk  
20 about patients appreciating oral therapies because  
21 it's something they can do at home. But I note  
22 you're recommending weekly monitoring during the

1 first 8 weeks, and given the high incidence of  
2 symptomatic AEs, are you recommending that that be  
3 done in clinic?

4           Additionally, there is over 20 percent of  
5 patients with grade 3 to 4 hyponatremia, so that's  
6 sodiums in ranges of 125. And as Dr. Jagannath  
7 said, you're attributing this to anorexia and  
8 dehydration. So do you have any data on how many  
9 patients actually required IV fluid repletion, and  
10 on average how often?

11           I think these are all things that affect  
12 tolerability and patient's experience on this drug,  
13 which I would like some more information about.

14           DR. SHACHAM: Okay. I will answer all the  
15 questions one by one. If the team can first put  
16 the quality-of-life data. Thank you.

17           These are the quality-of-life results, and  
18 as you mentioned, on the slide on the left, we have  
19 83 patients that have at least one post-baseline.  
20 We did not look specifically at the reason why we  
21 don't have quality of life for the other 40  
22 patients, but we did look to see is there a bias

1 and are we selecting only patients that responded,  
2 and the answer to that is no. The response rate  
3 was among 40 patients that did not fill out the  
4 questionnaire, and the response rate among the  
5 83 patients that filled out the questionnaire was  
6 similar.

7 I should mention that we do see this pattern  
8 of reduction in quality of life that is below the  
9 10 percent reduction and then returns to baseline,  
10 which we also -- in the other question.

11 I will answer quickly on your question about  
12 hyponatremia, for the team to provide the number of  
13 hydration and repeated [indiscernible], and then I  
14 will ask Dr. Chari to answer your last question  
15 about the weekly monitoring. If the team can  
16 provide the hyponatremia and the number of  
17 hydration. And maybe before -- until the team can  
18 find the slide, I will ask Dr. Chari to answer, and  
19 then I'll get to you about the hyponatremia.

20 DR. CHARI: Hi. Ajai Chari at Mount Sinai  
21 where we dosed 34 patients on STORM, and I'm a  
22 director of clinical research. I think it's

1 important with this patient population, with a  
2 median of 7 lines of prior therapy, baseline  
3 cytopenia as you heard about the renal dysfunction,  
4 most of these patients are being seen quite  
5 regularly in clinic as it is, whether or not they  
6 were on a study, given the refractoriness of their  
7 disease. So I think the weekly monitoring is  
8 proactive.

9 To address some of the other questions, too,  
10 we did see that -- because of the short half-life  
11 of the drug, which I don't think has been  
12 emphasized, dose-holding interruptions leads to  
13 rapid improvement in symptoms, and that allows  
14 patients to stay on therapy. Also, there's not  
15 been any cumulative.

16 To the earlier question, most of the dose  
17 modifications occur in cycle 1 and 2, so  
18 subsequently, we see stabilization of the dose. I  
19 think that is partly to explain why even though we  
20 have the median PFS of around 3 and a half months,  
21 the patients who had a response had a median OS of  
22 15.6 months, which I think alleviates some of the

1 concern about cumulative impact on toxicity or  
2 ability to go to salvage therapies.

3 DR. SHACHAM: For your last question, most  
4 of the patients had only one IV hydration due to  
5 hyponatremia. We have the analysis. We can find  
6 it. We'll provide it after the break.

7 DR. RINI: Dr. Hawkins?

8 DR. HAWKINS: Thank you. To my panel  
9 members that actually asked, it is my concern as  
10 well, but I'm going to mention just for emphasis.  
11 One was objective assessment of quality of life  
12 for those who are able to tolerate the drugs, and  
13 you've answered that to some degree.

14 The second one, since this is a new drug, we  
15 understand that side effects are being mitigated by  
16 standard of care but also dose reduction. Maybe on  
17 the scope of this study, this presentation, any  
18 study by Karyopharm about new approaches to prevent  
19 or mitigate side effects based on this novel class?

20 DR. SHACHAM: I will ask Dr. Kauffman and  
21 Dr. Chari to respond to the question.

22 DR. KAUFFMAN: The biggest best learning we

1 have to date is that the anorexia, which we've seen  
2 in animal models; it's the most prominent toxicity,  
3 and patients describe it truly as satiety  
4 induction, is rapidly mitigated with olanzapine  
5 and/or megesterol. For patients that are at risk  
6 for that side effect, if they've had it before,  
7 their slim body weight, et cetera, we would  
8 recommend that that be used up front as a  
9 prophylactic measure. And we showed some data  
10 during the presentation that prophylactic use of  
11 those agents can actually mitigate, substantially,  
12 not only anorexia but nausea and fatigue as well.

13 As far as additional modes to do this, the  
14 difficulty is I think -- just quickly to hit home  
15 these numbers because I ran through it quickly.  
16 For looking at any AEs at that first column after  
17 the description of the event, for patients who  
18 received no prophylactic supportive care across all  
19 of our myeloma program -- so this is a larger  
20 safety data set -- 87 percent of patients will  
21 experience at least one event of nausea, vomiting,  
22 fatigue, or anorexia, but that will reduce to

1 two-thirds if we do implement supportive care. You  
2 can see that each of the three components of that  
3 will be reduced significantly with prophylactic  
4 supportive care, so that's quite helpful.

5 The population is very difficult, and I'll  
6 Dr. Chari now to talk about how to interact in that  
7 population.

8 DR. CHARI: Several novel interventions seem  
9 to be beneficial to your question. For example,  
10 with nausea and the GI symptoms, we did use, per  
11 NCCN guidelines, the NK inhibitors, and those seem  
12 to be helpful in patients. With platelets, we did  
13 use TPO agonists because we know that,  
14 preclinically, selinexor blocks thrombopoietin in  
15 the megakaryocytes, and we saw that patients  
16 were able to recover platelets faster. For  
17 patients with fatigue, we did also occasionally use  
18 Ritalin.

19 So all of these in our site, out of the 34  
20 patients, I think 5 came off for AEs, and most of  
21 those were early on. So I think it speaks to the  
22 ability to dose these patients with appropriate

1 supportive care.

2 DR. RINI: Dr. Cristofanilli?

3 DR. CRISTOFANILLI: Thank you; a couple of  
4 questions. One is, obviously, you see the  
5 module [indiscernible] criteria for approval of  
6 this drug to make this easier for the patient, and  
7 at the same time we don't have a comparison arm, so  
8 one is the design of the study that you probably  
9 were discussing internally. You have very generous  
10 criteria from [indiscernible], so many of these  
11 patients had thrombocytopenia and anemia. Have you  
12 ever thought about making this more restrictive if  
13 possible?

14 Second, if you were to design a control arm,  
15 which one was going to be a control -- was it even  
16 possible or if there was any possibility of choice?

17 A third question, very quickly, is it seems  
18 like this is a synergistic effect with the  
19 steroids. What's the molecular mechanism? Do you  
20 think the regulation of steroid receptor has  
21 something to do with it or you are trying to  
22 understand what the mechanism is?

1 DR. SHACHAM: I'll respond about the  
2 mechanism of the synergy. I would ask  
3 Dr. Jagannath to speak about the ability to have a  
4 control arm. Finally, to your last question, I  
5 will answer why we have permissive enrollment  
6 criteria.

7 About the synergy with dexamethasone, we  
8 know that once dexamethasone binds with the  
9 glucocorticoid receptor, the complex  
10 [indiscernible] to the nucleus. Once the myeloma  
11 cells are then treated with selinexor, we see  
12 nuclear localization of the activated  
13 glucocorticoid receptor. This leads to marked  
14 inhibition on NF-kappa-B signaling by selinexor  
15 itself as well as NF-kappa-B inhibition by the  
16 active glucocorticoid receptor.

17 Finally, only when the two drugs are treated  
18 together, we see inhibition of the mTOR pathway,  
19 which we don't see with each of the drugs alone.  
20 Taking together what we can see on the graph on the  
21 right, while this is an xenograft in a  
22 myeloma -- while each of the drugs alone had only

1 partial inhibition of myeloma growth, when the two  
2 drugs are given together, we see very significant  
3 anti-myeloma activity.

4 Dr. Jagannath, can you comment now on the  
5 other two questions?

6 DR. JAGANNATH: Yes. This is a tough  
7 population who have already seen all the available  
8 drugs and have actually recycled the drugs because  
9 by the time they came on the clinical trial, the  
10 median number of prior treatment has been 7. Not  
11 only that, in this trial itself, we showed from the  
12 time of enrollment, within 2 weeks to get to the  
13 first dose, there was a 22 percent increase in the  
14 paraprotein.

15 We allowed patients with renal impairment,  
16 severe renal impairment, up to an eGFR of 20, and  
17 we had thrombocytopenia with a platelet count down  
18 to 50 already. It doesn't take much to become  
19 grade 3. Also the same thing for ANC, just about  
20 1,000, and we allowed hemoglobin about 8.

21 So that was designed simply because that is  
22 the only way we can manage the patient. I don't

1 think we could have an equipoise to have a control  
2 arm, and I will have my colleague Dr. Paul  
3 Richardson also comment on that to talk about that  
4 control arm.

5 DR. RICHARDSON: Thank you, Sundar.

6 No, I agree that in the triple-class  
7 refractory patient population -- and it's critical  
8 to recognize that these patients are refractory to  
9 daratumumab based treatments, so daratumumab has  
10 failed them. This is an exquisite unmet medical  
11 need in our clinic, and there is an absolute  
12 profound difficulty with equipoise in these  
13 patients.

14 I'll bring your attention to a phase 3 trial  
15 that was conducted using carfilzomib in a similar  
16 very advanced population but not as refractory as  
17 this. It was the so called FOCUS trial, and that  
18 trial actually failed. It did not show benefit to  
19 carfilzomib, which we have shown in different  
20 settings has clearly shown survival benefit and  
21 it's now broadly used across the world, in fact.  
22 So there's a precedent here to show that controlled

1 trials in this setting are very challenging.

2 DR. RINI: Dr. Klepin?

3 DR. KLEPIN: Thank you. Regarding the  
4 discussion about toxicity, could you provide us  
5 some data with respect to particularly serious  
6 adverse events by age? So about half of the  
7 patients on this study I believe were 65 years of  
8 age or older or close to that. Could you show us  
9 the adverse events by age?

10 DR. SHACHAM: I will ask Dr. Shah to discuss  
11 these results.

12 DR. SHAH: Thank you. It's an important  
13 question, especially as our patients are older, in  
14 general, for myeloma; so it's an important patient  
15 population to discuss. I do want to highlight,  
16 number one, that we did have 19 patients above the  
17 age of 75 that were enrolled. Before I get into  
18 the adverse events, I do want to note that these  
19 patients had a similar efficacy with a response  
20 rate for these patients at 27.8 percent, so there's  
21 preserved efficacy in this patient population.

22 Specifically, when we look at the adverse

1 event profile, there are a couple of things I just  
2 want to highlight here. Number one, they had  
3 broadly a very similar side effect profile, but  
4 what you will notice here is that there is an  
5 increased incidence from -- overall, their adverse  
6 event profile looks similar. When you look at  
7 grade 3 and grade 4 events, there was an increased  
8 number of patients with a decreased appetite and  
9 asthenia, as we'd expect in our older patients.  
10 But they also had, on the same hand, less nausea  
11 and cytopenias.

12 When we looked at specifically SAEs, these  
13 patient populations really had a very similar SAE  
14 profile, however, they did have an increased  
15 incidence of pneumonia but no other evidence of  
16 increased sepsis or deaths.

17 DR. RINI: Dr. Halabi?

18 DR. HALABI: Thank you. I have two  
19 questions to the sponsor. Obviously, like everyone  
20 else, I'm concerned about the AEs. One thing that  
21 I'm struggling with is the dosing of selinexor. In  
22 one trial, you used 60 mg, in the STORM trial, you

1 used 80 mg, and in the BOSTON trial, you're using  
2 100 mg. Based on the collective data, did you look  
3 at the dosing and the incidence of AE by the dose?

4 DR. SHACHAM: We have. First, to your first  
5 point, in the STORM study, we are using the highest  
6 weekly dose compared to all other studies. This is  
7 due to the highly progressive disease that the  
8 patients has at study entry and the immediate need  
9 to halt the disease. In that dose, if we look at  
10 the weekly dose, it's 160.

11 In the BOSTON study, we are using the dose  
12 of 100 mg once weekly in combination with  
13 bortezomib and dexamethasone, and this is due to  
14 the marked synergy that we observed in preclinical  
15 studies of selinexor with proteasome inhibitor.  
16 I'll just show it briefly that is due to the  
17 inhibition of the I-kappa-B signaling by both  
18 agents. This allows us to use a once weekly of  
19 both selinexor as well as bortezomib.

20 I will ask Dr. Bahlis to comment on the  
21 safety of the STORM study compared to the STORM  
22 study.

1 DR. BAHLIS: Good afternoon. I'm Nizar  
2 Jacques Bahlis, a clinician scientist from the  
3 University of Calgary and lead investigator on the  
4 STORM trial. The STORM trial was the rationale for  
5 the BOSTON trial, and it was based on the marked  
6 response rate seen in the STORM trial, the high  
7 safety and tolerability of this study.

8 Indeed, we enrolled over 20 patients on the  
9 STORM trial. In this study, selinexor was given  
10 weekly at a dose of 100 milligrams in combination  
11 with bortezomib 1.3 milligrams. And importantly,  
12 relevant to the population that will be cited on  
13 the BOSTON trial, as you can see on the slide in  
14 front of you, the toxicity profile was very well  
15 tolerable and manageable.

16 As you can see, in particular for the weight  
17 loss and anorexia, it was very low, 19 percent;  
18 thrombocytopenia was at 40 percent; and overall  
19 with a very well tolerable and manageable toxicity  
20 profile. And again, this reflects the weekly  
21 dosing of selinexor with low-dose bortezomib and  
22 the high efficacy in this combination.

1 DR. SHACHAM: Do you want to add [inaudible  
2 - off mic].

3 DR. BAHLIS: The time on therapy, in  
4 particular, if you consider the population that  
5 will be studied in the BOSTON trial, which is a  
6 non-refractory population, the response rate was  
7 very high, 84 percent. Importantly, the median  
8 progression-free survival on this study, was 17.9  
9 months; again, reflecting that the patient did  
10 tolerate the treatment very well and the response  
11 was very durable; again, resulting from the low  
12 toxicity and also the high efficacy,

13 DR. HALABI: Thank you. Then the next  
14 question is the sponsor presented an analysis of  
15 overall survival by response in slide CO-421, and I  
16 was wondering why did you include the MR responders  
17 as part of the ORR? Did you do the analysis just  
18 based on ORR versus the other groups, and can you  
19 share that survival data by these groups?

20 DR. SHACHAM: I will answer about the  
21 numbers, and then I will ask Dr. Richardson to  
22 discuss the significance of including MR in the

1 prediction of survival in patients with myeloma.  
2 We did look at the results separately. The overall  
3 response rate of patients with CL [ph] or above  
4 15 months. If we are looking only on the 16  
5 patients that have minimal response, their overall  
6 survival was 12.5 months, and together, the overall  
7 responses of all patients with MR and above, as we  
8 are showing, was exactly like those with 15 months.

9 DR. RICHARDSON: Yes. I would just like to  
10 add that minimal response in the myeloma space has  
11 been validated as a surrogate for clinical benefit  
12 in randomized prospective phase 3 trials and  
13 similar populations of relapsed refractory myeloma,  
14 albeit much less heavily pretreated. This is in  
15 contrast to, for example, the AML study, where you  
16 saw responses that didn't appear to correlate. And  
17 in that setting, we don't see a correlation in the  
18 AML world that is anything remotely like we see in  
19 myeloma. In myeloma, minimal response clearly  
20 matters.

21 DR. HALABI: Thank you. And my last  
22 question is for the FDA. I would like to get

1 clarification on the accelerated approval. If  
2 selinexor has accelerated approval and the results  
3 of the BOSTON trial were negative, where do we go  
4 from there?

5 DR. PAZDUR: That's a big problem.

6 (Laughter.)

7 DR. PAZDUR: That is a big problem because  
8 here again, you have a situation where it's a  
9 different situation; obviously, a different  
10 clinical situation. One is in a much earlier phase  
11 of disease. That's why this would be a very  
12 difficult decision to make, and we would have to  
13 have a discussion of what other trials could be  
14 done, perhaps. One other option is withdrawal of  
15 the drug, obviously.

