FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Thursday, November 6, 2014
8:00 a.m. to 11:56 a.m.

Morning Session

FDA White Oak Campus
Building 31, The Great Room (Room 1503)
White Oak Conference Center
Silver Spring, Maryland
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Call to Order

Introduction of Committee

DR. ARMSTRONG: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you haven't already done so. I'd also like to identify the FDA press contact, Tara Goodwin. If you are present, please stand. We'll identify her later.

I'd now like to introduce the members and consultants. I'll start with myself, and we'll work around the table. I'm Deborah Armstrong. I'm a medical oncologist from Johns Hopkins and chair of ODAC.

DR. BRIGGS: Caleb Briggs, designated federal officer, ODAC.

DR. TAYLOR: Dr. Wayne Taylor, patient representative.

DR. LIEBMANN: James Liebmann, medical oncologist, University of Massachusetts.

DR. KO: Chia-Wen Ko, statistical reviewer,
DR. GORMLEY: Nicole Gormley, clinical reviewer with the FDA.

MR. MILLER: Barry Miller, clinical reviewer, FDA.

DR. FARRELL: Ann Farrell, division director, Division of Hematology Products and adult hematologist/oncologist.

DR. PAZDUR: Richard Pazdur, office director.

DR. BAYNES: Roy Baynes. I'm from Merck. I'm the industry rep. I'm a hematologist by training.

DR. ZONES: I'm Jane Zones. I'm the consumer representative.

DR. ROTH: Bruce Roth, medical oncologist from Washington University in St. Louis.

DR. FOJO: Tito Fojo, medical oncologist, National Cancer Institute.

DR. COLE: Bernard Cole, biostatistics, University of Vermont.

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

Thus, 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 care 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 the 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 breaks or lunch. Thank you.

Now I'll pass it on to Caleb Briggs, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. BRIGGS: The Food and Drug Administration, FDA, 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 USC 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 USC 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 particular
individual's services outweighs his or her
potential financial conflict of interest.

Related to the discussions 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 USC 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.

This morning's agenda involves new drug
application 205353, panobinostat capsules,
application submitted by Novartis Pharmaceuticals
Corporation. The proposed indication for this product is in combination with bortezomib and dexamethasone for the treatment of patients with multiple myeloma who have received at least one prior therapy. This is a particular matters session during which specific matters related to Novartis' 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. Dr. Brian Rini and Dr. Louis Diehl have been recused from participating in this morning's session of the meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue. With respect to FDA's invited industry representative, we would like to disclose that Dr. Roy Baynes is participating in this meeting as a nonvoting industry representative, acting on behalf of
regulated industry. Dr. Baynes' role at this meeting is to represent industry in general and not any particular company. Dr. Baynes is employed by Merck and Company.

We'd 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. ARMSTRONG: Thank you. We'll proceed now with opening remarks from Dr. Ann Farrell.

Opening Remarks - Ann Farrell

DR. FARRELL: Good morning. I want to especially welcome the public, the ODAC members, and Novartis to this important advisory committee meeting to discuss panobinostat. The agency is keenly interested in having safe and effective
medicines to treat multiple myeloma, available for widespread use through commercial marketing. Hence, we are bringing this application to the committee today. Both Novartis and the agency review team members will present their findings from the conducted trials.

We would appreciate the committee focusing on the following two key issues: whether a PFS benefit has been established, and whether the PFS benefit outweighs the risk. Novartis submitted their NDA with several PFS, or progression-free survival, analyses within the last several -- with the original NDA, and then within the last several weeks, have presented additional PFS analyses.

The agency review team has spent a great deal of time and energy trying to find the clearest way to describe the trial's result in terms of an effect on PFS. Novartis' statistical analysis plan dictated that the data would be analyzed based on investigator assessment.

The reason for the multiple PFS sensitivity analyses is due to the fact that data were not
collected as stipulated in the protocol. When data is not collected as outlined in the protocol, this issue presents significant problems and raises concern about study conduct and data quality. Due to the data issue, there have been multiple sensitivity analyses conducted by Novartis as well as the agency, resulting in uncertainty about whether an improvement in PFS exists, and if it exists, what is the magnitude of improvement.

The response to panobinostat was captured according to EBMT criteria for response, requiring documentation by protein electrophoresis, immunofixation, and in some cases bone marrow biopsy. In the majority of patients, response to therapy is seen with changes in the level of serum paraprotein and/or urinary light chain excretion. In the minority of patients, disease progression will be manifested by increasing marrow, or skeletal involvement, or other complication.

