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

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(12:30 p.m.)

Call to Order

Introduction of Committee

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. TESH: Lauren Tesh, designated federal officer.

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

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

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

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

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

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

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

DR. PAZDUR: Richard Pazdur, FDA.

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

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

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

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

Conflict of Interest Statement

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

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

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

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

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

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

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

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

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

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

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

DR. RINI: Thank you, Lauren.

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

FDA Introductory Comments - Nicole Gormley

DR. GORMLEY: Good afternoon. I'm Nicole

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

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

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

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

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

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

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

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

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

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

endpoint of the trial was overall response rate.

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

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

All patients had received prior dexamethasone but were not refractory to

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

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

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

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

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

The results may seem expected and even

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

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

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

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

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

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

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

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

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

dose has not been identified.

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

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

protocols.

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

We would like for the committee to discuss whether the 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 risk. The voting question is should the approval of selinexor be delayed until results of the randomized phase 3 trial, BOSTON, are available. Thank you very much.

DR. RINI: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Applicant Presentation - Paul Richardson

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

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

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

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

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

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

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

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

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

Response rates correlate with clinical

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

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

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

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

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

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

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

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

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

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

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

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

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

The recommended dose for patients with

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

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

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

well as overall survival.

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

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

All patients had documented triple-class

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

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

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

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

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

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

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

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

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

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

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

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

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

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

and a VGPR rates similar to these other drugs.

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

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

Applicant Presentation - Michael Kauffman

DR. KAUFFMAN: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

and then at least monthly thereafter.

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

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

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

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

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

Applicant Presentation - Sundar Jagannath

DR. JAGANNATH: Thank you.

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

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

recycling therapies using the same drugs in different combinations.

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

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

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

In addition, the rate of infections is consistent with other studies in heavily pretreated multiple myeloma. The median overall survival of 15.6 months in 40 percent of patients with a minimal response or better highlights the favorable benefit-risk ratio. The pivotal study results were meaningful, particularly for a group of patients in dire need of an effective fast-acting treatment. The 26.2 percent response rate and the duration of response observed is clinically meaningful and included patients who achieved both stringent complete responses and very good partial responses.

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

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

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

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

allowed him to participate in another clinical trial.

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

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

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

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

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

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

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

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

Applicant Presentation - Sharon Shacham

DR. SHACHAM: Thank you, Dr. Jagannath.

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

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

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

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

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

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

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

DR. RINI: Thank you for that nice presentation.

We'll now proceed with presentations from FDA.

FDA Presentation - Andrea Baines

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

determination for selinexor challenging.

We are seeking the committee's advice on whether the data from the pivotal trial KCP-330-012, referred to as STORM, 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 risk, especially considering the limitations of the STORM trial that I will discuss. The voting question will be should be approval of selinexor be delayed until the results of the randomized phase 3 BOSTON trial are available?

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

The pivotal trial, part 2 of STORM, has

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

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

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

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

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

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

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

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

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

STORM.

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

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

In fact, historical trials have demonstrated

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

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

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

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

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

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

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

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

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

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

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

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

The inclusion criteria for STORM more

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

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

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

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

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

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

patients with a missing ECOG status.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Of note, although selinexor resulted in

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

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

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

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

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

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

There were 23 deaths on or within 30 days of

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

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

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

A substantial proportion of patients required dose modifications and permanent discontinuation of study treatment. Eighty-nine percent of patients required at least one dose modification, including either a dose reduction, dose interruption, or permanent discontinuation of selinexor due to a treatment-emergent adverse event, and the majority of patients required more than one dose modification. Twenty-nine percent of patients permanently discontinued selinexor due to a treatment-emergent adverse event.

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

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

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

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

with selinexor in a randomized-controlled trial.

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

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

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

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

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

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

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

Thank you. This concludes the FDA clinical presentation.

Clarifying Questions

DR. RINI: Thank you.

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

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

You guys have characterized this population,

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. RINI: Dr. Harrington?

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

So should we expect that your algorithms for

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

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

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

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

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

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

Thank you.

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

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

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

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

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

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

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

DR. SHACHAM: For both cycles?

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

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

DR. RINI: Dr. Thanarajasingham?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. RINI: Dr. Hawkins?

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

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

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

DR. KAUFFMAN: The biggest best learning we

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

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

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

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

DR. CHARI: Several novel interventions seem to be beneficial to your question. For example, with nausea and the GI symptoms, we did use, per NCCN guidelines, the NK inhibitors, and those seem to be helpful in patients. With platelets, we did use TPO agonists because we know that, preclinically, selinexor blocks thrombopoietin in the meguiar karyocytes, and we saw that patients were able to recover platelets faster. For patients with fatigue, we did also occasionally use Ritalin.

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

supportive care.

DR. RINI: Dr. Cristofanilli?

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

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

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

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

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

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

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

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

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

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

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

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

DR. RICHARDSON: Thank you, Sundar.

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

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

trials in this setting are very challenging.

DR. RINI: Dr. Klepin?

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

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

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

Specifically, when we look at the adverse

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

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

DR. RINI: Dr. Halabi?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. PAZDUR: That's a big problem.

(Laughter.)

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

DR. RINI: Thank you. Dr. Hinrichs?

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

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

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

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

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

Dr. Richardson?

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

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

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

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

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

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

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

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

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

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

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

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

DR. RINI: Yes, please.

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. RINI: Thank you. Dr. Uldrick?

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

DR. RINI: Sure.

DR. SHACHAM: -- that the FDA mentioned.