16 DR. RINI: Thank you. Dr. Hinrichs?

17 DR. HINRICHS: I have a question for the  
18 sponsor about the rationale behind the clinical  
19 trial design. It's a single-arm combination  
20 clinical trial that was conducted. The FDA  
21 guidance on this is pretty clear, and the  
22 complexities and the interpreting data that comes

1 out of that kind of a trial are I think well  
2 understood, and that's what we're grappling with  
3 now.

4 Can you explain your rationale for doing the  
5 trial in that way, and did you have conversations  
6 with the FDA beforehand about how you would  
7 interpret the results and what would lead to  
8 approval?

9 DR. SHACHAM: Yes. We did discuss with the  
10 FDA, and they mentioned several times in the  
11 meeting that this will be a real issue and that  
12 they prefer randomized studies.

13 I will ask Dr. Richardson to comment more  
14 about the design of the study and why it is  
15 designed like that, but I should mention that  
16 similar studies with the similar endpoint were done  
17 in other accelerated approvals in myeloma.

18 Dr. Richardson?

19 DR. RICHARDSON: It's very clear in this  
20 particular relapsed refractory population that any  
21 kind of randomization is very difficult, and we've  
22 discussed that previously. I think the critical

1 point here with this particular trial design was an  
2 effort to address an exquisite area of unmet  
3 medical need of triple-class refractory patients  
4 and with a signal that had been seen from the  
5 combination of selinexor with dexamethasone in the  
6 earliest phase trials.

7 Given the exquisite unmet medical need in  
8 the triple-class refractory group, a single-arm  
9 trial was embarked upon. The part 1 was  
10 encouraging and part 2 followed. That I think  
11 would be a fair summary.

12 DR. SHACHAM: Maybe also we can discuss that  
13 all of our patients except -- or received 6 lines  
14 of [indiscernible] or dexamethasone, so their  
15 disease was refractory to dexamethasone. And even  
16 the vast majority of them, all but 6, received  
17 dexamethasone containing regimen in the very last  
18 regimen, and all entered the study, as we showed,  
19 with very rapidly progressing disease.

20 DR. HINRICHS: I have one more question  
21 about the rationale for the combination. You  
22 showed us one slide with an experiment as the

1 unigraph model that was carried out 17 days that  
2 appeared to show that the combination was better  
3 than either one alone.

4 Do you have more data than that to support  
5 the combination?

6 DR. SHACHAM: Yes. We have done it in many  
7 cell lines, including those cell lines like the  
8 MM1R that is resistant to dexamethasone, and we  
9 managed to show the synergy between the two drugs,  
10 if the team can provide the previous slide. And we  
11 have shown this in many xenograft models.

12 In addition, when we are looking at the  
13 biopsy for patients in myeloma in the phase 1  
14 itself, as I can see here on this slide, that were  
15 treated with selinexor 45 metered-squared, which is  
16 equivalent to the 80-mg dose and dexamethasone,  
17 what we can see is the increase, and the  
18 understanding here is for the active glucocorticoid  
19 receptor. We see an increase in nuclear  
20 localization of the active glucocorticoid  
21 receptors, and when we look at cell lines, we see  
22 the downstream signaling is coming into effect.

1 DR. HINRICHS: So just to follow up on that,  
2 do you have other translational research from the  
3 clinical trial that you've conducted that suggests  
4 that there is cooperation between or synergy  
5 between the two agents?

6 DR. SHACHAM: We have several of those  
7 looking at the glucocorticoid receptor. In  
8 addition, if the team can provide the biopsy  
9 results, what we definitely see in these clinical  
10 trials from the phase 1 is that selinexor penetrate  
11 the tumors. It does what it's supposed to do, that  
12 it increases to p53, PLB. It increased nuclear  
13 localization of cell [indiscernible] and induction  
14 of apoptosis. So we definitely see the activity of  
15 selinexor in biopsies from patient tumors.

16 DR. GORMLEY: Can I respond a little bit as  
17 well?

18 DR. RINI: Yes, please.

19 DR. GORMLEY: I just wanted to make sure  
20 that we're clear about one aspect. The applicant  
21 just mentioned that there are other scenarios where  
22 there are single-arm trials of a combination that

1 led to approval. I don't know if you have the  
2 backup slides for the FDA. If you could pull up  
3 slide 12; and I'm not sure what examples the  
4 sponsor is referring to, but they're very different  
5 situations, so I'd just like to flesh that out a  
6 little bit.

7 Most recently in 2017 -- I'll wait a moment  
8 until the slide comes up. So most recently in  
9 2017, daratumumab was approved in combination with  
10 pomalidomide and dexamethasone. Although this was  
11 a single-arm trial of a combination, it arose in a  
12 setting of a very different situation. Daratumumab  
13 had already been approved. It was initially  
14 approved as monotherapy in 2015 and showed a  
15 single-arm response rate at that time of about 29  
16 percent.

17 It was subsequently then approved in  
18 combination with lenalidomide and dexamethasone and  
19 bortezomib and dexamethasone based on randomized  
20 control data in 2016. Pomalidomide was approved in  
21 2013 and '15 in combination with dexamethasone, an  
22 ORR response rate of 29 percent, so then the

1        dara-pom-dex approval, which was a single-arm trial  
2        of a combination, showed a response rate of 60  
3        percent.

4                So in some ways, although this was a  
5        single-arm trial of a combination, these were both  
6        already approved products that had clear response  
7        rates, known safety and efficacy profile, and in a  
8        way sort of did the factorial design outside of a  
9        single-trial setting.

10               One other aspect that I would like to just  
11        point out is that we have and do have a history of  
12        relying on single-arm trials for approval, but  
13        generally there are not single-arm trials in  
14        combination. These are oftentimes patients at the  
15        end of therapy. But if you're combining it with  
16        another product, because that's what's needed for  
17        synergy or activity of your product, then  
18        randomized trials or other data are really needed  
19        to support that.

20               I guess the other aspect to consider is that  
21        there are other options for these patients, just  
22        generally, such that there could be clinical

1        equipoise for trials to be conducted, either  
2        allowing, as was done in the AML trial, physician's  
3        choice of various retreatment, et cetera. And  
4        there is a history and experience for retreatment  
5        with agents that patients have previously seen in  
6        multiple myeloma.

7                Again, if you wouldn't mind pulling up  
8        backup slide number 10 from the FDA presentation,  
9        in this application, this was a retrospective  
10       center. Again, this was a looking at a  
11       dara-pom-dex, which we were just discussing, as an  
12       approved regimen for the treatment of patients with  
13       multiple myeloma. This study was a retrospective  
14       single-center study, evaluating patients receiving  
15       treatment with dara-pom-dex.

16               A lot of these patients in cohort 2 were  
17       refractory to either dara or pomalidomide. In  
18       cohort 3, they were refractory to dara and pom, and  
19       we see response rates between 40 and 30 percent.  
20       Again, this is a small cohort, but dara-pom-dex is  
21       approved for the treatment of multiple myeloma.  
22       And there have been other studies, which I can

1 show you if that would be helpful, other small  
2 cohorts also evaluating this.

3 If you go to the next slide, there was a  
4 small study by Lakshman, a small study by Hussain,  
5 again, showing similar response rates for patients  
6 that are either refractory to dara or pom or dara  
7 and pom. In general, retreatment with various  
8 combinations is an option for patients. So a trial  
9 design, if your trial does require a combination  
10 with another medication, could be against best  
11 supportive care or a physician's choice. So I just  
12 wanted to clarify that regarding our position.

13 DR. RINI: Thank you. Dr. Uldrick?

14 DR. SHACHAM: If we ma, can we have  
15 Dr. Jagannath and Dr. Richardson discuss the  
16 retreatment because it's an issue --

17 DR. RINI: Sure.

18 DR. SHACHAM: -- that the FDA mentioned.

19 DR. JAGANNATH: Yes, we do retreat the  
20 patient. As I mentioned, we also recycle the  
21 chemotherapy. That is very evident in this patient  
22 population that we've taken into account. These

1 patients have had not only triple class refractory;  
2 they have been exposed to alkylating agents and  
3 other monoclonal antibodies such as elotuzumab.  
4 They have gone through a median of 7 lines of  
5 therapy.

6           So the discussion between me and the patient  
7 at this particular juncture, when they came for  
8 selinexor, is whether supportive care and comfort  
9 care and hospice is an acceptable option because I  
10 do not have a curative treatment option for this  
11 patient at this time, or whether they would still  
12 like to try a particular drug, which has is a new  
13 drug with a completely novel mechanism of action,  
14 so the patients were enrolled on this particular  
15 clinical trial.

16           In our center, we find it difficult, in New  
17 York, to enroll patients on a randomized clinical  
18 trial. Especially when the patients are coming at  
19 this advanced refractory stage, they come for  
20 consultation, whether you have an option for me,  
21 not looking for whether I have a randomized trial  
22 and I'm willing to participate.

1 DR. RICHARDSON: I would simply add that,  
2 indeed, there is an algorithm for retreatment as  
3 pointed out. But in this setting of triple-class  
4 refractory, penta-refractory patients in terms of  
5 the amount of prior therapy, the lack of equipoise  
6 in doing that is very difficult, and this  
7 single-arm effort to explore this signal obviously  
8 therefore followed.

9 So I would just go back to that point about  
10 equipoise being very challenging for such an  
11 approach.

12 DR. SHACHAM: I'd like to summarize and add  
13 that 70 percent of our patients actually received  
14 already daratumumab in combination. The vast  
15 majority of them received it in combination with  
16 pomalidomide. So the dara-pomalidomide  
17 dexamethasone combination was already used in our  
18 patients.

19 I also would like to highlight -- and if the  
20 team can provide -- that only 13 out of our 122  
21 patients actually were able to be retreated with  
22 IMiDs, proteasome or daratumumab, pointing to the

1 fact that the physician on the study chose, after  
2 the disease of the patient progressed on selinexor,  
3 not to recycle because of the lack of activity of  
4 recycling at this stage. Thank you.

5 DR. RINI: Dr. Uldrick, now.

6 DR. ULDRICH: In looking at the safety data  
7 in this triple refractory patient population, one  
8 of the concerns I have is that the dosing has not  
9 been optimized to prevent serious adverse events.  
10 And I was hoping you could expand on the SAE  
11 observed in the study. Sixty percent of the  
12 patients had SAEs and 90 percent had dose  
13 reductions.

14 How many of the SAEs occurred during the  
15 first cycle of therapy, and can you give a  
16 breakdown of what percent of the SAEs were  
17 attributed to progressive disease versus the  
18 medication?

19 DR. SHACHAM: Yes. I'll ask Dr. Kauffman to  
20 answer the question and for the team to provide the  
21 SAE slide.

22 DR. KAUFFMAN: In this heavily pretreated

1 population with refractory myeloma, the most common  
2 SAEs were unfortunately what's expected in this  
3 population, which is pneumonia and sepsis and other  
4 infections. These are reported in essentially all  
5 other trials to be very common in myeloma. There's  
6 to 7- to 15-fold increased risk for these  
7 infections in patients, in general, with Myeloma.  
8 And I should mention that what you don't see on  
9 here is febrile neutropenia or a lot of other cases  
10 of neutropenia.

11 We did have low rates of serious adverse  
12 events from thrombocytopenia and anemia. Despite  
13 the fact that these were common cytopenias, they  
14 were generally not symptomatic. And the cases of  
15 mental status changes that were mentioned and are  
16 shown here, which can be coupled also to  
17 confusional state, were generally accompanied by  
18 multiple other symptoms, including infection in  
19 most of these cases, acute kidney injury and  
20 dehydration.

21 Most of the serious adverse events did occur  
22 typically in the first cycle when there is, if

1 you'll pardon the analogy, a kind of war between  
2 the drug in this rapidly escalating myeloma. Once  
3 we got the myeloma under control, we could  
4 generally reduce the dose somewhat and allow the  
5 patients to have better tolerability, reduced  
6 overall side effects, and control their myeloma for  
7 a prolonged period.

8 DR. ULDRICH: Just as a related question, I  
9 saw on one of the previous slides, when you were  
10 showing the treatment-emergent adverse events from  
11 STORM, which I believe was 100 milligrams once  
12 weekly, that there were far fewer cytopenias but  
13 more GI AEs. Do you have the data on the SAE  
14 profile of that dosing as well?

15 DR. SHACHAM: We do not have the SAE. We  
16 can try and get it after the break. I will just  
17 mention that some of the increase that you see is  
18 because patients were staying over a year on  
19 therapy, so that chances of getting any is bigger  
20 than in the STORM study.

21 DR. RINI: Dr. Morrow?

22 DR. MORROW: Hi. I just wanted to go back

1 to the toxicity again. You alluded to -- Dr. Chari  
2 actually alluded to, in addition, the prophylactic  
3 regimens that you alluded to in CO-60, utilization,  
4 for example, of TPO agonists, NK1 antagonists, and  
5 others.

6 Can you expand and explain what are the  
7 plans to incorporate additional agents such as that  
8 into your comprehensive algorithm for management of  
9 toxicity, and then also comment a little bit about  
10 the rates of these AEs within your institution or  
11 others with that utilization?

12 DR. SHACHAM: I'm going to ask Dr. Kauffman  
13 to answer the first question, and then for  
14 Dr. Chari to speak, and for the team to provide the  
15 five key steps slide.

16 DR. KAUFFMAN: We're in the process of  
17 constructing a number of publications that are  
18 underway already that include all of these kinds of  
19 things that we've learned about selinexor,  
20 particularly in this very difficult to treat  
21 population. We have implemented a nurse liaison  
22 team at Karyopharm who will be able to help prevent

1       these things and educate treating physicians with  
2       that as our major point, and we will provide as  
3       many -- with FDA's blessing, of course, we'll  
4       provide as many supportive and educational  
5       materials to treating physicians as possible.

6               We'll also be working with the myeloma  
7       advocacy groups -- we work with the IMF and the  
8       MMRF -- to provide the step therapy that we found  
9       effective for nausea, vomiting, and anorexia, which  
10      has been discussed, and the use of potential other  
11      supportive types of agents such as platelet support  
12      or neutrophil support, which will be appropriate in  
13      this end-stage population. We have a number of  
14      other management options that you've heard, and I  
15      think I'll turn it over to Dr. Chari now.

16             DR. CHARI: I think the vast majority of  
17      patients with, for example, GI, did respond to  
18      olanzapine used up front. Again, that's an agent  
19      that we in hematology have not used very much  
20      because most of our drugs do not have significant  
21      GI tox. So olanzapine with 5-HT3 antagonists for  
22      the vast majority of patients I think is adequate.

1 But that previous comment about NK was more  
2 directed for novel approaches, for those patients  
3 where perhaps that's not enough, we could escalate  
4 further.

5 With respect to the TPO question, I think  
6 what we saw is that the thrombocytopenia clearly  
7 correlates with baseline platelet entry, so we saw  
8 a lot more thrombocytopenia in patients who had  
9 grade 1 and grade 2 thrombocytopenias you would  
10 expect. These patients typically had more marrow  
11 burden, and that first cycle is very important  
12 because we need to get the myeloma dbALT, and then  
13 you're going to have that crossing of the platelet  
14 count dropping with drug but also improving with  
15 disease control.

16 So in that critical juncture I think is  
17 where TPO agonists may be helpful because a vast  
18 majority of patients who started with higher  
19 platelet count do not need TPO agonists. It's  
20 these patients who have the duality of high bulk of  
21 disease and starting low counts.

22 DR. RINI: Thank you. Dr. Harrington?

1 DR. HARRINGTON: I have a couple of  
2 questions for the FDA. Let me start with a tougher  
3 one that's imponderable here. Typically looking at  
4 accelerated approval in a single-arm study, we're  
5 all faced with uncertainty and we all have at least  
6 the security blanket that the FDA will solve this  
7 for us in the confirmatory trial. But in fact, the  
8 BOSTON study doesn't really solve anything here  
9 because it's a different clinical profile. It's  
10 different dosing. It's a different combination  
11 agent, and it doesn't actually isolate the  
12 single-arm activity of selinexor.

13 So this is a follow-up to Dr. Halabi's  
14 question, but I'm now completely confused about  
15 what the link is between this trial and it's  
16 approval in this particular patient population and  
17 the BOSTON trial.