Prior to the database lock, Novartis determined that at least 23 percent of patients enrolled had at least one disease assessment
performed by a method other than the methods described in the protocol. This led Novartis to convene an independent review committee and to conduct at least one of several sensitivity analyses to address the fact that so many patients had an ineligible assessment, including those at baseline.

In addition, the review team has spent significant time identifying the toxicities associated with use of panobinostat in combination. The study results are notable for the following: a higher number of deaths in the panobinostat combination arm that are not due to disease progression.

The top three causes of death in the panobinostat arm were infection, hemorrhage, cardiac sudden death, serious adverse reactions, which were also more numerous in the panobinostat arm, or diarrhea, thrombocytopenia, fatigue, pneumonia, and sepsis.

So again, we ask the committee to consider, during the presentations, whether a PFS benefit has
been established and whether the benefit, if established, outweighs the risk. Thank you very much.

DR. ARMSTRONG: Thank you, Dr. Farrell.

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 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 non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue such as consulting fees, travel expenses, honoraria, and interest in the sponsor, including equity interest and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the committee if you do not have any 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.

We will now proceed with the sponsor's presentation.

**Applicant Presentation – Renaud Capdeville**

DR. CAPDEVILLE: Good morning, members of the committee, FDA staff, and guests. My name is Renaud Capdeville. I am vice president of oncology global development at Novartis oncology. I am pediatric hematologist, and I have worked in drug development in oncology for more than 20 years. Today, my colleagues and I will present to you the NDA of panobinostat for the treatment of patients with relapsed and refractory multiple myeloma.

Multiple myeloma remains a disease for which there is no curative therapy and for which there is a pressing need for new treatment options. Despite the introduction of new drugs in the last ten years, the vast majority of patients ultimately died because of their disease.
Following progression, patients typically go through successive lines of therapy with diminishing response and diminishing tolerability. And these therapies are limited to only three classes of agents. We need new agents addressing a new target, a new mechanism of action. The panobinostat data that you will hear today will present the first report of a new and a different class of drug in myeloma in nearly 10 years.

Panobinostat is a highly potent pan-deacetylase inhibitor. It targets both histone and non-histone deacetylase. Consequently, the effects that are relevant to multiple myeloma include, first, an epigenetic modulation of important target genes, shown on the left, including the re-expression of tumor suppressor genes; second, an inhibition of the aggresome and HSP90, shown on the right, which are important in the clearance of misfolded proteins that are abandoned in myeloma. Ultimately, both lead to cell deaths and apoptosis.

The rationale for panobinostat in myeloma is
strong. In particular, there is robust evidence supporting the synergy between panobinostat and bortezomib. First, consistent in vitro synergy was observed in cell lines, as well as in patient-derived cells. Secondly, in an in vivo mouse model of myeloma, the treatment combination of panobinostat, bortezomib, and dexamethasone, highlighted in green here, showed superior anti-tumor activity compared with single agents and doublets.

The development program of panobinostat in myeloma included two single-agent studies, one dose-finding study in a variety of hematologic malignancies, and one phase 2 study in advanced myeloma. Importantly, the emphasis of that program was on the combination with bortezomib, shown here in the yellow box. It included three trials. First, a dose-finding phase 1 study was started in 2007. This led to the initiation of the phase 3 pivotal study in 2010. Shortly after, a supportive phase 2 single-arm study was conducted in patients of refractory to bortezomib.
There have been several interactions with the agency during this program. In 2012, an agreement was reached with the FDA on the adequacy of the study design endpoint and statistical plan. The NDA was submitted in March of this year, and a priority review was granted in May.

Now, let me summarize the basis of this NDA. First, panobinostat introduces a novel mechanism of action relevant to myeloma. The pivotal study met its primary endpoint, demonstrating a significant and clinically meaningful 3.9 months promulgation of progression-free survival. The other ratios were consistent across all prespecified sensitivity and subgroup analysis, demonstrating the robustness of the PFS benefit.

Of note, in their question, the FDA mentioned one sensitivity analysis and the post doc time to treatment failure analysis to further estimate a treatment effect. However, the purpose of this analysis was to assess the robustness and the magnitude of the PFS benefit.

In addition, 28 percent of patients in the
panobinostat arm, versus 16 percent in the placebo arm, achieved complete and near-complete response. A longer median overall survival was observed in the current interim analysis, although not statistically significant. Furthermore, even though there is added toxicity with this three-drug regimen, the safety profile is well characterized, involving adverse events that are only observed in the treatment of myeloma with other regimens and are generally manageable.