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

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

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

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

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

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

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

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

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

DR. RINI: Dr. Uldrick, now.

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

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

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

DR. KAUFFMAN: In this heavily pretreated

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

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

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

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

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

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

DR. RINI: Dr. Morrow?

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

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

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

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

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

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

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

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

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

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

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

DR. RINI: Thank you. Dr. Harrington?

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

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

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

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

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

DR. HARRINGTON: But in a very different population.

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

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

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

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

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

DR. HARRINGTON: No, I know.

(Crosstalk.)

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

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

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

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

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

DR. HARRINGTON: Okay.

DR. PAZDUR: So it gives us additional information.

DR. HARRINGTON: Yes.

Do I have time for one follow-up?

DR. RINI: Sure.

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

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

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

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

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

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

Open Public Hearing

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. RINI: Thank you.

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

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

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

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

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

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

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

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

that option.

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

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

DR. RINI: Thank you.

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

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

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

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

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

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

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

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

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

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

share my story."

DR. RINI: Thank you. Speaker number 4?

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

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

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

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

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

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

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

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

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

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

DR. RINI: Thank you. Speaker number 5?

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

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

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

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

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

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

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

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

DR. RINI: Thank you. Speaker number 6?

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

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

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

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

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

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

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

DR. RINI: Thank you. Speaker number 7?

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

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

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

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

Back in 2000, the options were extremely

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

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

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

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

DR. RINI: Thank you. Speaker number 8?

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

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

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

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

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

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

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

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

DR. RINI: Thank you. Speaker number 9?

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

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

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

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

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

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

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

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

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

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

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

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

During the time I was in treatment numbers 12 through 14, I was in the hospital 1 week out of every 2 with fevers as high as 1043 degrees; C. difficile colitis, which is a very unpleasant condition; confusion; and expressive aphasia. I was alive but hospitalized an average of 50 percent of the time, and eventually all of the drug stops

working.

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

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

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

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

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

DR. RINI: Thank you. Speaker number 11?

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

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

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

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

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

DR. RINI: Thank you. Speaker number 12?

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

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

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

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

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

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

I really think we do need this drug because

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

DR. RINI: Thank you. Speaker number 13?

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

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

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

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

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

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

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

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

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

you for listening.

DR. RINI: Thank you. Speaker number 14?

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

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

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

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

It is difficult, if not impossible, to

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

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

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

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

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

DR. RINI: Thank you. Speaker number 15?

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

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

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

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

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

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

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

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

She achieved 8 years of stringent complete remission.

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

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

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

Please give us a choice. Thank you.

DR. RINI: Thank you. Speaker number 16?

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

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

many chemotherapy treatments.

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

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

massage most weeks as I think complementary medicine is very important to my full recovery.

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

DR. RINI: Thank you. Speaker number 17?

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

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

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

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

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

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

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

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

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

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

Clarifying Questions (continued)

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

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

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

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

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

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

no increase in sepsis compared to the positive control.

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

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

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

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

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

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

comparator arm.

DR. SHAW: I have one other question, a separate question, though. I'm wondering in the context of STORM part 2 if you've been looking at biomarkers that may predict response, XPO1 levels, for example, in malignant plasma cells; any other biomarkers to identify the patients who are most likely to drive benefit?

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

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

DR. RINI: Thank you. Dr. Klepin?

DR. KLEPIN: I just wanted to circle back to

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

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

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

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

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

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

DR. RINI: Dr. Thanarajasingam?

DR. THANARAJASINGAM: It was answered.

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

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

DR. PAZDUR: That would be one possibility.

DR. HALABI: Can you discuss other possibilities?

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

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

DR. HALABI: Thank you.

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

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

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

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

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

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

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

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

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

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

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

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

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

DR. GORMLEY: The question that we're asking

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

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

How do we interpret this data that we see

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

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

DR. SHACHAM: And I would just clarify the

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

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

DR. RINI: Dr. Pazdur?

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

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

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

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

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

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

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

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

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

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

Using a comparator of real-world or

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

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

DR. RINI: Thank you for those thoughtful comments.

Other comments around the discussion question? Dr. Hinrichs?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

every single time it comes back.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

to the drug.

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

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

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

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

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

DR. RINI: Thanks for the comments.

Dr. Farrell, you want to make a comment?

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

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

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

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

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

DR. RINI: Other comments around that?

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

DR. SHACHAM: Can you repeat the question?

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

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

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

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

in their institutions.

DR. RINI: Okay. Quickly.

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

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

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

DR. RINI: Thank you. Very last comment,

quickly.

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

DR. RINI: Thank you.

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

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

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

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

question, we'll take them now.

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

Are there any questions about the voting question

(No response.)

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

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

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

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

(Voting.)

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

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

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

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

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

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

here next.

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

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

(Dr. Morrow gestures no.)

DR. RINI: Okay. Doctor Mo?

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

(Laughter.)

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

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

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

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

DR. RINI: Thank you.

Dr. Harrington?

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

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

DR. RINI: Thank you.

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

DR. RINI: Thank you. Dr. Hawkins?

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

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

DR. RINI: Thank you. Dr. Shaw?

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

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

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

DR. RINI: Thank you. Dr. Uldrick?

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

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

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

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

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

substantial toxicity.

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

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

DR. RINI: Thank you.

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

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

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

DR. RINI: Thank you.

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

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

DR. RINI: Thank you.

Any final FDA comments?

(Dr. Pazdur gestures no.)

Adjournment

DR. RINI: No?

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

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