18 DR. PAZDUR: Well, first of all, I think  
19 it's important. Many of the accelerated approval  
20 confirmatory studies are done in a different  
21 setting at the disease, And you could see that  
22 almost universally for all of our accelerated

1       approvals; because once we approve a drug, it's  
2       very difficult, then, to do a trial to confirm it  
3       in the same disease setting, and we also believe  
4       that it really moves the field forward here to look  
5       at a different disease setting.

6               As far as your comparing it to do different  
7       options, at least we will have acknowledged that  
8       there was a benefit from the addition of this drug  
9       to a regimen in multiple myeloma here, so there is  
10       that benefit that would be demonstrated.

11              DR. HARRINGTON: But in a very different  
12       population.

13              DR. PAZDUR: Correct, and that is not unique  
14       to this situation. I just want to make that real  
15       clear. This is something that we have done rather  
16       routinely with the accelerated approval  
17       confirmatory studies to look at an earlier setting  
18       of the disease and for the reasons that I've  
19       outlined.

20              First of all, when you approve a drug, if we  
21       approve this drug, we can't tell -- the equipoise,  
22       as has been alluded to, would be lost. How could

1       you ask somebody to go on a randomized study if the  
2       FDA approved the drug already in that disease  
3       setting? So if one wanted to get that setting, one  
4       would have to take a very stringent approach that  
5       before we did any regulatory action, a confirmatory  
6       study in that disease setting would have to be  
7       completely accrued at that time, and that's  
8       difficult to do, especially when you're saying that  
9       when one gives accelerated approval, it's our  
10      belief that this is better than available therapy.

11             DR. HARRINGTON: All right. I think I  
12      understand, but we can parse that later.

13             DR. PAZDUR: It's just how you want --

14             DR. HARRINGTON: No, I know.

15             (Crosstalk.)

16             DR. PAZDUR: -- the case here. We're  
17      interested in, obviously, a public health mission  
18      here of moving therapies rapidly along, rather than  
19      just looking at refractory disease settings. We  
20      want to move them into an earlier disease status  
21      and that accelerated approval, and looking at a new  
22      indication allows us to do that.

1 DR. HARRINGTON: I agree. But the draft  
2 question here is should we wait? The draft  
3 question isn't should we give this drug accelerated  
4 approval and it may be validated at some point down  
5 the line. This is should we wait?

6 I guess maybe I'll phrase my question  
7 differently. What are we waiting for? If the  
8 BOSTON works and still doesn't really tell us what  
9 the effect of selinexor was in this triple  
10 refractory population, if it doesn't work, it  
11 doesn't tell us that the empirical uncontrolled  
12 data in this trial were wrong. So maybe that's a  
13 more poignant way to ask my question. What does  
14 the delay get us?

15 DR. PAZDUR: I think the delay would get us  
16 additional information as far as the activity in a  
17 different disease setting; that this is a drug in  
18 this disease. One of the problems, as has been  
19 indicated in the FDA discussion here is, in  
20 contrast to other disease settings where we have  
21 used single-arm trials, we have seen activity of  
22 the single agent here, and this is a problem that

1 we're having with this. The single-agent activity  
2 is missing here.

3 DR. HARRINGTON: Okay.

4 DR. PAZDUR: So it gives us additional  
5 information.

6 DR. HARRINGTON: Yes.

7 Do I have time for one follow-up?

8 DR. RINI: Sure.

9 DR. HARRINGTON: A different question; well  
10 a related question. The FDA has proposed options  
11 for patients with this profile getting the drug  
12 through compassionate approval, single, patient  
13 protocols, et cetera. Since I don't treat -- I'm  
14 not a clinician -- I don't know the hoops that are  
15 presented by that versus being able to write a  
16 prescription. So perhaps you could help me  
17 understand if we don't approve and those other  
18 mechanisms are available, how difficult are they to  
19 access and to use?

20 DR. FARRELL: Well, you can actually call up  
21 the agency, and 24 hours a day, we actually  
22 respond. To get a drug on an individual patient

1 use, it requires agreement between the company, and  
2 you usually speak to a physician at night, and we  
3 discuss the case, and if you have approval from the  
4 company, it's usually granted over the phone.

5 A treatment IND or treatment protocol is a  
6 much easier way of getting access. It can be  
7 instituted like a study. So it's a submission to  
8 the agency. It goes to certain centers that are  
9 willing to participate, and it's just like  
10 enrolling any patient on a trial.

11 DR. RINI: So we're going to take our  
12 scheduled break now on that note. There are other  
13 questions. We'll come back to them after the open  
14 public hearing, so there's still time for questions  
15 and discussions. We'll take a 15-minute break and  
16 be back promptly at 3:10. Thank you.

17 (Whereupon, at 2:55 p.m., a recess was  
18 taken.)

### 19 **Open Public Hearing**

20 DR. RINI: Both the Food and Drug  
21 Administration and the public believe in a  
22 transparent process for information gathering and

1 decision making. To ensure such transparency at  
2 the open public hearing session of the advisory  
3 committee meeting, FDA believes that it is  
4 important to understand the context of an  
5 individual's presentation.

6 For this reason, FDA encourages, the open  
7 public hearing speaker, at the beginning of your  
8 written or oral statement, to advise the committee  
9 of any financial relationship that you may have  
10 with the sponsor, its product, and if known, its  
11 direct competitors.

12 For example, this financial information may  
13 include the sponsor's payment of your travel,  
14 lodging, or other expenses in connection with your  
15 attendance at the meeting. Likewise, FDA  
16 encourages you at the beginning of your statement  
17 to advise the committee if you do not have any such  
18 financial relationships. If you choose not to  
19 address this issue at the beginning, it will not  
20 preclude you from speaking.

21 The FDA and this committee place great  
22 importance in the open public hearing process. The

1 insights and comments provided can help the agency  
2 and this committee in their consideration of the  
3 issues before them. That said, in many instances  
4 and for many topics, there will be a variety of  
5 opinions. One of our goals today is for this open  
6 public hearing to be conducted in a fair and open  
7 way where every participant has listened to  
8 carefully and treated with dignity, courtesy, and  
9 respect. Therefore, please speak only when  
10 recognized by myself, and thank you for your  
11 cooperation.

12 Will speaker number 1 step up to the podium  
13 and introduce yourself? State your name and any  
14 organization you are representing for the record.

15 DR. VOGL: Good afternoon. My name is Dan  
16 Vogel, and I'm an assistant professor of medicine  
17 and director of the Clinical Research unit for the  
18 Abramson Cancer Center at the University of  
19 Pennsylvania. I'm one of the principle  
20 investigators for the STORM study. I've served as  
21 a consultant for several pharmaceutical companies,  
22 including Karyopharm, and Karyopharm has provided

1 for my travel here to this meeting. However, I'm  
2 not being compensated for my time here today, and  
3 I'm providing this testimony on my own behalf as a  
4 STORM investigator who treated 15 patients with  
5 selinexor; as a physician who would like to  
6 prescribe selinexor for my patients; and as a  
7 family member of a patient with myeloma who would  
8 like selinexor to be a treatment option.

9 I face many challenges in my clinic, but the  
10 biggest is that my patients eventually run out of  
11 treatment options. Patients who are eligible for  
12 the STORM study represent the most difficult aspect  
13 of that challenge. They truly did not have any  
14 other reasonable treatments available.

15 When I see these patients in clinic, I do  
16 not offer single-agent dexamethasone therapy  
17 because I do not believe that it will result in  
18 meaningful responses. What I do have to offer is a  
19 short list of treatments that each has significant  
20 disadvantages with a low chance of working, a high  
21 likelihood of toxicity, or both, and the  
22 alternative for these patients is to decide that

1 the risk-benefit profile of these options is  
2 insufficient and to concentrate on comfort care.

3 Selinexor is better than these other options  
4 for patients with triple-class refractory myeloma.  
5 They represent a novel class of medication with a  
6 novel mechanism of action, and its response rate of  
7 25 percent is significantly better than the 10  
8 percent that I typically quote for other outpatient  
9 treatments in this patient population.

10 I'm sure you've gotten the message that's  
11 selinexor is not an easy drug for patients to take  
12 or for that matter a simple drug to manage as a  
13 physician. However, I can say with confidence that  
14 many patients can tolerate selinexor, especially  
15 with careful monitoring for and management of side  
16 effects.

17 I had the privilege of caring for a  
18 69-year-old woman with a long history of myeloma  
19 that had become refractory to every available  
20 agent. When I met her in early February 2016, she  
21 was probably only a couple of weeks away from dying  
22 from progressive myeloma. She would not have been

1 eligible for most clinical trials, but she started  
2 selinexor on the STORM study a few days later. She  
3 had a partial response for almost 10 months and  
4 then stayed on selinexor for another 4 months after  
5 starting to progress. In that 14-month period, she  
6 was able to see her granddaughter get engaged to be  
7 married and was able to vacation at the Jersey  
8 shore and go on a cruise with her family.

9 We should not have to wait to be able to  
10 give more of our patients these opportunities, and  
11 at my institution, we do not have the resources to  
12 routinely treat patients on expanded access  
13 protocols. Approving selinexor now will improve  
14 survival now for patients with highly refractory  
15 myeloma who need this option urgently. Thank you.

16 DR. RINI: Thank you.

17 Speaker number 2, if you could introduce  
18 yourself and any affiliations.

19 MS. CHMIELEWSKI: Hello. My name is Cindy  
20 Chmielewski, and Karyopharm is supporting my train  
21 fare and hotel so I can be here today. I was  
22 diagnosed with stage 3 multiple myeloma in 2008.

1 At the time of my diagnosis, the median life  
2 expectancy for someone like me was 29 months.  
3 Thankfully, I have far exceeded that median  
4 survival number. In general, myeloma patients are  
5 living longer now than ever before, not because the  
6 biology of their disease is any easier to treat,  
7 but because there are more treatment options  
8 available.

9 In the last decade, I saw over a half dozen  
10 new myeloma drugs brought to market. The one thing  
11 they all had in common was they gave myeloma  
12 patients options when they became refractory to all  
13 their given therapies. Unfortunately, even with  
14 all this progress, myeloma patients are still in  
15 need of more options.

16 Myeloma is a disease of relapse and  
17 remission. For some  
18 individuals, these remissions last long and the  
19 relapses are few. But for those individuals who  
20 are diagnosed with high-risk multiple myeloma  
21 remissions are typically short and they soon become  
22 refractory to all currently available therapies.

1 This group of myeloma patients are desperately in  
2 need of new treatments now. They don't have the  
3 luxury of waiting months or years. Days matter to  
4 them. This is an unmet need that selinexor can  
5 address immediately.

6 Patients are always asked to weigh the risk  
7 and benefits of a treatment option before they make  
8 their decision. Some of the risks associated with  
9 selinexor are low blood counts, GI toxicities, and  
10 fatigue. Considering these side effects should be  
11 part of that risk-benefit discussion a patient  
12 who's considering treatment will have with their  
13 doctor before making their personal decision. Some  
14 patients will be willing to risk unpleasant side  
15 effects with the hopes that they can be managed  
16 with proactive supportive care.

17 Presently, there is not a cure for myeloma.  
18 Although there are promising therapies and clinical  
19 trials, many of these individuals we're talking  
20 about do not qualify for trials because a very  
21 stringent eligibility criteria. These patients  
22 need a treatment option now, and selinexor can be

1 that option.

2 Another important point to note is that even  
3 in patients that didn't respond to selinexor, the  
4 toxicities associated with this treatment were not  
5 long-lasting. Some of these individuals were able  
6 to go on to other therapies.

7 Selinexor will be a welcomed addition to the  
8 myeloma treatment arsenal by the patient population  
9 and should be FDA approved sooner and not later.  
10 Thank you for allowing me to share my testimony  
11 today, which is the 10th anniversary of my stem  
12 cell transplant.

13 DR. RINI: Thank you.

14 Speaker number 3, if you'll step up and  
15 introduce yourself and any affiliations.

16 MS. TUOHY: Hello. My name is Robin Tuohy,  
17 and I'm reading this testimony for my friend Aldo  
18 Del Col.

19 "Good afternoon. My name is Aldo Del Col,  
20 and I am a myeloma patient currently on selinexor.  
21 I am unfortunately unable to be here in person  
22 today on account of an ongoing snowstorm, grounding

1 all flights out of my hometown in northern Ontario  
2 where I am visiting my mother. I do not hold any  
3 commercial interest in Karyopharm.

4 "When I was diagnosed with multiple myeloma  
5 17 years ago, treatment options were extremely  
6 limited and the prognosis was bleak. I was only 48  
7 years old and was told I had 3 to 5 years to live.  
8 At that time, the only option was high-dose therapy  
9 with stem cell transplantation. Since my  
10 diagnosis, however, there has been a rapid  
11 advancement in targeted myeloma therapies with less  
12 toxicity and improved clinical efficacy.

13 "Following the stem cell transplant, the  
14 disease remained more or less in control for a  
15 little over 2 years. I was then able to access  
16 lenalidomide, a new immunomodulatory drug, which  
17 kept my disease under control for about 7 years.  
18 This was followed by 4 other treatment regimens  
19 with varying degrees of clinical effectiveness. I  
20 have never, however, been in complete remission.

21 "Despite the innovative breakthroughs,  
22 myeloma patients remain an incurable disease with

1 periods of disease control followed by relapse. As  
2 patients live longer, there is a growing unmet need  
3 for new treatment options. As of a year ago, I had  
4 gone through 6 different therapies. Last spring,  
5 the disease was progressing, and the only viable  
6 option was selinexor.

7 "Since starting selinexor last May, my  
8 paraprotein level has decreased by 50 percent, a  
9 remarkable clinical response given the length of  
10 time I have been living with myeloma and the number  
11 of treatments I have been on. I have experienced  
12 some adverse events, most notably nausea and  
13 anorexia. Despite the side effects, I remain  
14 actively engaged with life pursuing my love of  
15 travel and the arts. Since December, I have  
16 visited friends in London, attended an opera at La  
17 Scala in Milan, enjoyed a daiquiri or two in  
18 Havana, and celebrated my 65th birthday with a  
19 week-long visit to Venice.

20 "I am exceptionally grateful for the  
21 extended life that selinexor has given me, and I am  
22 thankful to have been given the opportunity to

1 share my story."

2 DR. RINI: Thank you. Speaker number 4?

3 MS. AHLSTROM: My name is Jenny Ahlstrom,  
4 and I'm speaking today on behalf of myself and a  
5 nonprofit I created called the CrowdCare Foundation  
6 and The Myeloma Crowd. Karyopharm has covered my  
7 travel so I could be here but is not paying for my  
8 time.

9 I was diagnosed with multiple myeloma at the  
10 age of 43. Our treatment strategy was to hit it as  
11 hard as possible to buy myself time until a cure  
12 could be found. After tandem transplants, I  
13 started advocacy work that included a myeloma crowd  
14 radio program with over a million listeners and a  
15 website with over 800,000 users. We built a  
16 software tool called HealthTree to help patients  
17 understand their relevant treatment options and to  
18 aggregate data to help find the right treatment for  
19 the right patient at the right time.

20 I understand what's coming in the myeloma  
21 drug pipeline and it's very exciting. While we  
22 have over a dozen approved drugs in myeloma, none

1 of them are curing the disease; not transplant,  
2 proteasome inhibitors, IMiDs, or monoclonal  
3 antibodies. The silver bullet has not yet arrived  
4 for myeloma. As my myeloma friends relapse on  
5 multiple treatment minds, doors close to them even  
6 for clinical trials. The CAR-T treatments, BiTEs,  
7 and antibody drug conjugates look promising, but  
8 half of patients in early clinical trials on CAR-T  
9 have relapsed, so possibly it may not be the hope  
10 we're looking for.

11 While patients desperately wait to get into  
12 these CAR-T trial spots to open up and the data to  
13 come out over the next 2 to 5 years, there are  
14 patients who need help today. They're looking for  
15 bridge strategies that will keep them alive until  
16 we discover a cure. They need to buy time.

17 Two things make me excited about selinexor.  
18 The first is that selinexor has proven clinical  
19 benefit for patients who have relapsed after every  
20 available approved therapy. Second, the selinexor  
21 data in phase 2 showed a 35 percent overall  
22 response rate for high-risk patients specifically.