So this finding supports the following indication, panobinostat, in combination with bortezomib and dexamethasone, is indicated for the treatment of patients with myeloma who have received at least one prior therapy, and this indication corresponds to the patient population enrolled in the phase 3 trial.

Following my brief introduction, Dr. Keith Stewart will summarize the treatment landscape and the challenges in managing patients with previously treated myeloma. Then I will present the efficacy and the safety data from the pivotal phase 3 trial.
and the phase 2 study. Finally, Dr. Paul Richardson will put the data in the context on how patients with myeloma are managing clinical practice today.

We also have a number of experts with us today who can help to address any questions you may have. Dr. Voorhees is the chair of the Independent Review Committee in phase 3. Dr. Shah is also a member of the IRC. And finally, Dr. John Ware is an expert in patient-reported outcomes.

With that, it is my pleasure to introduce Dr. Keith Stewart.

**Applicant Presentation - Keith Stewart**

DR. STEWART: Thank you, Dr. Capdeville, and good morning. My name is Keith Stewart, and I’m a hematologist with over 20 years of experience in myeloma treatment, research, and clinical trials. It is my pleasure this morning to introduce to you the current treatment landscape for multiple myeloma and highlight for you the ongoing challenges, which make the clinical deployment of therapies with novel mechanisms of action so
critical to prolonging remissions and advancing
therapy in this still incurable disease.

My employer has received compensation for my
participation in today's proceedings, and I've
personally received compensation for pre-meeting
preparation, but I've no financial interest in the
outcome of this meeting.

Myeloma is the second most common
hematologic malignancy, constituting 10 to 15
percent of all blood cancers. Today, as a direct
consequence of regulatory approvals, which have
advanced therapy over the past decade, disease
survival duration has dramatically improved.
Consequently, the prevalence of this chronic,
relapsing, but still incurable disease, has
increased with more than 80,000 patients living
with multiple myeloma in the United States today.

Once myeloma becomes symptomatic and therapy
is deemed necessary, initial response rates to
chemotherapy using these novel agents are high.
Typically, after initial therapy, first remissions
last between one and three years, but are
inevitably followed by relapse in the majority of patients. At relapse, second and subsequent lines of therapy are sequentially introduced or recycled. The potential benefit to patients with each relapse and subsequent therapy is therefore reduced and progressively lower response rates and remission duration are seen. In today's treatment paradigms, patients often receive three, four, or even more lines of therapy, until, ultimately, drug resistance or refractory disease exhaust therapeutic options.

Relapse has been the most common setting for testing of new therapeutics in myeloma. The most common endpoint employed is time to progression. In the panobinostat trial, you will hear presented progressive-free survival, which includes both progression and deaths, and is recommended as a more conservative endpoint.

Disease progression is most commonly determined in myeloma through serial measurement of serum or urine monoclonal proteins. Because of test-to-test variability, however, international
response guidelines recommend and demand that progression should be declared only after confirmatory tests. If confirmation is not employed, then progression can be inaccurately attributed.

Six new therapeutics representing two main classes of compounds have been approved in the last 10 years for the treatment of myeloma. The first class is the proteasome inhibitors, bortezomib and carfilzomib. The second class of agents are the so-called immunomodulatory agents, or IMiDs, thalidomide, lenalidomide, and pomalidomide, each of which share a common target and mechanism of action. With the exception of high-dose melphalan for autologous stem cell transplant, conventional chemotherapy agents are becoming much less commonly employed.

These studies led to the approvals of currently used drugs at relapse and are shown here. Intravenous panobinostat received full approval based on improvement in time to progression of 2.7 months over dexamethasone alone. Lenalidomide
was first approved for use in combination with
dexamethasone when two phase 3 trials demonstrated
superiority to dexamethasone alone. Doxil was
approved for use in combination with panobinostat
with the combination improved time to progression
by 2.8 months and is a useful adjunct in some
patients.

The pivotal trial for panobinostat was in
the same early relapse setting as the approved
drugs in this table. The combination of
panobinostat and dexamethasone was considered by
myeloma experts to be an acceptable standard of
care for the control arm of the panobinostat trial,
and a three-month improvement in progression-free
survival was deemed clinically significant and in
keeping with prior approvals.

Bortezomib is also approved for use in the
newly diagnosed patient and is the most common
backbone of therapy both at diagnosis and at first
relapse. Patients treated with lenalidomide up
front or at relapse can still use bortezomib in
subsequent therapies and examples of bortezomib use
in relapse are shown here -- sorry. The examples
of bortezomib use in relapse, which are shown here,
are also the setting in which the panobinostat
phase 3 trial was conducted.