1           My friend Liz who helped build The Myeloma  
2 Crowd was one of these patients. Diagnosed at 44,  
3 she received tandem stem cell transplants that  
4 never put her into remission. She had a deletion  
5 of 13 and 17p, and she easily blew through the  
6 proteasome inhibitors, IMiD, daratumumab, and  
7 elotuzumab. Two years ago, she tried to get into a  
8 spot in a CAR-T trial, and they wouldn't let her in  
9 because she had no measurable BCMA. She died of an  
10 infection at the age of 48, leaving behind two  
11 teenage daughters.

12           This combination might have given her a few  
13 more months to bridge to a CAR-T trial, or for  
14 patients who do not no longer qualify for a  
15 clinical trial, it may give them a few more months  
16 to be with their families, or we might find, for  
17 high-risk patients, it may be their right treatment  
18 at the right time.

19           No patient wants toxicity and it can be  
20 incredibly inconvenient, but what's more  
21 inconvenient is dying too soon because you weren't  
22 alive long enough to take advantage of curative

1 therapies when they finally enter the clinic. I  
2 ask you to approve this combination to by patients  
3 what they want the most, which is time.

4 DR. RINI: Thank you. Speaker number 5?

5 MS. MORAN: Good afternoon. I have no  
6 disclosures. My name is Diane Moran. I'm the  
7 senior vice president of strategic planning at the  
8 International Myeloma Foundation. I'm an  
9 experienced nurse, and I had two decades in the  
10 pharmaceutical industry before coming to the  
11 International Myeloma Foundation 13 years ago.

12 The International Myeloma Foundation is the  
13 oldest and largest organization serving the myeloma  
14 community for almost 30 years, so we speak from  
15 experience. In my work, I meet myeloma patients  
16 who are living full lives, and this is far beyond  
17 the 3 to 5 years that was once the prognosis for  
18 this disease.

19 Now fortunately, for some patients, the  
20 disease can be managed with drugs, using  
21 combination, used in sequence, to build a long-term  
22 remissions back to back to back. But as we all

1 know, a string of remissions does not constitute a  
2 cure, and tragically today, myeloma patients  
3 continue to relapse and die.

4 Patients desperately need more drugs. They  
5 need new drug combinations like selinexor. I  
6 witnessed this unmet need firsthand in my work with  
7 the IMF Nurse Leadership Board. The Nurse  
8 Leadership Board works to improve the day-to-day  
9 care of myeloma patients across the country, and  
10 although we have made tremendous strides in  
11 treatment in the past few years, it's frankly not  
12 enough. And that's why the IMF support the  
13 approval of selinexor in combination with low dose  
14 dexamethasone for patients in this challenging  
15 population.

16 For this population of myeloma patients,  
17 news that a next-step drug combination is on the  
18 horizon gives them hope. Hope is so important. Of  
19 course, we're aware that new advances in medical  
20 treatment are often accompanied by risk, and this  
21 is true probably of old new cancer treatments. But  
22 risk has a whole different meaning when you are

1 suffering from a terminal disease. Myeloma  
2 patients in this position are often willing to  
3 endure that risk if there's a chance that a new  
4 drug will be available when they have nothing else.

5 The IMF's role as a patient advocacy  
6 organization is to educate patients and doctors to  
7 make sure that if drugs have shown efficacy,  
8 they're used safely, and we want patients and  
9 doctors to be able to make those treatment  
10 decisions and to have the tools to help them manage  
11 the toxicity. The most important message I can  
12 impart today is that patients must have more and  
13 newer drugs and combinations, and approval of  
14 selinexor will give those patients a much needed  
15 life-extending option. Thank you.

16 DR. RINI: Thank you. Speaker number 6?

17 MS. GRAFF: Good afternoon. My name is Deb  
18 Graff, and I'm a multiple myeloma patient and  
19 survivor, at least so far. Karyopharm is covering  
20 my travel, however, I'm here because I am invested  
21 in my future, and I am a candidate for selinexor  
22 when my current protocol stops working.

1           Ten years ago when I was first diagnosed,  
2           there were very few drugs available in the  
3           treatment of multiple myeloma. A diagnosis then  
4           was unusual to be caught in its early stages and  
5           most often involved debilitating fractures,  
6           signaling the progression of the disease. I was  
7           one of the lucky ones. I had it detected by my GP  
8           in routine blood work and followed up by a  
9           prominent myeloma specialist.

10           The news, however, was not good. I was told  
11           that I had a particularly aggressive form of the  
12           disease with a 17p deletion and would be treated  
13           accordingly. I had researched enough to know that  
14           17p was called the kiss of death by many patients  
15           and that it would be treated aggressively. It  
16           became clear early on that although this was the  
17           case, the RVD, the following stem cell transplant,  
18           and the RVD maintenance was not to control the  
19           rising numbers for long.

20           I then entered the world of trials, and the  
21           trials were hope. Pomalyst, Velcade, and the dex  
22           trial gave me another year. It returned again in

1 the form of extramedullary tumors; radiation, and  
2 then I waited for the next trial, which was  
3 daratumumab, and it has been successful for a while  
4 for me.

5 The importance of trials, and more  
6 importantly, the approval of this drug, cannot be  
7 measured just in side affects. Over 10 years, my  
8 side effects of gastrointestinal issues,  
9 neutropenia, neuropathy, longer lasting colds, all  
10 pale in comparison to what I have had in return.  
11 The time I've had with my husband, family, and  
12 friends, the weddings of children and the birth of  
13 grandchildren would not be traded.

14 I'm dependent on research and trials for my  
15 future, but more importantly, there are younger  
16 people here who have exhausted all the options.  
17 They need to have hope and the choice to take the  
18 risk for a life ahead. Our hope is dependent upon  
19 you.

20 DR. RINI: Thank you. Speaker number 7?

21 MR. TUOHY: My name is Michael Tuohy. I'm a  
22 19-year myeloma survivor. As a patient, on behalf

1 of the thousands of other patients across the  
2 country, I would like to share with the committee  
3 how critical it is to have another drug to treat  
4 myeloma when you have exhausted all other courses  
5 of action.

6 I was diagnosed with myeloma when I was 36  
7 years old in August of 2000. My children at the  
8 time were 2 and 7 years old. Needless to say, my  
9 wife Robin and I were devastated. The life  
10 expectancy in 2000 ranged between 18 months and  
11 5 years. That was not good enough. I was afraid  
12 my children would not even remember me.

13 Thanks to research by many of you here  
14 today, there are more options available to  
15 patients, and we are living longer and better  
16 quality of life. Continued research and approval  
17 of drugs is imperative so patients have access to  
18 them and are able to live to see the next drug  
19 approved. We live from treatment to treatment to  
20 treatment, and the options need to continue so that  
21 we can be here for the cure.

22 Back in 2000, the options were extremely

1 limited, and we lived with the heavy burden of  
2 trying to keep something in our back pocket, a big  
3 gun for when you really needed it. Today, we are  
4 able to treat myeloma in sequence and in  
5 combination. There's much more hope for our  
6 futures. Each new drug extends our lives.

7           There is no cure to date for myeloma, so now  
8 he live from drug to drug combination. In a  
9 relapse refractory setting, when a disease comes  
10 back, it is always more aggressive. The drugs  
11 needed to combat myeloma in this setting are key  
12 and must be available to patients. Despite the  
13 approval of several new myeloma drugs in recent  
14 years, there is still an unmet need in the relapsed  
15 refractory patient population. Many patients have  
16 numerous remissions and relapses. Each time we  
17 relapse, the disease is harder to fight.

18           Patients know that every treatment comes  
19 with its own set of side effects, but our myeloma  
20 specialists and nurses are able to treat us with  
21 myeloma therapies and manage side effects. The  
22 more options we have, the greater chance I have of

1 living a longer life. A stem cell transplant  
2 brought me a 3-year remission before I relapsed.  
3 Fortunately, there was another drug in clinical  
4 trials which I was able to access. I've been on  
5 this drug for 14 years and in complete remission.  
6 I wish this for all other patients out there that  
7 are in this position. Thank you.

8 DR. RINI: Thank you. Speaker number 8?

9 MS, YOUNG: Good afternoon. I'm Ann Quinn  
10 Young, chief marketing and development officer of  
11 the Multiple Myeloma Research Foundation, where  
12 I've worked for the past 16 years. The MMRF is a  
13 national 501(c)(3) nonprofit organization, and  
14 we're the largest province private funder of  
15 myeloma research in the world. As part of our  
16 mission to accelerate new and better treatments for  
17 patients, the MMRF has invested resources,  
18 including funding in a number of compounds and  
19 companies, including the sponsor.

20 I am here today, though, to speak on behalf  
21 of the hundreds of thousands of patients, patient  
22 family members, and friends that the MMRF

1 represents. Most everyone in this room is aware of  
2 the tremendous progress this community has seen  
3 since myeloma patient Kathy Giusti and her twin  
4 sister found the MMRF in 1998. The gains in  
5 treatment options and survival are truly stunning  
6 and nearly unprecedented than any other cancer.  
7 This is the result of an extraordinarily committed  
8 and collaborative community working tirelessly  
9 together.

10           The MMRF not only works with the community  
11 to accelerate drug discovery and development, but  
12 also to provide the education required for every  
13 patient to maximize his or her outcome on any given  
14 treatment. This means we place a significant focus  
15 on helping them manage potential and actual side  
16 effects to enjoy the full benefit of each and every  
17 treatment, and this is because a 5-year survival is  
18 still just 50 percent and many patients still cycle  
19 far too quickly through all available treatment  
20 options.

21           Clinical trials or clinical trial has shown  
22 that response rates, duration of response,

1 progression-free survival, they all decrease with  
2 every line of therapy. Furthermore, myeloma not  
3 only differs from patient to patient but within  
4 patients. As we seen from our own CoMMpass study,  
5 there's a median of 5 different clones within a  
6 single patient. The result is that the hardy  
7 survive, leading to an increased incidence of  
8 high-risk features the more lines of therapy a  
9 patient sees.

10           Nearly half of the patients in the STORM  
11 trial had high-risk features and they had seen a  
12 median of 7 prior lines of therapy. I cannot  
13 emphasize enough that these patients have very few  
14 treatment options available. Just over the last  
15 couple of weeks, I've spoken to families of two  
16 patients who are emblematic of this population.  
17 Both have progressed through many lines of  
18 therapies in less than five years. Both progressed  
19 on daratumumab within months. Both are ineligible  
20 for trials because of the presence of  
21 extramedullary disease, and both could potentially  
22 benefit from selinexor.

1           It's important to appreciate that patients  
2           in this situation have a much higher risk tolerance  
3           of side effects than less heavily pretreated  
4           patients, and we strongly believe that they deserve  
5           that choice. If there is an option that could  
6           potentially extend their lives, let them and their  
7           doctor determine if the risk-benefit ratio is  
8           acceptable. It is our hope that the committee will  
9           appreciate that despite the significant and amazing  
10          progress made in the last 15 years, more options  
11          are urgently needed, particularly in this heavily  
12          relapsed and highly refractory population. Thank  
13          you.

14                 DR. RINI: Thank you. Speaker number 9?

15                 DR. NOOKA: My name is Ajay Nooka. I'm an  
16                 associate professor of hematology and oncology at  
17                 Emory University, Winship Cancer Institute. I'm  
18                 the principal investigator for several clinical  
19                 trials evaluating selinexor, including the STORM  
20                 trial and the BOSTON trial. I have filed 5  
21                 individual INDs for patients that I believe would  
22                 benefit from selinexor in the past. With my

1 familiarity of selinexor as an investigational  
2 agent and having seen the benefit as far as advent  
3 profile of the drug, I believe I'm qualified to  
4 speak on the benefits of selinexor.

5 From a disclosure prospect, Karyopharm paid  
6 for my travel and accommodation, but I've not  
7 received any consulting fee for this meeting. In  
8 the STORM trial, among the 123 patients that were  
9 heavily pretreated, the overall response rate was  
10 25.4 percent and the duration of response was 4.4  
11 months with a median survival of 9 months.

12 I'll put this in the perspective -- among  
13 patients who are refractory to bortezomib, an  
14 immunomodulatory agent, Shaji Kumar from the  
15 International Myeloma Working Group has put a  
16 multicenter analysis -- this was back in  
17 2009 -- showing an overall survival of 9 months.  
18 Of course, this was a time when we did not have  
19 data to map carfilzomib or elotuzumab. A similar  
20 analysis was done again in 2017. This involved a  
21 cohort from 2006 to 2014. The overall survival  
22 change to 13 months.

1           In this context, daratumumab was a wonder  
2 drug, which was approved in November of 2015  
3 showing the overall response rate of 30 percent  
4 managed for toxicities. They did have great PFS  
5 benefits, but [indiscernible] myeloma options are  
6 really needed for these patients that are  
7 refractory to daratumumab with more novel  
8 mechanisms of action.

9           If you're talking about [indiscernible]  
10 therapies, I was at the TCT meeting last week, and  
11 the idea of getting CAR-T cell therapy treatments  
12 for the myeloma patients is really minimal. Among  
13 the 646 patients from 84 centers that were offered  
14 the CAR-T cell therapies in 2016 to 2018, only  
15 6 persons were myeloma patients. So this really  
16 leaves us with less options for triple refractory  
17 patients, and of course we do understand that  
18 selinexor can be associated with adverse events.  
19 In the STORM trial, almost every patient had a  
20 treatment-emergent adverse event, including a  
21 quarter of patients discontinued due to a  
22 treatment-emergent adverse event.

1           From our experience, with their ability to  
2 manage these toxicities with the appropriate dose  
3 modifications and dose reductions, offering  
4 supportive care with the anti-[indiscernible] and  
5 appropriate appetite stimulants, they have seen  
6 clinically meaningful results, including patients  
7 that travel for 14 months from outside the state  
8 for the study drug to be obtained.

9           I would strongly urge the committee to make  
10 their decision based on the risk-benefit equation  
11 for these daratumumab refractory patients and that  
12 new drugs with novel mechanisms of actions are  
13 needed.

14           DR. RINI: Thank you. Speaker number 10?jj

15           MS. STUDZIENKO: My name is Sharon  
16 Studzienko, and I was diagnosed with multiple  
17 myeloma in spring of 2011, Karyopharm has  
18 generously paid for travel and hotel, so my family  
19 and I could be with you today to share our  
20 experience with selinexor. Neither my family nor I  
21 have any other financial ties to the company.  
22 Today, you've reviewed the data and heard about the

1 trial subjects. I'm one of those patients. I  
2 choose to testify today because I think it's  
3 important that you hear from and see patients like  
4 me when making your life-changing recommendations  
5 to the FDA.

6 Multiple myeloma is not like breast cancer  
7 or prostate cancer. There is no cure. When I was  
8 diagnosed, the average life expectancy was 5 years.  
9 I have been alive for 7 years, a 2-year bonus. Why  
10 me? Because I've had treatment options and  
11 opportunities. In fact, selinexor is the 15th  
12 therapy or weapon in my battle with myeloma. The  
13 other 14 treatments were effective for me in  
14 achieving at least a partial response in my  
15 multiple myeloma, but at a cost.

16 During the time I was in treatment numbers  
17 12 through 14, I was in the hospital 1 week out of  
18 every 2 with fevers as high as 104.3 degrees;  
19 C. difficile colitis, which is a very unpleasant  
20 condition; confusion; and expressive aphasia. I  
21 was alive but hospitalized an average of 50 percent  
22 of the time, and eventually all of the drug stops

1 working.

2           Let's fast forward to my experience on  
3 selinexor. Put bluntly, selinexor gave me the  
4 other half of my life back. During the time, I was  
5 taking selinexor, their worst side effects, but  
6 they were shorter and milder, and importantly to my  
7 family and me, there were no hospitalizations  
8 because of side effects. Fatigue was the worst of  
9 the side effects, but compared to what I had been  
10 through on the other treatments, it was bearable.

11           With information options and great care,  
12 many things are possible. I'd like to share a  
13 personal story. When my son was diagnosed with  
14 autism spectrum disorder at age 7, his neurologist,  
15 neurologist told me he would probably be in an  
16 institution by age 18. She was right. However,  
17 the institution turned out to be a college.

18           Despite this, I know I will not survive  
19 multiple myeloma and that the worse is yet to come,  
20 but each drug I've tried has kept me alive long  
21 enough to get to the next drug. Each few extra  
22 bonus points are so important to patients like me

1 and my family. I'm lucky. I live an hour and a  
2 half away from the University of Pennsylvania where  
3 they have a whole nest of top-notch multiple  
4 myeloma researchers, and I have access to clinical  
5 trials. But not every patient is as fortunate, so  
6 I speak on their behalf as well.