In the second line here, you will note that
one of the most frequently utilized first-line
therapies today is in fact the combination of both
lenalidomide and bortezomib. Thus, patients today
are commonly exposed early to the most active
drugs, which are reintroduced at relapse. When
patients fail or become intolerant of both of these
drugs, they are deemed refractory.

Carfilzomib and pomalidomide were recently
approved in this refractory setting in patients
who'd received a median of five prior lines of
treatment. As you have seen, both of these
treatment options utilize drugs targeting pathways,
the proteasome or immunomodulation, already
exploited earlier in the disease course. And
that's why representing a subtle advance and
providing oncologists with expanded therapeutic
options, the overall impact is modest.
You will also hear today about support of phase 2 study of panobinostat in the same refractory setting. In this study, patients were refractory to bortezomib, but the combination of panobinostat, bortezomib, and dexamethasone still demonstrates its efficacy.

Each of the approved drugs can be accompanied by toxicities that limit their use in multiple lines of therapy, and drug intolerance can become a significant clinical impediment. As example, the immunomodulatory drugs, or IMiDs, are associated with neuopenia and resulting infection, particularly pneumonia. Venous thromboembolism, fatigue, and GI effects such as constipation and diarrhea are common.

When used with alkylating agents, second primary malignancies, while uncommon, are a threat with prolonged use. The signature toxicity of proteasome inhibitor bortezomib is painful peripheral neuropathy. The proteasome inhibitors are both also frequently associated with thrombocytopenias and GI effects, including
diarrhea. Carfilzomib can be associated with cardiac and renal toxicity, albeit in a small percentage of patients.

Providers have learned to manage such toxicities through dose reductions and support of care. You will hear shortly about the side effects of panobinostat, which are predictable and generally familiar to the treating physician.

Proteasome inhibitors and immunomodulators induce more frequent and deeper responses. This results in longer remission and, consequently, as shown here, significant improvement in myeloma patient survival can be observed over the past decade. Despite the success, the figure also vividly illustrates the ongoing challenges.

Specifically, the graph illustrates the limitations of available drugs with 25 percent of patients, especially those with high-risk disease, dying of their disease within three years of diagnosis. Second, and most significantly perhaps, the survival curves further demonstrate an absence of a definable cure plateau. This statistic then
crystallizes the ongoing need for new advancements in therapy.

In summary, a majority of patients with myeloma will eventually relapse, despite two new and important classes of compounds that have been introduced in the past decade. These drugs, the immunomodulators and proteasome inhibitors, are now used earlier and for longer. But multiple lines of therapy are inevitable and choice is quickly limited by overlapping mechanisms and toxicities of available agents.

Thus, increasingly shorter remissions are seen with each additional line of treatment. Availability of a new class of drugs with a non-overlapping mechanism of action that can deeper remission, and thus extend disease control and relapse, would therefore represent a further advance in myeloma.

Now, I'd like to reintroduce Dr. Capdeville to present the efficacy and safety data for the panobinostat, bortezomib, and dexamethasone combination in patients with multiple myeloma.
Thank you for your attention.

**Applicant Presentation - Renaud Capdeville**

DR. CAPDEVILLE: Thank you, Dr. Stewart.

In the next few minutes, I will summarize for you the dose and schedule, the phase 2 study, the phase 3 study, and finally the safety results and overall conclusion. The starting dose of panobinostat in the phase 2 and 3 trials was 20 milligram, which was selected on the basis of the phase 1 study B2207, where the dose was formerly characterized as the MTD in combination with bortezomib at 1.3 milligram per meter square, using standard phase 1 methodology.

Importantly, this dose was associated with a high response rate and, more importantly, a long duration of treatment consistent with prior bortezomib trial, suggesting that this regimen is tolerable. Of note, the starting dose of bortezomib was also the standard label dose. Bortezomib was used with the intravenous formulation. For both agents, the protocol provided guidance for individualized titration of
the dose to manage toxicity.

The treatment schedule was similar in the phase 2 and 3 trials. It included a 3-week cycle in which treatment was given in the first 2 weeks followed by 1 week of drug all day. Panobinostat was given on a 3 times a week schedule.

The treatment plan included two phases. The first phase included up to 8 cycles, and patients benefitting from this phase continued in treatment phase 2. The only difference between these two phases is that the frequency of bortezomib injection was decreased from twice a week in the first to once a week in the second phase.

The phase 2 trial was conducted only in the U.S. in patients who were refractory to prior bortezomib. The study was designed to test the hypothesis of whether panobinostat could recapture response to bortezomib. It enrolled heavily pretreated patients who had received the major and the full lines of prior therapy. In addition to being refractory to bortezomib, all patients except one had been treated with lenalidomide. This
patient represented the difficult-to-treat population. A response rate of 35 percent was observed, which is quite remarkable in this population. Very interestingly, patients with poor-risk cytogenetics also had a high response rate. Overall survival in these patients was fairly long at 17 and a half months.

Now, let's move to the phase 3 study. The pivotal study was conducted in patients with a relapse or relapse under refractory multiple myeloma who had received 1 to 3 lines of prior therapy. In addition, the patients who were refractory to bortezomib were excluded.

The trial is the largest phase 3 study conducted in previously treated myeloma. It was a placebo-controlled, double-blind study that enrolled a total of 768 patients. Patients were randomized to receive the standard regimen of bortezomib and dexamethasone with placebo or with panobinostat.

The maximum duration of treatment was 48 weeks. Importantly, in this study, no crossover
was allowed between the arms and an independent data monitoring committee conducted safety analyses every six months and recommended that all of them, that the trial continue without change. The primary endpoint was PFS by modified EBMT criteria as assessed by the investigator and using local laboratories. The key secondary endpoint was overall survival.

Let's now move to the results. The baseline demographics were generally well-balanced between treatment arms. It is important to note that the median age of the study population was 63 years, which is typical for phase 3 trials conducted in this patient population. Similarly, baseline disease characteristics were well-balanced between the arms. In particular, 49 percent of patients had received between 2 and 3 lines of prior therapy. And importantly, the most frequent prior therapies included bortezomib, thalidomide, and lenalidomide.

At the time of the primary analyses, all patients had completed treatment per protocol, and
the reasons for treatment discontinuation are listed on the slide. So there are two important points on this slide. First, about twice as many patients discontinued because of disease progression in the placebo arm compared to the panobinostat arm. Conversely, more patients stopped treatment because of an adverse event in the panobinostat arm.

The primary objective of the study was met. It showed a prolongation of median PFS of 3.9 months a risk reduction of 37 percent. The Kaplan-Meier curve diverged early and remained separate for the duration of follow-up. The difference of PFS was highly statistically significant with a hazard ratio of .63 for favoring panobinostat. The risk reduction translated into a prolongation of median PFS from 8.1 months to 12 months, and the effect of PFS was consistent in all prespecified sensitivity analyses.

We conducted prespecified analyses to evaluate the effect of factors that could potentially influence the robustness of the primary
endpoint. These included the use of different endpoint and measurement methods, the impact of non-measurable disease at baseline, and the use of alternative censoring methods. Of note, these sensitivity analyses were not designed to estimate the true treatment effect but rather to assess the robustness of the primary endpoint by means of hazard ratio and 95 percent confidence interval.

Let's start with the analysis to see the assessment of response by the Independent Review Committee. The IRC was implemented to assess the impact of different methods of M-protein measurement used in that trial, and these were well-balanced between the treatment arms. The IRC was provided with patient listings of all efficacy data, which were blinded to treatment assignment and blinded to investigator assessment. Following the EBMT criteria, the IRC recorded response on a visit-by-visit basis until two consecutive values of M-protein qualified for disease progression.

We see here first the analysis by IRC with the confirmation of progressive disease. Then we
have the per protocol analysis by investigator and
by IRC that excludes patients with major protocol
deviation, also consistent with the primary
analysis. Of note, the IRC analysis reported in
the FDA briefing document does not take into
account the confirmation of progression according
to the EBMT criteria. In summary, all these
analyses were highly consistent with the primary
analysis.

Three sensitivity analyses using alternative
censoring methods further support the robustness of
the primary endpoint. In their question, the FDA
mentioned our dropout analysis as potentially
representing a treatment effect of 1.9 months. As
mentioned before, sensitivity analyses are not
intended to estimate a treatment effect. However,
this analysis, as with all the sensitivity
analyses, is used to examine the consistency of the
hazard ratio and to a different assumption of
censoring. You can see that the hazard ratio in
the three analyses consistently support trends of
evidence with a confidence interval well below 1.
The FDA also refers to time-to-treatment failure analysis, which was not prespecified. Such analyses are usually not recommended because they do not distinguish efficacy from safety variable, and this will be measured by separate criteria. In addition, time to treatment failure analysis potentially ignores the long progression-free period observed after treatment discontinuation, and this will be described later.

Looking at the subgroups' analysis by baseline characteristics, the hazard ratio consistently favored panobinostat in all subgroups and were consistent with the primary analysis. Importantly, the benefit was consistent in the elderly patients as well as in patients with the highest stage disease.