7 I hope you approve selinexor now. I  
8 appreciate the opportunity to speak to you today.  
9 Thank you.

10 DR. RINI: Thank you. Speaker number 11?

11 MR. STUDZIENKO: Hi. My name is Ignach  
12 Studzienko, and I am the husband of Sharon  
13 Studzienko, so I'm here to give the caregiver's  
14 perspective of things. She has been diagnosed with  
15 multiple myeloma in 2011.

16 That's right. I've forgotten. I don't have  
17 any financial relationship with Karyopharm other  
18 than they paid for my traveling expenses.

19 She was on several protocols prior to  
20 selinexor, and during the last 2 and a half years  
21 prior to selinexor, she said 16 emergency room  
22 visits. Most of them were 4 days long. After

1 that, when she got on selinexor, there were no 4  
2 days hospitalizations during the selinexor  
3 protocol. There were notably fewer pain episodes.  
4 All of that translated into improved quality of  
5 life for the family, mostly myself. I'm selfish.

6 I found it easier to get out of the house,  
7 participate in temple activities, volunteer  
8 activities, lunch with friends, and just going for  
9 a walk. It was nice not to have to bring my cell  
10 phone to the temple. I used to bring it to the  
11 temple, set it on mute, and hoped it never goes  
12 off. Now I just leave the damn thing in the car  
13 and I don't worry about it. I can be at peace and  
14 enjoy services. I got at least some of my life  
15 back. Thank you.

16 DR. RINI: Thank you. Speaker number 12?

17 DR. GABRAIL: Good afternoon. My name is  
18 Nash Gabrail. I am a medical oncologist in Canton,  
19 Ohio. I'm a general oncologist, but my practice,  
20 Gabrail Cancer Center, focuses on clinical trials  
21 phase 1 and 2. As disclosure, yes, Karyopharm has  
22 paid for my hotel.

1           I came hear to speak on behalf of my  
2 patients with multiple myeloma, and I have many of  
3 them, and to also speak on behalf of other  
4 community oncologists. Everybody's mentioning the  
5 statistics about how long patients with myeloma  
6 have been living. Well, that was during my  
7 fellowship in Scotland. In those days, the median  
8 survival of myeloma patients was 26-27 months. Now  
9 data from 2015 is about 60 months plus.

10           What does that mean? Well, that means these  
11 people are living longer, which is great. It also  
12 means they are having a better quality of life, but  
13 they also have more cumulative side effects from  
14 all the drugs we give them. They also have  
15 more -- when they relapse, they have more tumor  
16 burden and they have more mutation burden. That  
17 makes life difficult for investigators like me to  
18 come up with drugs that actually work in that  
19 difficult situation.

20           To me, that means for the regulators and for  
21 everybody else, maybe we shouldn't be as strict as  
22 we are in that patient population where they have

1       been exposed to 7-8 lines of therapy and expect  
2       that we will achieve a CR rate of 20-30 percent.  
3       Unrealistic because mutation burden is real and is  
4       a fact.

5               I have treated 72 patients, different cancer  
6       types with selinexor. I don't think anybody in  
7       this room has as much experience as I do. Yes, as  
8       any other drug, it has side effects. There's no  
9       mistake about it, but this is our job. Actually,  
10      we train to manage side effects more than train to  
11      three diseases. And I do believe -- I think one of  
12      the panelists asked a question, has there been an  
13      experience as time goes? I think in my opinion,  
14      and looking at my staff and myself, we enrolled 72  
15      patients on selinexor clinical trials. I think we  
16      did get better by being proactive from the  
17      beginning in detecting and more importantly in  
18      combating side effects even before they happen,  
19      like giving them for the fatigue, Vyvanse or just  
20      simply drink cappuccino every morning or every  
21      afternoon.

22              I really think we do need this drug because

1 when these patients have failed all the three  
2 classes, believe it or not, we don't have a fourth  
3 class. This is a unique class of drugs and we need  
4 it. I do hear you saying that we can recycle  
5 drugs. I am a believer in Einstein. Insanity has  
6 a definition, repeating the same thing, expecting  
7 different results. I don't do that. When somebody  
8 is resistant to daratumumab, guess what? I don't  
9 give it; well, give me something else, selinexor.  
10 Thank you very much.

11 DR. RINI: Thank you. Speaker number 13?

12 MR. WALSH: Hello. My name is Michael  
13 Walsh. I'm 58 years old, a singer and a piano  
14 player, and I run a recording studio in midtown  
15 Manhattan called The Smooth Spot. I have taken  
16 selinexor. I have no financial relationship with  
17 the sponsor, but they did cover my travel to come  
18 here.

19 On November 8, 2013, I was diagnosed with  
20 lambda light chain multiple myeloma. This type of  
21 myeloma produces excessive particles called light  
22 chains that cause severe bone and kidney damage.

1 For 5 and a quarter years, I have been fighting  
2 this disease nonstop with various chemotherapy  
3 treatments. I have done 3 bone marrow transplants.

4 I am refractory to at least 7 lines of  
5 treatment, including both proteasome inhibitors,  
6 bortezomib, and carfilzomib, 1 anti-CD38 monoclonal  
7 antibody daratumumab, and both pomalidomide and  
8 thalidomide in the immunomodulatory agent group. I  
9 have participated in 6 clinical trials so far.  
10 Five of these trials were not effective at  
11 controlling my disease. In fact, my light chain  
12 numbers spiked dramatically, putting me at great  
13 risk for kidney failure and serious infections such  
14 as pneumonia.

15 In the fall of 2017, I spent 55 days in the  
16 hospital working to get my disease under control.  
17 In January of 2018, I took part in a selinexor  
18 clinical trial. After just a few weeks taking  
19 selinexor, my light chains dropped dramatically  
20 from over 12,000 milligrams per liter to under 800.

21 Now, my particular cancer has always been  
22 very aggressive in its assault on my kidneys. As

1 such, my kidney function is impaired and  
2 disqualifies me from most clinical trials.  
3 Dr. Ajai Chari, my oncologist, and I have discussed  
4 using selinexor again to bring down my light chain  
5 numbers and improve my kidney function so I can  
6 qualify for one of these trials. The accelerated  
7 approval of selinexor could quite literally save my  
8 life.

9           Selinexor is not an easy drug to take. The  
10 difficult side effects include nausea, fatigue, and  
11 taste alteration. Nausea was strong, but  
12 anti-nausea medications were effective for me. On  
13 the positive side, there is no neuropathy, as is  
14 the case with so many other chemotherapy drugs.  
15 Also, since it is taken as a pill, it does not  
16 require a hospital visit or an IV infusion.

17           At this point in my struggle with this  
18 cancer, I have exhausted almost all of the possible  
19 approved lines of treatment. Please approve  
20 selinexor. I want to use it again. I've been on  
21 it. I know the side effects. They're worth it to  
22 me given the benefits I have experienced. Thank

1 you for listening.

2 DR. RINI: Thank you. Speaker number 14?

3 DR. FOX-RAWLINGS: Thank you for the  
4 opportunity to speak today on behalf of the  
5 National Center for Health Research. I am  
6 Dr. Stephanie Fox-Rawlins. Our center analyzes  
7 scientific and medical data to provide objective  
8 health information to patients, health providers,  
9 and policymakers. We do not accept funding from  
10 drug or medical device agencies, so I have no  
11 conflicts of interest.

12 We all agree that patients with relapsed  
13 refractory multiple myeloma need more treatment  
14 options, especially options that work by new  
15 mechanisms. Unfortunately, selinexor has serious  
16 risks that can cause death. It is crucial to  
17 determine the size of the benefit because of the  
18 known risks. It is essential to determine if the  
19 benefits outweigh the risks for most patients. At  
20 this point, we lack the information needed for  
21 patients and their doctors to make informed  
22 decisions about whether to try this new drug.

1           Let's consider the risks. All patients in  
2 the STORM trial suffered adverse events. Almost  
3 all suffered a severe adverse event and 58 percent  
4 experienced a serious adverse event. Ninety  
5 percent of the patients taking the drug died due to  
6 an adverse event. Even if many of the adverse  
7 events are manageable, they do harm patients'  
8 quality of life. These side effects and even the  
9 risk of death may be acceptable to some patients if  
10 the drug can help them live longer, but if the drug  
11 cannot provide a meaningful benefit, these risks  
12 are not worth it.

13           The single-arm open label study found that  
14 25 percent of patients responded to the drug based  
15 on a biomarker response, but because it's a  
16 single-arm trial, there's no controlling for unique  
17 aspects of this patient population. More over, the  
18 25 percent response rates when given with an older  
19 drug is very similar to the response rate of that  
20 drug alone, so it's not possible to tell what, if  
21 any, effect this drug has.

22           It is difficult, if not impossible, to

1 compare the results of the combination to just the  
2 old drug alone since many clinical trials included  
3 different patients and the treatments and practice  
4 of medicine varied over time. I am very glad that  
5 the sponsor has already begun a  
6 randomized-controlled trial. Some of the results  
7 are expected at the end of the year, and this  
8 should provide much needed information about  
9 efficacy.

10 In addition, it is important to evaluate  
11 outcomes that affect patient's health and quality  
12 of life and not just considered surrogate  
13 endpoints. The trial that we are discussing today  
14 and the randomized study that's ongoing focus on  
15 surrogate endpoints, overall response rate, and  
16 progression-free survival. These don't directly  
17 tell us anything about the impact of the new drug  
18 on patients' lives. Surrogate endpoints are even  
19 more of a problem when studying this drug because  
20 the drug itself increases risk for death.

21 A previous clinical trial comparing this  
22 drug against physician's choice of other drugs for

1 patients with relapsed  
2 or refractory AML found better remission rates, but  
3 patients did not live longer. In fact, there was a  
4 trend for shorter life. Similarly, in this  
5 clinical trial, there was no improvement in quality  
6 of life due to the drug. In summary, we know the  
7 drug has serious risks and we don't know if it  
8 works.

9 How can patients and doctors weigh the ratio  
10 of risks to benefits when the risks are serious and  
11 the benefits are unknown? I respectfully urge you  
12 to tell the FDA to wait until the randomized trial  
13 is analyzed to make a decision. While patients  
14 need new treatments, they need new treatments that  
15 help them live longer or have a better quality of  
16 life. Thank you.

17 DR. RINI: Thank you. Speaker number 15?

18 MR. AHLSTROM: Hello. My name is Paul  
19 Ahlstrom. I'm a caregiver and support team for my  
20 wife, Jenny Ahlstrom. She's a wonderful  
21 mother -- I have 6 children -- an amazing cook, a  
22 myeloma patient, a patient advocate, and a pretty

1 good singer. I have no disclosures. I have no  
2 relationship with the pharma company, Karyopharm.  
3 They paid for my travel but not for my time.

4 In 2003, my younger brother David Ahlstrom  
5 was 33 years old with 6 children when he was  
6 diagnosed with late stage AML. After 6 months of  
7 treatment, he became refractory to all approved  
8 standard of care treatments available to him at  
9 Huntsman Cancer Institute. Leukemia was so  
10 pervasive that he was in the ICU [ph] with acute  
11 respiratory distress syndrome, ARDS. His heartbeat  
12 was 175 beats per minute and he was given 48 hours  
13 to live. The head of oncology told me there was  
14 nothing else they could give David other than  
15 palliative care. They were out of options.

16 Unwilling to accept this, I had identified a  
17 drug called Mylotarg that had shown to be effective  
18 for older patients with a CD33 protein present in  
19 the cancer cell. David's cancer did have the CD33  
20 protein present, and we obtained permission to  
21 obtain the drug for off-label use for David.  
22 Within 48 hours of receiving the drug, David's

1 numbers dropped to remission levels. He was  
2 released from intensive care and went home. He  
3 received a remission that lasted for 6 months. He  
4 was able to spend that time with his family until  
5 he eventually passed away and ran out of options.

6 At the end of life, we tried other trials.  
7 We tried calling the FDA. We had Senator Hatch  
8 involved. We had many people trying to get us  
9 other drugs that were in the similar situation, but  
10 we couldn't get through to them.

11 It wasn't until 9 years later that Mylotarg  
12 was eventually approved for young AML refractory  
13 patients with the CD33 protein present, basically  
14 salvage therapy for David's exact situation. We  
15 accidentally ran into this. It's interesting to  
16 note that Mylotarg was the first antibody drug  
17 conjugate. It was a new class of drug.

18 Six years later in 2010, my wife Jenny was  
19 diagnosed with late-stage multiple myeloma, another  
20 terminal blood cancer. Learning from my brother  
21 David's situation, we hit it as hard as we could up  
22 front and we did tandem bone marrow transplants.

1 She achieved 8 years of stringent complete  
2 remission.

3           There's currently not a cure for myeloma.  
4 It keeps coming back and eventually becomes  
5 refractory as we've heard today. Having new lines  
6 of therapy and options available is important to  
7 patients and caregivers and children and everybody  
8 involved. Like Mylotarg, selinexor is a completely  
9 new class of drug with a new mechanism of action.

10           We hope that a cure for myeloma is on the  
11 horizon. We don't want to run out of options and  
12 want to extend life until that day comes. Because  
13 Mylotarg was available, we had access. Eventually  
14 patients, caregivers, and researchers working  
15 together will figure out the optimal use case for  
16 myeloma.

17           We hope that you approve selinexor and dex  
18 so that it can be used for patients who are running  
19 out of options. It is only by having these options  
20 available that the clinic working with the patients  
21 and the caregivers can optimize these options and  
22 eventually identify the most beneficial use case.

1 Please give us a choice. Thank you.

2 DR. RINI: Thank you. Speaker number 16?

3 MS. STOVELL: Good afternoon. My name is  
4 Ann Stovell. First, I would like to thank  
5 Karyopharm for covering my hotel in D.C. for me and  
6 my husband. I was diagnosed with multiple myeloma  
7 in 2010, and for the last 16 months I have been a  
8 selinexor patient. Selinexor worked for me  
9 immediately. I'm not saying that will happen to  
10 everyone, but everyone, especially the ones who  
11 have run out of options, should also have this  
12 opportunity.

13 I have always been a very active person. I  
14 was a disco rollerskater and I used to live on the  
15 5th floor of a New York City brownstone walk-up,  
16 which I always thought of as my free gym. I have  
17 always eaten well as my mother was always very  
18 conscious that good food was important. Then  
19 9 years ago, I was diagnosed with multiple myeloma  
20 and I started down the path of x rays; PET scans;  
21 MRIs; blood tests; having my stem cells harvested,  
22 and having a stem cell transplant, radiation; and

1 many chemotherapy treatments.

2           Everybody is different. When my body could  
3 not handle a drug, my doctors would try another  
4 chemotherapy. When I had exhausted the FDA  
5 approved drugs, then trial drugs were my only  
6 option. I received my first trial drug by  
7 injection with saline by IV twice a week. I went  
8 back to the hospital on other days to treat side  
9 effects, but that drug did not work at all  
10 for me. I was then hospitalized to receive strong  
11 chemotherapy 24 hours a day for 4 days, and I lost  
12 my hair again. Then in October 2017, I was  
13 accepted in a selinexor trial. I feel very  
14 fortunate and grateful because after 9 years it is  
15 the first drug that put me in remission.

16           Since selinexor is a pill that you can carry  
17 with you, I was able last year to travel to France  
18 to see my husband's family and then to Australia to  
19 celebrate my mother's 90th birthday. Over the last  
20 9 years, I have seen many advantages in medicine,  
21 and I'm excited to see what progress will come up  
22 in the next 5 years. I also have acupuncture or

1       message most weeks as I think complementary  
2       medicine is very important to my full recovery.

3               Today besides some of the side effects from  
4       selinexor, I am in remission and I continue to have  
5       quality of life. Thank you very much.

6               DR. RINI: Thank you. Speaker number 17?

7               MS. TUOHY: Hello again. My name is Robin  
8       Tuohy. I'm a caregiver to my husband Michael, who  
9       was diagnosed with myeloma 19 years ago in August  
10       of 2000, who you heard testify earlier today. I  
11       speak as a loving wife, who has throughout the year  
12       has been fortunate to have met so many other  
13       caregivers just like me, wives and husbands, sons  
14       and daughters, who also stand by the sides of their  
15       loved ones stricken with this disease, awaiting  
16       news of the next new treatment, and trying to stay  
17       on top of all the research so we can have the best  
18       shared decision-making conversations with our  
19       specialists.