The PFS by treatment history was again very consistent from one subgroup to the next and favored panobinostat in all of them. Of note, the benefit was significant in patients regardless of their prior therapy.

Let's turn our attention to the survival.
In the second interim analysis, the survival data there shows longer median survival of 38 months in the panobinostat arm versus 35 months in the placebo arm. With a hazard ratio of .87, this difference is however not statistically significant.

The response rate also favored the panobinostat arm. The overall response rate, although not statistically significant, favored panobinostat. But more remarkably, the rate of complete and near-complete responses were nearly doubled in the panobinostat arm. And in addition, the duration of responses was also longer with panobinostat. The results were very consistent when considering the response by IMWG response criteria, an exploratory endpoint of the study.

In conclusion, the pivotal study is the largest double-blind, randomized, phase 3 conducted in previously treated myeloma. The trial met its primary endpoint, demonstrating a significant and clinically meaningful prolongation of median PFS of 3.9 months. The hazard ratios are consistent
across all prespecified sensitivity and subgroup analyses. There was a trend towards prolonged overall survival favoring panobinostat.

There was a higher rate of response, including complete responses, and these responses were durable. Furthermore, these results are supported by the results of the phase 2 conducted in bortezomib refractory patients, which suggest that panobinostat can also recapture response to bortezomib.

Let's now move to the safety data. The median duration of treatment was fairly consistent between the phase 3 and the phase 2 study and was roughly 5 months. In the context of the median PFS presented before, this implied that patients had a longer treatment-free period of 7.5 months with panobinostat versus 4 months with placebo, and this was estimated by a PFS partitioning analysis.

As shown previously, more patients in the panobinostat arm discontinued treatment because of an adverse event, and the most frequent reason was diarrhea and peripheral neuropathy. Importantly,
no patient discontinued -- only 1 percent of
patients discontinued in that study because of
cardiac event. Importantly, thrombocytopenia was
infrequently the reason for treatment
discontinuation, and this is despite the high
frequency of thrombocytopenia that I will present
later.

Now, let's have a look at mortality.
Overall, there were more deaths in the placebo arm,
190 compared with panobinostat 169. However, there
were more on-treatment deaths in the panobinostat
arm. The most frequent cause of on-treatment
deaths, not attributed to progressive disease, was
infection and hemorrhages. Finally, after
treatment discontinuation, there were more deaths
with placebo, 172 versus 139 with panobinostat. Of
note, treatment related to deaths was reported in
2.8 percent in the panobinostat arm versus
1.8 percent in the placebo arm.

Let's now have a look at the non-hematology
adverse events. The most frequent adverse event
reported with panobinostat was diarrhea followed by
peripheral neuropathy. Importantly, the incidence and the severity of peripheral neuropathy, a well-known adverse event with bortezomib, were similar in both arms. The next most frequent adverse event reported as a higher frequency in the panobinostat arm included asthenia and fatigue and nausea and vomiting.

The frequency of grade 3–4 neutropenia and thrombocytopenia were higher in the panobinostat arm. However, with regard to thrombocytopenia, there are two very important points to make. First, as shown in the graph, the platelet can return to baseline before the start of the next cycle after the one week of treatment holiday in the treatment schedule. Importantly, there was no evidence of cumulative toxicity over time, and this was also the case for neutropenia.

The incidence of severe hemorrhages was higher in the panobinostat arm. There were 5 deaths due to hemorrhage on panobinostat, including one patient who had a progressive myeloma in the brain and died of a cerebral hemorrhage, 2 patients
with GI hemorrhage and 2 patients with pulmonary hemorrhage. There was one death due to hemorrhage also in the placebo arm, a CVA. All hemorrhages occurred in patients with grade 3-4 thrombocytopenia and in 2 patients on panobinostat who were taking anti-platelet drugs.

This slide shows how the incidence of severe thrombocytopenia decreases following dose titration of both panobinostat and bortezomib. The left panel shows the median actual dose intensity of panobinostat and bortezomib. In this graph, the panobinostat is shown in red and bortezomib in blue. The right panel shows the incidence of grade 3-4 thrombocytopenia by cycle in the panobinostat arm.

In the first treatment phase, the incidence decreased after initial dose titration, but it decreased further to low single-digit levels in treatment phase 2, where the dose intensity of panobinostat was by [indiscernible] by design in contrast to the dose intensity of panobinostat, which remained stable.
We then focused on diarrhea, which occurred more frequently with panobinostat compared with placebo. The median time to onset of diarrhea was 2 months, and diarrhea was managed with concomitant medication and dose adjustment of both drugs. Only 5 percent of patients on panobinostat discontinued therapy because of diarrhea. The grade 3-4 diarrheas were typically of short duration, 4 days, and the majority of patients with severe diarrhea had a single episode.

Now, I will examine the safety in the elderly patients. This patient had an increase in the rate of grade 3-4 diarrhea, fatigue, and thrombocytopenia. This translated into an increasing rate of treatment discontinuation and on-treatment deaths, which was apparent in both arms. In this study, the rate of pneumonia did not increase in elderly patients. The risk of increased toxicity in elderly patients was confirmed in a multivariate analysis of risk factor, and this data indicate that elderly patients require more frequent monitoring to manage
this adverse event.

In conclusion, panobinostat introduces a novel mechanism of action. The data presented today support a positive and clinically important benefit/risk profile in patients with previously treated myeloma. The benefit was demonstrated in the large, double-blind, phase 3 study, which met its primary endpoint. The median PFS is improved by 3.9 months, corresponding to a risk reduction of 37 percent.

The hazard ratio was consistent across all prespecified sensitivity and subgroup analyses, demonstrating the robustness of the PFS benefit. The rate of complete and near-complete responses was almost doubled. Overall survival, while not statistically significant, favored panobinostat.

The safety profile is well characterized, adverse events are predictable with adequate and rigorous monitoring, and can be managed with individualized dose titration and supportive care. This is also supported by the data from the phase 2 study in bortezomib refractory patients with a high
rate of response and encouraging overall survival. Overall, the data supports a positive benefit/risk profile in the population of patients with previously treated multiple myeloma.

I will stop here and ask Dr. Paul Richardson to put this data in the clinical context on current patient management.

Applicant Presentation – Paul Richardson

DR. RICHARDSON: Thank you very much, indeed, Dr. Capdeville, and good morning, ladies and gentlemen. It's my pleasure to present to you this morning.

My name is Dr. Paul Richardson from the Dana-Farber Cancer Institute, and I've been caring for myeloma patients for over 20 years and have been focused in clinical research in myeloma for the last 15. My disclosure statement is as follows, that I have not received any compensation for my participation in this meeting or for stop spent in preparation for today's proceedings. And I have no financial interest in the outcome of this meeting.
Now, as you've heard this morning, the major challenge that we face in treating myeloma is that it remains incurable and will inevitably relapse and become refractory to current therapies, and patients experience an increasing symptom burden as the disease progresses. There is, thus, an urgent need for new agents with novel mechanisms of action that target other pathways to overcome resistance to the two major classes of currently available novel compounds, namely the IMiDs and proteasome inhibitors.

Now, I'd like to provide you my clinical perspective for the efficacy and safety of panobinostat combined with bortezomib and dexamethasone. As you heard from Dr. Capdeville, we saw very encouraging responses in our phase 1 experience with panobinostat, bortezomib and dexamethasone, which led to us examining the same dose and schedule in both our phase 3 study, which you've just heard about, and our phase 2 study, which I show here.

Importantly, you'll hear later from
Ms. Tuohy about a patient who participated in our phase 1 study, a patient of mine in fact. And I think she's emblematic of what we were so encouraged to see in our phase 1 experience. But let me focus now on our heavily pretreated patients in our phase 2 study. This study specifically enrolled only patients with relapse in bortezomib refractory disease.

The trial demonstrated an overall response rate of 35 percent, and importantly, patients with adverse cytogenetics had a response rate of 43 percent. Patients also had a favorable median overall survival in this population. We also saw encouraging progression-free and overall survival as well as duration of response, as I've mentioned. And interestingly, I think, the progression-free survival is longer than that reported in similar single-arm trials of pomalidomide and carfilzomib in this same advanced disease setting. But of course, I think we have to be careful here.

Having said that, the safety profile that we saw in this multicenter trial was acceptable, and
importantly, our AEs proved manageable with appropriate support of care and dose reduction when indicated. And we'll hear a lot about that as we go forward. But I want to emphasize that in this phase 2 trial, for example, we saw manageable toxicity in terms of the management of thrombocytopenia. We did not see treatment-related deaths. And in fact, in addition to that, we saw manageable GI toxicity as well as a low rate of cardiac events.

Now, in terms of the primary endpoint in our phase 3 trial, there was this statistically significant 37 percent reduction in the risk of disease progression or death. Now, this translated into a median progression-free survival of 12 months with a median progression-free survival benefit of 4 months compared to the control.