20               Myeloma is a rollercoaster ride, and if I  
21       had a slide up here to show you, I would put the  
22       myeloma timeline -- and noticed I've said

1 timeline -- and a life timeline. And we're  
2 talking about time here. I hope you can see that  
3 it's really important.

4           So thanks to new drug treatments, my husband  
5 has not only survived well beyond the life  
6 expectancy we were originally quoted at his  
7 diagnosis, but Michael has mentored other patients  
8 and enjoyed family milestones. Together, we have  
9 seen our daughter Ally [ph] graduate from college,  
10 become a teacher, and this past summer get married.  
11 It's a good, beautiful tear. I have to say that I  
12 shed more than a tear of joy and thanks when  
13 Michael walked our daughter down the aisle, and  
14 they danced together at the reception.

15           Our son, who was only 2 when Michael was  
16 diagnosed, is now a junior in college in the honors  
17 program for biomolecular science and recently  
18 presented a poster at a cell biology conference.  
19 That's pretty cool. Our lives may not have been  
20 the same if the drug Michael went on, when it was  
21 still in clinical trials and which he remains on  
22 today, was not approved. But like all the other

1 patients and caregivers who are living with  
2 myeloma, we are guaranteed two things. This  
3 disease will return. If a patient is one of the  
4 lucky ones who lives long enough, it will return  
5 time and time again.

6 The treatment that worked miracles before  
7 will become completely ineffective. Each time  
8 myeloma returns, it is progressively more and more  
9 difficult to fight back with existing therapies.  
10 For these reasons, the availability of a new cancer  
11 drug like selinexor may be the only option for  
12 myeloma patients who have run out of effective  
13 drugs and our disease-fighting arsenal. Myeloma  
14 patients, like my husband Michael, and the tens of  
15 thousands of others across the U.S. are waiting for  
16 you to help them by providing them with a new  
17 option. Some of them cannot wait any longer.

18 As a caregiver, I know as well as my husband  
19 that each drug has side effects, and patients have  
20 to weigh this risk-benefit ratio that we're all  
21 talking about, along with our specialists. But it  
22 is our lives, and having a choice is always better

1 than the alternative of having nothing left. The  
2 longer we live, the closer we will be to that cure  
3 someday. Please give us the option to make  
4 well-informed decisions with our hematologists by  
5 approving a new drug application for selinexor for  
6 the treatment of patients with relapsed and  
7 refractory multiple myeloma.

8 Thank you for giving me the opportunity  
9 today to lend my voice to the support for the  
10 approval of selinexor. Thank you.

11 **Clarifying Questions (continued)**

12 DR. RINI: Thanks to you and to all the  
13 speakers for their comments. The open public  
14 hearing portion of this meeting is now concluded,  
15 and we will no longer take comments from the  
16 audience. The committee will turn its attention to  
17 address the task at hand, careful consideration of  
18 the data before the committee as well as the public  
19 comments.

20 Before we get to the discussion and vote, we  
21 have a few more folks with questions to the  
22 sponsor. Dr. Papadimitrakopoulou?

1 DR. PAPADIMITRAKOPOULOU: My questions have  
2 been answered through Q&A before.

3 DR. RINI: Okay. Thank you. Dr. Shaw?

4 DR. SHAW: I have two questions for the  
5 sponsor. The first one has to do with the  
6 randomized study in AML, and you had shown no  
7 difference in infections or AEs leading to death in  
8 that study. But in a prior version of that study  
9 when selinexor was tested at a higher dose, there  
10 was apparently a signal of increased SAEs sepsis.  
11 So I was wondering if you could provide a little  
12 more information about that.

13 DR. SHACHAM: The first portion of the  
14 study, the dose that we used was equivalent to  
15 100 mg twice weekly, so higher than the dose used  
16 in this study. There was an [indiscernible]  
17 increase in sepsis that didn't meet statistical  
18 significance or any other criteria for a marked  
19 increase, but due to what we already knew from the  
20 phase 1 study that the 100 mg is not well  
21 tolerated, we chose to reduce the dose. In the  
22 summary of the study, across all doses, there was

1 no increase in sepsis compared to the positive  
2 control.

3 DR. SHAEW: Thank you. I have one other  
4 question about toxicity. In reviewing the  
5 narratives for the 10 patients who died in STORM  
6 part 2 due to a treatment-emergent AE, 8 seemed to  
7 have possibly died due to an infection or with an  
8 associated infection. And I'm just wondering,  
9 these patients must have all met eligibility, but  
10 was there any marker of worse disease in these  
11 patients? Did they have lower blood counts than  
12 other patients or other markers to identify  
13 high-risk patients?

14 DR. SHACHAM: I'll ask Dr. Kauffman to  
15 answer the question and maybe for Dr. McCarthy, the  
16 DSMB member, to also provide his comments.

17 DR. KAUFFMAN: We reviewed very carefully all  
18 10 cases of treatment-emergent death on the study,  
19 and none of these deaths were actually accompanied  
20 by neutropenia. Some of them had lymphopenia. The  
21 one thing we can say is they were very disparate  
22 causes of death. For example, one case of

1 Pneumocystis jiroveci; one case of fungal candida  
2 infection probably that was present at diagnosis or  
3 at the start of the trial; standard bacterial  
4 pneumonia, one case associated with C. difficile  
5 pneumonia.

6 We did review the DSMB, and I'll let  
7 Dr. McCarthy discuss those.

8 DR. MCCARTHY: Thank you very much. My name  
9 is Philip McCarthy. I work at Roswell Park  
10 Comprehensive Cancer in Buffalo, New York.  
11 Karyopharm has paid for my travel here today, my  
12 presence on the DSMB, and I'm representing the DSMB  
13 today. During the conduct of this trial, we found  
14 that there was no increased incidence of adverse  
15 events, and the deaths that were caused were in the  
16 context of progressive disease. So many of these  
17 patients had progressive disease as they were  
18 having adverse events, and these are the adverse  
19 events that we would expect to see in the heavily  
20 treated patient population, and we found no signal  
21 that would suggest to us that they were something  
22 that was out of the ordinary in the absence a

1 comparator arm.

2 DR. SHAW: I have one other question, a  
3 separate question, though. I'm wondering in the  
4 context of STORM part 2 if you've been looking at  
5 biomarkers that may predict response, XP01 levels,  
6 for example, in malignant plasma cells; any other  
7 biomarkers to identify the patients who are most  
8 likely to drive benefit?

9 DR. SHACHAM: We have looked and are still  
10 looking, but so far we have not found a biomarker.  
11 We also did several subgroup analyses. Some of  
12 them you can see here, and we can see that  
13 responses were equivalent across many looking at  
14 different demographics. All of them were around  
15 the 25-26 percent response.

16 But it is important to keep in mind that  
17 many of the patients -- over 70 percent of  
18 them -- actually did see clinical benefit, and we  
19 saw reduction in the myeloma marker, and we are  
20 still actively looking for a biomarker.

21 DR. RINI: Thank you. Dr. Klepin?

22 DR. KLEPIN: I just wanted to circle back to

1 the questions about the quality-of-life data. You  
2 touched upon it a little bit. I just wanted to  
3 clarify if there were any clinically meaningful  
4 differences in quality of life using any of the  
5 subscales. You mentioned that pain -- there was a  
6 suggestion that pain improved. Some of the other  
7 subscales looked like patients had declines of  
8 quality of life. For example, I think it was the  
9 physical wellbeing subscale that looked like it  
10 might have met a clinically meaningful decrement in  
11 quality of life.

12 So I just wanted to hear especially a  
13 comparison from baseline to cycle, the first cycle  
14 evaluation where you might have more of the same  
15 patients before you have attrition, if you have any  
16 comments on clinically meaningful differences in  
17 quality of life.

18 DR. SHACHAM: So several points to make on  
19 that. First, when we look at the first cycle in  
20 which you have the majority of the patients, there  
21 was no difference in the changes in quality of life  
22 in the patient that received 60 or less compared to

1 those who receives 80. This 10 percent or just  
2 below 10 percent reduction in the overall FACT-MM  
3 score was seen in both populations to the same  
4 magnitude.

5 The second phone to make is that in that  
6 group was in the cycle -- until cycle 2/day 1, two-  
7 thirds of the patients reported no change in  
8 quality of life or improvement. Ten percent of  
9 them actually reported improvement in their quality  
10 of life. So that included about 70 percent of the  
11 patients.

12 The third point is, as you mentioned, the  
13 scales that were impacted the most were not the  
14 myeloma markers and not the emotional marker, but  
15 we did see changes in the physical wellbeing or the  
16 functional wellbeing. With some patients, we noted  
17 10 percent, but even in those, in many cases, it  
18 went back with continuous therapy.

19 DR. RINI: Dr. Thanarajasingam?

20 DR. THANARAJASINGAM: It was answered.

21 DR. RINI: Okay. Thank you, And  
22 Dr. Halabi?

1 DR. HALABI: I would like to circle back to  
2 my earlier question to the FDA. My understanding  
3 is that accelerated approval is sort of contingent  
4 on the phase 3 trial results. If the results come  
5 back negative, would the FDA withdraw the approval  
6 of the drug?

7 DR. PAZDUR: That would be one possibility.

8 DR. HALABI: Can you discuss other  
9 possibilities?

10 DR. PAZDUR: Other possibilities would be to  
11 take a look at other ongoing trials that they have,  
12 why the trial was negative. You obviously as a  
13 statistician know that there are many reasons a  
14 clinical trial can be negative, but one would look  
15 at other trials that might be able to be  
16 substituted for that trial as an ongoing.

17 This is a difficult situation, but we have a  
18 drug out there that has not demonstrated clinical  
19 benefit, and I think our concerns about this drug,  
20 with the absence of single-agent activity, has been  
21 explained in our presentations. But that is one  
22 possibility.

1 DR. HALABI: Thank you.

2 DR. SHACHAM: If I am ask the chairman, this  
3 was one of the questions that was asked before the  
4 break, about the single-agent activity, If my team  
5 can provide slides. I will discuss the results,  
6 and then I would appreciate if Dr. Jagannath and  
7 Dr. Richardson can help with the definition of  
8 single-agent activity in patients with heavily  
9 pretreated myeloma.

10 These are the results of the phase 1. We  
11 have here all 81 patients, and we are looking not  
12 only on partial responses, which is a criteria  
13 defined by the IMWG, but also in minimal responses,  
14 which is at least 25 percent reduction, as well as  
15 stable disease. In that study, all patients that  
16 were involved in a range of doses came into the  
17 study with actively progressing disease, and that  
18 was monitored and documented.

19 In the doses of 80 and above 80, we had very  
20 few patients. So in order to look at the  
21 single-agent activity, we believe it makes sense to  
22 look at the group of 27 patients that received no

1 dex, and what did selinexor demonstrate in this  
2 population, and we highlighted, just to simplify  
3 the slide, in yellow. Out of these 27 patients, 5  
4 of them -- so about 20 percent; 19 percent to be  
5 exact -- achieved a minimal response, which is at  
6 least 20 percent reduction. And 12 of them coming  
7 into the study with actively progressing disease  
8 had stable disease, some of those for a long period  
9 of time.

10 So taken together, actually, in most of the  
11 patients, we saw some activity. It is correct that  
12 with the addition of text, we saw deeper and longer  
13 responses, but the single-agent activity was  
14 demonstrated at least by achieving disease control  
15 or any minimal responses.

16 DR. JAGANNATH: I can just provide a  
17 clinical context to the minor response. At a lower  
18 dose, 70 milligram, as a single agent, as shown  
19 here, these minor responses in advanced refractory  
20 myeloma are still meaningful. As I've said before,  
21 by controlling the disease progression prevents,  
22 for the renal deterioration, hyperviscosity, bone

1 lesions, et cetera. It has also been shown in  
2 phase 3 clinical trial, minor responses do have  
3 clinical benefit to the patient.

4 DR. RICHARDSON: I guess my only addition to  
5 that comment is this whole construct around the  
6 idea that this is somehow a combination strategy  
7 and that there was a confounder from low-dose  
8 dexamethasone. In this uniquely heavily pretreated  
9 refractory population, the influence of  
10 dexamethasone has to be considered as a single  
11 agent negligible. There is clearly a synergy, but  
12 the argument that somehow that confounds  
13 interpretation of the efficacy of the single-arm  
14 study is difficult when one considers how  
15 refractory these patients are.

16 DR. JAGANNATH: One other thing I wanted to  
17 say is in the mechanism of action, we know that  
18 selinexor induces the glucocorticoid receptor,  
19 binding to the glucocorticoid receptor, goes into  
20 the nucleus where it binds to the glucocorticoid  
21 receptor elements, which is important for  
22 NF-kappa-B down regulation. And up regulation is

1 separate because this particular drug blocks the  
2 expotin, so you can completely shut down the  
3 NF-kappa-B. Just like the Velcade also synergizes  
4 with this drug, glucocorticoid also synergizes with  
5 the drug.

6 So I wanted to say that I know there is a  
7 lot  
8 of discussion of whether we can isolate selinexor  
9 alone, but in this advanced refractory population,  
10 I believe that the glucocorticoid or the  
11 dexamethasone also adds synergy to this drug  
12 selinexor in controlling the disease.

13 DR. RINI: Thank you. We're going to do one  
14 more question from Dr. Hawkins.

15 DR. HAWKINS: I apologize. I just need  
16 clarity. It's a follow-on of Dr. Halabi and  
17 Dr. Harrington. I understand the question -- this  
18 is a question for the FDA. I understand what a yes  
19 vote means, but I'm not sure I understand what a no  
20 vote means or if a no vote even applies to the  
21 question.

22 DR. GORMLEY: The question that we're asking

1 you is -- and I really just want to frame this a  
2 little bit, take a step back a little bit. The  
3 question is -- and part of this, we get at this a  
4 little bit with a discussion and then into the  
5 question -- what is the risk-benefit profile for  
6 this product in light of all of the information  
7 that we've heard today and discussed?

8 Our concerns, as we've related, are that  
9 this is a single-arm trial of a combination in a  
10 product that demonstrated no single-agent activity.  
11 IMWG criteria are written as such, and um, it's  
12 been validated that progression, or PR and CR are  
13 correlated with overall survival. That's why we  
14 have accepted response rate defined as PR and CR as  
15 a surrogate endpoint in multiple myeloma with a  
16 product that did not show that alone. And we have  
17 a single-arm trial of a combination with these  
18 toxicities in a product that has demonstrated  
19 toxicity, substantial toxicity in particular in the  
20 AML trial where we did have randomized data and see  
21 a worse overall survival.

22 How do we interpret this data that we see

1 from this current single-arm trial in terms of the  
2 risk-benefit? Then ultimately, given that this  
3 trial, the randomized phase 3 trial, has been  
4 completely accrued at this point, and we're talking  
5 about top-line data at the end of this year, how do  
6 we then -- should we -- the question is basically,  
7 should the approval decision wait until we have  
8 randomized trial data given this risk-benefit  
9 profile that we see with a single-arm trial?

10 I'm hoping I'm answering your question, but  
11 a yes vote was basically -- or saying yes we should  
12 wait until we have randomized data, or we should  
13 wait and delay the approval decision until we have  
14 randomized data. No, we don't need to wait. The  
15 risk-benefit profile is robust enough. And that's  
16 why I went through the evidentiary criteria for  
17 accelerated approval is that there's still the same  
18 standard for safety and effectiveness that must be  
19 demonstrated. Have we met that standard? That's  
20 what a no vote would say, is that we have met that  
21 standard.

22 DR. SHACHAM: And I would just clarify the

1 timing of the results, we expect results from the  
2 BOSTON study based on the accrual to come next  
3 year, in the first half of next year, and with NDA  
4 submission towards the end of the year, giving the  
5 option for approval in about two years from now.

6 DR. GORMLEY: And just one last point, I'd  
7 just like to highlight that generally at the FDA,  
8 we really try and take a very accelerated review of  
9 applications that we think are game changing, and  
10 we have really put that into place for products  
11 such that the review time frame does not need to be  
12 the necessary traditional 6-12 months. If we think  
13 your product has activity and provides an unmet  
14 need, we can do this quickly.

15 DR. RINI: Dr. Pazdur?

16 DR. PAZDUR: Just to give a plug here, we  
17 have this concept of real-time review where we  
18 actually accept the data as it's coming into the  
19 company. So we're not taking a year to review the  
20 material here. This material could be transferred  
21 to the FDA as it comes into the sponsor after it's  
22 cleaned up.

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**Questions to the Committee and Discussion**

DR. RINI: Thank you.

We'll now proceed with the discussion and questions to the committee. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. So we'll go into the discussion section. I'll just read this to you.

Discuss whether KCP-330-012, also known as STORM data, are conclusive to allow for an adequate assessment of the safety and efficacy in the proposed patient population and whether selinexor provides a benefit that outweighs the risks.

DR. SHACHAM: Dr. Chairman, just one question. There were questions that we promised to provide answers after the break. Do you want us to provide those or do you want --

DR. RINI: I think we're going to move on. Thank you.

DR. SHACHAM: Okay.

DR. RINI: So I'll ask the committee to now

1 weigh in, as they've heard both sides of the  
2 argument here, for discussion around this question.  
3 Go ahead.

4 DR. THANARAJASINGAM: I just have several  
5 comments about toxicity and tolerability, which  
6 have been a lot of what we're discussing here. I  
7 absolutely recognize the high unmet need of  
8 patients with triple-class refractory myeloma.  
9 There's precedent for accelerated approval of novel  
10 agents in myeloma based on single-arm phase 2  
11 studies. This was done for carfilzomib,  
12 pomalidomide, and dara.

13 With these agents, there was a signal of  
14 efficacy, and the toxicity was comparatively low,  
15 overall toxicity, not just SAEs. However, for  
16 selinexor, the frequency, severity, and character  
17 of the adverse events raises substantial unique  
18 concerns about tolerability. It appears to bear a  
19 high incidence in grade of AEs and a substantial  
20 rate of dose modification and discontinuation due  
21 to AEs, which the sponsor has indicated are  
22 tolerable.

1           Recently the Friends of Cancer Research  
2 published a white paper with the following  
3 definition of tolerability, with input from  
4 industry and regulatory authorities. Tolerability  
5 is the degree to which symptomatic and  
6 non-symptomatic AEs associated with the product's  
7 administration affect the ability or desire of the  
8 patient to adhere to the dose or intensity of  
9 therapy.

10           Tolerability is a subjective concept and  
11 evaluating it requires direct measurement from  
12 patients on how they are feeling and functioning on  
13 treatment. This includes patient-reported  
14 symptomatic AEs, disease related symptoms,  
15 functional status, global side effect burden,  
16 quality of life, and other elements. The FACT  
17 multiple myeloma used in this study is a static  
18 instrument that addresses some but not all of these  
19 domains. Sixty-eight percent of the patients  
20 provided data, so we're missing that in about a  
21 third of the patients, and it's concerning that on  
22 what we have, some of the patients report an

1 increase in the overall side effect burden over  
2 time based on the FACT GP5 item. Some symptomatic  
3 AEs of high incidents such as nausea and fatigue  
4 were assessed, while others like diarrhea,  
5 constipation, and anorexia were not evaluated by  
6 the patients.

7 So for a drug like selinexor, or any or any  
8 other that appears to confer a high burden of  
9 symptomatic AEs, I encourage the implementation of  
10 validated flexible tools like the PRO-CTCAE, which  
11 can capture this directly from patients.

12 Systematic and comprehensive assessment of  
13 tolerability is essential even in a sick refractory  
14 population with few remaining options. It's first  
15 to do no harm, even and especially in this  
16 population. I'm uncomfortable with an incomplete  
17 understanding of whether the GI effects, the weight  
18 loss, the dehydration, the need for frequent  
19 visits, the lab monitoring, the IV fluids made this  
20 treatment intolerable to many of the patients on  
21 it.

22 Using a comparator of real-world or

1 retrospective data might be acceptable when the  
2 toxicity signal of a novel agent is low, but when  
3 it appears to be high, a randomized comparison of  
4 clinical outcomes, including toxicity, is  
5 warranted, we do not otherwise truly know if  
6 patients receiving investigator's choice  
7 dexamethasone only or supportive care and hospice  
8 might have lived longer or lived better.

9           So the question was asked about whether the  
10 information from BOSTON will help. I think a phase  
11 3 randomized comparison will help when you are  
12 looking at a drug where toxicity and tolerability  
13 are huge concerns in the context of a disease that  
14 has a lot of symptoms because at least you can  
15 compare the arms there. So I eagerly anticipate  
16 the results of that study to better inform us of  
17 the tolerability of selinexor, and as a clinician I  
18 am very sympathetic and I want more drugs to be  
19 approved. But as physicians and investigators and  
20 regulators, we also have a responsibility to ensure  
21 that we are making things better and not worse, and  
22 incorporating the perspective of the patient.

1 DR. RINI: Thank you for those thoughtful  
2 comments.

3 Other comments around the discussion  
4 question? Dr. Hinrichs?

5 DR. HINRICHS: I have a couple of comments  
6 on this question. It asks if the data are  
7 conclusive to allow for an adequate assessment of  
8 safety and efficacy in the proposed patient  
9 population, and I think that there are two issues  
10 that I'm struggling with. One is the trial design,  
11 and the other is the trial results.

12 If we look at this as a combination therapy  
13 trial, then the trial design is not adequate to  
14 assess the safety and efficacy, and that is  
15 consistent with FDA guidelines on how a trial ought  
16 to be conducted to assess that in this setting, and  
17 I think those guidelines are sound. They just make  
18 sense. They're practical. That's the way all of  
19 us would think about answering these questions  
20 about safety and efficacy in a combination setting.

21 If we look at this instead as more of a  
22 single-arm trial of a single agent, like the

1 combination is actually just one agent and that dex  
2 really doesn't have any activity, which seems to be  
3 a subject of some debate, then all we can do is  
4 look at the trial results. So what would we want  
5 to see in the trial results?

6 Well, you'd want to see some kind of  
7 remarkable activity and a good safety profile that  
8 convinces you that this is a good thing in the  
9 absence of really rigorous data that would come  
10 from a randomized trial. What might that look  
11 like? Well, you'd be looking for a remarkably high  
12 response rate, for example. So if 80 percent of  
13 the people responded, we'd have a pretty good idea  
14 that this has a lot of activity. Now here we have  
15 25 percent responded, and again the confounder of  
16 the deck, so I think that makes it a little bit  
17 unclear.

18 We'd also be looking for if there's a subset  
19 of patients who really benefit profoundly. For  
20 example, if we cured some people, then a low  
21 response rate in this setting, if it cures some  
22 people, that would be somewhat compelling that this

1 is an effective approach. But we don't really see  
2 that. We see one patient with a better than a PR.

3 Next, we might be looking for really durable  
4 responses from the people who respond, and here  
5 we're seeing about 4-month responses. That does  
6 seem to represent a response rate, but it's not  
7 profoundly long. Then finally, what we'd look for,  
8 I think if you're looking at a single-arm situation  
9 is a really favorable side effect profile. The  
10 analogy in solid tumors might be for the checkpoint  
11 inhibitors where with a relatively low response  
12 rate, these drugs generally seem to be beneficial  
13 because they have such a favorable toxicity  
14 profile, and clearly that isn't the situation with  
15 this drug either.

16 So on the basis of those factors, the trial  
17 design and the trial results, I find it hard to  
18 conclude that this allows for an adequate  
19 assessment that safety and efficacy are favorable.

20 DR. RINI: Thank you. Dr. Mo, did you have  
21 a comment? Please.

22 DR. MO: First of all, I just want to say I

1 think nobody here would argue that there is not an  
2 unmet need in myeloma and everybody here is on the  
3 same team in that regard and doing their job, so I  
4 really appreciate all the points. I'm just trying  
5 to wrap my head around this difficult issue. I've  
6 been thinking of this both in terms of the  
7 scientific perspective as well as the historical  
8 perspective, and I think both of those perspectives  
9 are important, so these are just my thoughts.

10 In terms of the historical perspective,  
11 first of all, let me just say I don't think that  
12 anything should ever be approved, just based on  
13 historical context and precedent, but I do think  
14 that precedent is relevant and important, and I've  
15 been looking at it in that sense. In terms of  
16 historical comparisons between selinexor and other  
17 myeloma drugs that have been approved by the FDA,  
18 I've done my own analysis and this is what I've  
19 come up with.

20 In terms of overall response rate, it's not  
21 worse. Kyprolis and pomalidomide-dex were both FDA  
22 approved with similar response rates. The SAE

1 incidence is not worse. Pomalyst was approved with  
2 I think a slightly worse SAE incidence. The  
3 percent discontinuation rate of the study drug is  
4 not worse than it was with panabinostat, which  
5 actually had a higher discontinuation rate than  
6 selinexor. The rate of fatal treatment-emergent  
7 AEs is not worse than that of Kyprolis, which had I  
8 think the slide said 10 percent fatal AE rate.

9 So those are the things that aren't worse.  
10 The only two things that I could see that actually  
11 were worse was the percentage of patients who  
12 required a dose modification, which definitely was  
13 almost everybody, as both the investigators and the  
14 FDA have pointed out, but that was pretty much it.  
15 The only other thing, in my opinion, that was worse  
16 was the patient population. And by that I mean  
17 this is a patient population, two-thirds of which  
18 were penta-refractory, which is a category of  
19 myeloma patients that was nonexistent 10 years ago  
20 because we didn't have penta options. And what we  
21 do know about clonal evolution and the biology of  
22 this disease is biologically it's a worse disease

1 every single time it comes back.

2           So I think that when you look at AEs, when  
3 you look at response rates, when you look at  
4 duration of response, I think it's important to  
5 remember that -- to put it in a somewhat extreme  
6 but I think accurate wording -- these are different  
7 diseases, just as myeloma that's relapsed after one  
8 line of therapy and is now being studied on the  
9 BOSTON trial is a different disease than  
10 penta-refractory myeloma. So that is the one  
11 important difference in terms of what was worse  
12 with the STORM 2 study, was the patient population.

13           So in terms of precedence, I would say that  
14 Kyprolis was FDA approved on an accelerated basis  
15 based on a single-arm trial that had an overall  
16 response rate of 23 percent, and correct me if I'm  
17 wrong, but I'm pretty sure 10 percent fatal AEs.  
18 Darzalex was approved on an accelerated basis also  
19 based on a single-arm study with a 29 percent  
20 overall response rate. Panabinostat was FDA  
21 approved with 30 percent discontinuation approval  
22 as a combination with dexamethasone with poor

1 single-agent activity. There's actually precedent  
2 for that as well.

3 On the pom versus pom-dex study, I believe  
4 the single-agent pom response rate was only  
5 7 percent. It's not 2 percent, but it's 7 percent,  
6 which was pretty poor, and it was 29 percent with a  
7 combination. So I do think the investigator's  
8 point about looking at the combination of selinexor  
9 with dex as a combination regimen is somewhat of a  
10 misnomer and that there has been precedence for  
11 approving drugs with poor single-agent activity,  
12 specifically Pomalyst, which in my practice has  
13 been extraordinarily helpful for some of my  
14 patients.

15 The last precedent that I'll mention, this  
16 was on the -- I think I remember reading this  
17 somewhere. The age of the patients on study was  
18 significantly younger than the average age of  
19 myeloma diagnosis, but pretty much every other  
20 study that I've looked at historically, that's  
21 always been the case, and they have led previously  
22 to FDA approvals.

1           So that was my thoughts in terms of the  
2 historical context. In terms of the scientific  
3 perspective, I definitely appreciate the advantages  
4 of a randomized study, as very well laid out by the  
5 FDA. I also appreciate the difficulties, the  
6 pragmatic, realistic difficulties of conducting  
7 such as study as mentioned by the investigators. I  
8 think that the example of inferior survival in the  
9 AML study, I think the point is well taken, and it  
10 definitely shows in a perfect world, a randomized  
11 study is optimal to ensure that you know what the  
12 safety is and to best describe that. However, I  
13 don't think the analogy holds up completely because  
14 on that AML study, the control arm, many patients  
15 got hypomethylating agents, which is known to be a  
16 very efficacious therapy for AML. And even if it  
17 doesn't induce remissions, actually can keep  
18 patients with AML in stable disease for months to  
19 years.

20           So I think the point is well taken, but I  
21 don't think that the analogy holds up, and I don't  
22 think that that's an example that necessarily

1 compels us to perform a randomized study in this  
2 sense. I think that the quote that I saw that's,  
3 quote, "We cannot isolate the treatment effect of  
4 selinexor versus dex," I disagree with that.  
5 Patients in the STORM 2 study were steroid  
6 refractory. These were patients who were  
7 progressing through their most recent line of  
8 therapy, which it doesn't really matter what line  
9 of therapy that was; it included steroids and also  
10 a dose of steroids that was probably either  
11 equivalent or greater than the dose of steroids  
12 that patients got in the STORM 2 study. And  
13 actually the dose of dexamethasone in the STORM 2  
14 study is lower than the average dose of  
15 dexamethasone that patients would get with the most  
16 commonly used regimens of RVD, KRd, and such.

17 So I think, again, you can't scientifically  
18 prove this, but I think it's extremely unlikely  
19 that you would see anywhere close to a 25 percent  
20 response rate with any dose of dex. You could  
21 argue historically that you saw 20 to 30 percent  
22 response rates to high-dose dex, but as multiple

1 people have pointed out today in the modern era,  
2 again with a different disease of worse myeloma  
3 than existed in the '80s and '90s, you're seeing at  
4 best a 10 percent, and more likely probably a 4 to  
5 5 percent response to high-dose dex. And these  
6 patients are getting the opposite of high-dose dex,  
7 so I think you can't prove it scientifically, but I  
8 would bet a large sum of money that this is  
9 evidence convincing enough to me of synergistic  
10 activity of selinexor versus dex.

11 So I do disagree with the statement that we  
12 cannot isolate the treatment effect of selinexor  
13 versus dex. I think the way to look at it is as  
14 the combination as opposed to one or the other.

15 Lastly, in terms of the scientific  
16 perspective, I think that the BOSTON study and the  
17 STORM 2 study are answering different questions.  
18 Again, myeloma that's relapsed after one line of  
19 therapy is a different disease than myeloma that is  
20 progressing through the 10th line of therapy. So  
21 even if the BOSTON study is negative, I don't think  
22 that should be an automatic rescinding of the FDA

1 approval for truly highly refractory, especially  
2 penta-refractory myeloma patients.

3           The last thing I'll say is I definitely  
4 appreciate the points about the possibility of  
5 retreating patients. A penta-refractory patient is  
6 somewhat different than a triple-class refractory  
7 patient, and maybe there are some patients with  
8 triple-class refractory disease that could respond  
9 to another round of Pomalyst and Velcade or  
10 Kyprolis or what have you. But given that  
11 two-thirds of the patients on the STORM 2 study  
12 were penta-refractory patients, the worst of the  
13 worst diseases, we could argue back and forth about  
14 whether the design that was implemented versus a  
15 randomized study was the best way to go. But in my  
16 opinion, it's kind of a moot point because we have  
17 the data that we have, and that data is a 25  
18 percent response rate and an essentially  
19 end-of-the-line myeloma situation, a 25 percent  
20 response rate and a less than 10 percent rate of  
21 fatal AEs that could have potentially been related  
22 to the drug, that we don't know were even related

1 to the drug.

2 Just as a brief aside, the fatal AEs that we  
3 did see, 60 percent were due to infection, which is  
4 extraordinarily unfortunately common in this  
5 patient population. And going back to the  
6 precedent, there were other drugs that have been  
7 FDA approved that had fatal AEs that were the  
8 result of an unexpected organ dysfunction specific  
9 cause of death as opposed to infection, and we're  
10 not seeing that with selinexor.

11 So I think I might feel a little bit  
12 differently if it was a 10 percent fatal AE rate  
13 and it was 9 percent MIs or 9 percent catastrophic  
14 hemorrhage. But it just wasn't. It was the stuff  
15 that we unfortunately see in myeloma patients at  
16 this point of disease no matter what.

17 So again, we have the data that we have, 25  
18 percent response rate with a less than 10 percent  
19 fatal AE rate in patients, the large majority of  
20 which have no other FDA-approved treatment option.  
21 So at this point with the data that we have, in my  
22 opinion, it's probably not feasible, possible,

1 realistic, or ethical to conduct a study that  
2 randomizes patients to this drug versus best  
3 supportive care. I don't think at this point, with  
4 the data that we have, it's ethical to do that kind  
5 of study at this point.

6           So for all of these reasons -- and I'm sorry  
7 if I took too long. I think this is not the  
8 perfect situation. It's not the perfect study.  
9 It's not the perfect data. But as a physician who  
10 treats patients with myeloma, I would support its  
11 accelerated approval with the requested  
12 indications. Thank you.

13           DR. RINI: Thanks for the comments.

14           Dr. Farrell, you want to make a comment?

15           DR. FARRELL: I just wanted committee  
16 members to weigh in on whether or not the  
17 availability of an expanded access program would be  
18 influencing their decision about its availability  
19 on the market, and I just wonder if people could  
20 comment.

21           DR. RINI: I guess I would say we'd always  
22 feel better if there was a way for patients to get

1 drug. I think you hear from patients at all of  
2 these meetings that's what they want, access to  
3 drugs. So speaking for myself, and I see a lot of  
4 shaking heads, I think we always want patients to  
5 have access to drugs for all the reasons that the  
6 patients themselves mentioned.

7 I don't know if other people want to  
8 comment.

9 DR. COMPAGNI PORTIS: I feel that there will  
10 be expanded access, and there is a real need for  
11 treatments. In concert with conversation with  
12 their doctors and really looking at their  
13 particular situation, that makes me more  
14 comfortable to say we need to wait for more data  
15 because there's so much we don't know with the data  
16 that we have. So that makes a big difference to  
17 me.

18 DR. RINI: Other comments around that?

19 DR. MORROW: I haven't practiced for a  
20 while, but I just wanted to ask the clinicians  
21 around the room the feasibility of accessing this  
22 quickly for their patients.

1 DR. SHACHAM: Can you repeat the question?

2 DR. MORROW; Feasibly, not just reaching out  
3 to FDA, which is 24 hours availability, but just  
4 the feasibility of getting patients into the EAP  
5 program and getting them drug quickly.

6 DR. SHACHAM: I'll say as the company, when  
7 available, we provided -- all patient is available  
8 by institution and approved by the FDA  
9 compassionate use as of today, and we will continue  
10 to do so.

11 However, we are very concerned that  
12 providing selinexor to patient population through  
13 expanded access would actually reduce the overall  
14 patient access by limiting the number of patients  
15 in the institutions that can accept this; and more  
16 important by limiting the ability to support this  
17 institution, and the physicians, patients, and  
18 caregivers through the steps that they described,  
19 that we are building in order to help them with  
20 management of side effects.

21 I actually would like my two colleagues to  
22 comment about the availability of expanded access

1 in their institutions.

2 DR. RINI: Okay. Quickly.

3 DR. JAGANNATH: Individual patient INDs, an  
4 institution like mine, they're restricted. You can  
5 do only two. Then trying to do it as a clinical  
6 trial, this is not available for community  
7 oncologists. This will never be implemented  
8 nationwide, so it will be very restrictive.

9 DR. USMANI: Saad Usmani from the Levine  
10 Cancer Institute. I'm part of the IRC and have  
11 been compensated for my travel and lodging. It's  
12 simply impractical, from an institutional  
13 standpoint, to see that we will have single patient  
14 IDs available for every myeloma patient who may be  
15 eligible for selinexor.

16 None of the institutions have that kind of  
17 support. Think about two- or one-physician  
18 clinical practice in middle the of nowhere that's  
19 serving a 100-mile radius. Do they have the  
20 support or access to drugs? I think it's simply  
21 impractical.

22 DR. RINI: Thank you. Very last comment,

1 quickly.

2 DR. CHARI: As you know, we're losing 1000  
3 patients a month to this disease, and we see that  
4 the rate of progression is 22 percent in 2 weeks.  
5 We didn't even talk about the number of myeloma  
6 patients that can't meet the eligibility criteria  
7 because you are not allowed to transfuse  
8 [indiscernible] growth factors. So these patients  
9 will never make it to these expanded access, and  
10 the whole point of having an oral drug will be  
11 restricted again to the academic centers and not to  
12 the community doctors.

13 DR. RINI: Thank you.

14 I'm going to summarize quickly what I heard  
15 in the discussion, and then we'll move to the vote.  
16 I think I heard a lot that this is clearly an unmet  
17 need in a sick and symptomatic population who  
18 sounds like they have a lot of end organ damage  
19 heading into this trial in this space. It's a  
20 difficult drug development space, clearly, because  
21 of all the reasons and inherent, the toxicity of  
22 this population.

1 I heard that there's certainly a signal of  
2 activity here. I think Dr. Mo articulated it well,  
3 that it seems to be beyond dexamethasone  
4 monotherapy, certainly worthy of further study. On  
5 the other side, I heard a lot of people talk about  
6 toxicity seemed to be the major theme. In terms of  
7 objective response rate, I think there were  
8 concerns about depth and duration of response and  
9 also quality of life.

10 I think in this sick and symptomatic  
11 population, I would expect and hope that an active  
12 drug would produce more quality-of-life benefits.  
13 I think another overwhelming team was the  
14 challenging regulatory issues that we heard about  
15 many times about the challenges of interpreting a  
16 single-arm combo study, especially we keep going  
17 back to the minimal single agent activity.

18 So we're now going to turn to the voting  
19 question, which I will read to you. It says,  
20 should the approval of selinexor be delayed until  
21 results of the randomized phase 3, BOSTON, are  
22 available? If there are any questions about the

1 question, we'll take them now.

2 Again, a yes vote, you would be voting that  
3 you would delay the approval of this drug. You  
4 would recommend to delay the approval of this drug  
5 until these phase 3 trial results are available. A  
6 no vote would mean you do not think we would need  
7 to wait until those results are available, and you  
8 would recommend approval now under accelerated  
9 mechanism.

10 Are there any questions about the voting  
11 question

12 (No response.)

13 DR. RINI: We'll be using an electronic  
14 voting system for this meeting. Once we begin the  
15 vote, buttons will start flashing and will continue  
16 to flash even after you've entered your vote.  
17 Please press the button firmly that corresponds to  
18 your vote. If you're unsure of your vote and wish  
19 to change your vote, you may press the  
20 corresponding button until the vote is closed.

21 After everyone has completed their vote, the  
22 vote will be locked in. The vote will then be

1 displayed on the screen. Lauren will read the vote  
2 from the screen into the record, and then we'll go  
3 around the room, and each individual who voted will  
4 state their name and what they voted into the  
5 record. Then also, please state the reason why you  
6 voted as you did if you'd like to.

7           So we'll proceed to the voting process.  
8 Please press the button on your microphone that  
9 corresponds to your vote. You'll have  
10 approximately 20 seconds to vote. Press the button  
11 firmly. After you've made your selection, the  
12 light may continue to flash. If you're unsure of  
13 your vote or wish to change it, please press the  
14 corresponding button again before the vote is  
15 closed.

16           (Voting.)

17           DR. TESH: For the record, the yes vote is  
18 8; no vote is 5; abstentions, zero; no voting,  
19 zero. We'll pull it up as soon as we can, but we  
20 can start.

21           DR. RINI: We'll go around, We're going to  
22 let Dr. Portis and Dr. P go first, if they want to

1 say why you voted -- name into the record, why you  
2 voted, and any reasons.

3 DR. COMPAGNI PORTIS: Natalie Compagni  
4 Portis, and I voted yes. I think the data that we  
5 have doesn't meet the FDA standard for evidence on  
6 safety and effectiveness. We absolutely need more  
7 treatments that help patients live longer and/or  
8 improve quality of life, and not just treatments  
9 that are worse than those available. I feel like  
10 the trial leaves us with a lot of incomplete  
11 information on both of these issues.

12 Given the fact that there is expanded access  
13 for those willing to take on the risk in concert  
14 with support and education their physician, and  
15 given the serious side effects and even fatal  
16 adverse events, and the real lack of clarity on  
17 dosing, and we don't know if there is a subset of  
18 responders, it seems vital and responsible to wait  
19 for more data. We also need much more extensive  
20 data on the patient experience with this drug and a  
21 real complete report on quality-of-life issues.

22 DR. RINI: Thank you. I'm going to go over

1 here next.

2 DR. PAPADIMITRAKOPOULOU: So I voted no  
3 because I think patients need options in this line  
4 of therapy. I do realize that there are concerns  
5 about toxicity, which I share. I was convinced by  
6 the presentation that combination therapy and the  
7 response rate observed is a result of synergy that  
8 wouldn't be observed with dexamethasone alone,  
9 Feeling that the patients need more options in this  
10 setting, that was the main motivator for my choice.

11 DR. RINI: Thank you. We're going to jump  
12 back over. Dr. Morrow's not on voting, but do you  
13 want to make any comments.

14 (Dr. Morrow gestures no.)

15 DR. RINI: Okay. Doctor Mo?

16 DR. MO: I think I've pretty much said  
17 everything before the vote --

18 (Laughter.)

19 DR. MO: -- but again, I obviously respect  
20 the yes votes, but I invite my colleagues to take a  
21 look at all of the parameters of concern that are  
22 definitely valid concerns. Look at the historical

1 context in drugs that have already been approved by  
2 the FDA and have proven to be life-saving,  
3 game-changing drugs for thousands of patients, and  
4 other than the percentage of patients who required  
5 a dose modification, tell me what was actually  
6 worse about this drug compared to those drugs, and  
7 I would invite that discussion. But again, I  
8 respect the yes votes and already have made my  
9 other points clear.

10 DR. RINI: Just for the record, can you say  
11 your name and the way you voted?

12 DR. MO: Clifton Mo, and I voted no.

13 DR. RINI: Thank you.

14 Dr. Harrington?

15 DR. HARRINGTON: I'm Dave Harrington, and I  
16 voted no. The original question for discussion is  
17 are the data conclusive uh, for benefits and risks?  
18 No, they aren't conclusive in either direction  
19 here. I think what we have is a transient  
20 situation between now and when more data come in  
21 the BOSTON trial and other data, and I think we do  
22 patients some potential benefit here if this agent

1 is used constructively and intelligently while we  
2 wait for the additional data in a population that  
3 is not naive to side effects.

4 DR. RINI: Thank you.

5 DR. THANARAJASINGAM: I'm Gita  
6 Thanarajasingham, and I voted yes. I think  
7 absolutely patients need options, and even those  
8 who are running out of options are owed  
9 comprehensive safety and tolerability evaluation  
10 beyond just what are the SAEs, what are the  
11 high-grade events, but did we really assess  
12 tolerability and did we ensure these patients are  
13 living better in addition to living longer.

14 DR. RINI: Thank you. Dr. Hawkins?

15 DR. HAWKINS: I voted no. I was influenced  
16 by Dr Mo's analysis. I was also very much  
17 influenced by the consumers who presented. I was  
18 very, very concerned about adverse events  
19 initially, and I realized individuals who didn't  
20 tolerate this maybe are not here. But I thought  
21 with a new drug, they deserved the opportunity to  
22 have a go at this drug. Also, I wasn't sure that

1 this study was going to be comparable to the BOSTON  
2 study that we're waiting for.

3 DR. RINI: Thank you. Dr. Shaw?

4 DR. SHAW: Alice Shaw. I voted yes. It's  
5 one of the most challenging decisions actually. I  
6 believe there is a probable benefit of selinexor  
7 and dexamethasone for some triple-class refractory  
8 myeloma patients, and of course I completely  
9 understand the urgent need to develop novel agents  
10 with novel mechanisms of action for these patients  
11 who have exhausted standard options, but as we  
12 heard, there are real toxicities with this  
13 combination, and this may not be the right dose.

14 I find it really challenging to really  
15 fairly evaluate these toxicities given the  
16 single-arm study, and I do fully acknowledge that  
17 it may be that the high rate of AEs and SAEs and  
18 deaths from TEAEs may reflect the very heavily  
19 pretreated population of patients, but without  
20 having that comparator population in STORM, I can't  
21 say for certain, and hence, I can't definitively  
22 say that the clinical benefits outweighs the

1 significant toxicity. So in the interest of  
2 patient safety, I do favor waiting for the  
3 randomized trial.

4 DR. RINI: Thank you. Dr. Uldrick?

5 DR. ULDRICK: Thomas Uldrick. I also voted  
6 yes. I agreed with Dr. Mo's analysis for the most  
7 part. The things that concerned me most were the  
8 90 percent dose modification and that the dose is  
9 probably not optimized, and there was inadequate  
10 durability of response or other evidence of  
11 clinical benefit to help balance the adverse event  
12 profile and need for lower doses in almost all  
13 patients.

14 DR. HINRICHS: Christian Hinrichs. I voted  
15 yes. I think that this drug probably has some  
16 level of clinical activity, or this combination of  
17 drugs probably has some level of clinical activity.  
18 What I know is that it has substantial toxicity.  
19 And in this kind of situation, it's hard to know if  
20 it's a benefit or not, or if the benefits outweigh  
21 the risks. So what you need in that situation is a  
22 well-designed trial to answer the question. And we

1 don't have that, and we're lacking conclusive data  
2 that the benefits outweigh the risks and that we  
3 should proceed with giving this to patients outside  
4 of a clinical trial setting.

5 DR. RINI: Thank you. Brian Rini. I voted  
6 yes, a lot of which has already been discussed  
7 here. This is clearly a difficult drug development  
8 space. As somebody said, I think it's probably one  
9 of the most difficult votes I've had in many years  
10 now on this committee.

11 I think there's benefit here. What I'm  
12 struggling with is benefit and risk. This is  
13 clearly a refractory population. I wanted more  
14 data on how we're actually helping people beyond a  
15 response rate, the improvement in renal function,  
16 the improvement in pain and quality of life, and  
17 that's why I asked about all that. Again, a drug  
18 that has benefit will improve those things, and I  
19 just didn't see any objective evidence of it. I  
20 heard it from the clinicians and I believe it, but  
21 I think we need to see objective evidence of that  
22 in order to balance that against what I think is

1 substantial toxicity.

2 DR. KLEPIN: Heidi Klepin. I voted yes. I  
3 would have preferred to vote no, but I voted based  
4 on the evidence that was presented and based on the  
5 level of evidence that was expected for this  
6 particular approval. For all the reasons that were  
7 previously mentioned, I just don't believe that we  
8 yet have adequate evidence to assess the safety and  
9 efficacy, and in the interest of patient safety, I  
10 think we need to wait.

11 I do think that there will be information  
12 gained from the subsequent trial that we're waiting  
13 on that can help inform not exactly every question  
14 that we have, but I think it can make some of our  
15 questions and concerns hopefully lessen if that's a  
16 positive study and we see some safety data that's  
17 helpful.

18 DR. RINI: Thank you.

19 DR. CRISTOFANINLLI: Massimo Cristofannili.  
20 I voted no, and the reason being that this patient  
21 population clearly cannot be randomized study.  
22 They are in the terminal phase, essentially

1 pre-hospice. I think in this particular condition,  
2 as was explained very much in detail having a 25  
3 percent response, essentially the study met the  
4 primary objective.

5 Obviously, there's been a lot of talk about  
6 the side effects of this drug, but it has to be in  
7 the right context, and this particular patient had  
8 multiple organ dysfunction because of their  
9 disease. So because of infections, or sepsis, or  
10 these other reported side effects were clearly  
11 somewhat associated with the disease. So I felt  
12 the drug was clearly demonstrating efficacy and  
13 they showed that the management of the side  
14 effects, particularly GI, was possible in the  
15 proper setting.

16 DR. RINI: Thank you.

17 DR. HALABI: Susan Halabi, and I voted yes.  
18 I again struggled with this a lot. It wasn't an  
19 easy decision, but again, looking at the data, the  
20 totality of the evidence, overall whether you're  
21 using the STORM or the randomized trials, it seems  
22 to me it wasn't clear what's the benefit compared

1 to the risk here. Also, when I looked at the  
2 subset of patients and subgroup analysis in STORM,  
3 I thought that, clearly, there's no indication who  
4 are the exceptional patients who are responding to  
5 this drug.

6 DR. RINI: Thank you.

7 Any final FDA comments?

8 (Dr. Pazdur gestures no.)

9 **Adjournment**

10 DR. RINI: No?

11 We will now adjourn the meeting. Panel  
12 members, leave your name badge here so that they  
13 may be recycled. Take all your personal belongings  
14 with you at the end of the day. Thanks, everyone  
15 for their efforts and contributions. Thank you.

16 (Whereupon, at 5:00 p.m., the meeting was  
17 adjourned.)

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