Now, I think it's important to note that the combination of intravenous bortezomib and dexamethasone as the control in this study generated a median progression-free survival of 8 months, which is highly consistent with what has
been observed in other trials. In addition, as Dr. Capdeville mentioned, the second interim analysis demonstrated a trend towards an overall survival benefit, and although not statistically significant, this showed a sustained difference of approximately 3 months in favor of panobinostat.

Now, when you think of panobinostat in terms of its response signal, we know that response correlates with improved outcomes in myeloma and particularly in patients with relapse and refractory disease, where a rapid deep and durable response is important. The overall response rate was in favor of the panobinostat combination with a longer median duration of response. And what was especially exciting was that the quality of response was highly favorable for the panobinostat combination.

Very importantly, the panobinostat combination was associated with a consistent PFS benefit regardless of baseline demographics or disease characteristics. This PFS benefit included older patients, patients with advanced IS stage,
which actually typically reflects more aggressive biology and, very importantly, those with poor-risk cytogenetics.

This PFS benefit was also observed regardless of prior treatment. From a clinical standpoint, this is very important because, especially for patients with relapsed and refractory disease who have received prior IMiDs and proteasome inhibitors used together as part of therapy, this also helps us understand that panobinostat could be used as part of a combination in a variety of clinical settings, beginning with patients who have received at least one line of prior treatment, recognizing for these regimens today, these typically incorporate both immunomodulators and proteasome inhibitors together, as Dr. Steward alluded to. And of course, this also has major implications for our more heavily pretreated patients as well.

This next slide shows the results for the panobinostat combination in comparison with approved bortezomib containing regimens in relapsed
and refractory myeloma. The panobinostat combination produced a median overall survival of 38.2 months, as you can see. This in my view is a very hard endpoint. As you can also see, it compares favorably with the bortezomib based regimens listed.

I would also suggest the response rate in the median progression-free survival also compared favorably both to monotherapies and doublets in this comparison. I think we have to be careful about cross-trial comparisons, and these studies obviously therefore have to be seen in that context. The data are highly relevant in my view. For example, if one thinks of bortezomib generating a 3-month improvement in time to progression in a setting of relapsed myeloma, that's important. And similarly, if you think of also bortezomib plus liposomal doxorubicin, you see there a shorter improvement in TTP. But as Dr. Stewart alluded to, this combination does have value and is of course approved.

This next slide compares the efficacy of
current treatments in patients with relapsed and refractory disease. And I bring this out because this is for patients who have received 2 or more lines of treatment, including an immunomodulator and a proteasome inhibitor. And thus, this constitutes an area of exquisite unmet medical need.

Now, remarkably, panobinostat, bortezomib, and dexamethasone combined proved comparable to pomalidomide and calfixomib based therapies with respect to response rate, PFS, and overall survival in this highly refractory population. I recognize the numbers are limited by comparison to these other studies, but I'm impressed by the favorable outcome seen in this prospective multicenter U.S. trial.

In terms of side effects, I think it's very important to recognize that in relapsed refractory myeloma, current treatment options are associated with clinically important side effects. We must therefore place the side effects associated with panobinostat in this context.
Overall, we have seen a safety profile that is familiar to us as hemato-oncologists. We're keenly aware that side effect management is important. And we're also aware that each drug regimen carries with it the potential for toxicities that must be proactively monitored and managed to optimize any clinical benefit. For example, neutropenia infections and thromboembolism are risks that can be associated with immunomodulating therapy, in particular combined with high-dose dexamethasone, and significant cardiovascular, pulmonary, and renal toxicities have been observed with carfilzomib based therapy.

As you've heard, in panobinostat based therapies, high rates of thrombocytopenia, fatigue, and diarrhea have been observed. However, it's been my experience that with appropriate supportive care for diarrhea being essential, it can be managed accordingly with dose reduction, anti-diarrheal medications, and proper hydration. Similarly, thrombocytopenia can also be addressed with dose reduction and, for example, the use of
weekly bortezomib.

When we look at on-treatment mortality with
current treatments, I think it's very important to
look at data from pivotal clinical trials of
currently approved agents for myeloma. And as you
can see, on-treatment deaths can range from 3 to
9 percent. And what was seen in our phase 3 trial
is within this range.

Furthermore, we see that relatively few of
the on-treatment deaths were considered actually
drug related. And in my view, this is because our
patients with relapsed and refractory myeloma are
often battling preexisting comorbidities from both
the effects of advance disease and of course the
cumulative toxicities from prior therapies.

Now that being said, it's very important for
us as clinicians to optimally manage the regimens
we have. For example, bortezomib therapy in this
regard has evolved since this trial first began.
Obviously, intravenous bortezomib plus
dexamethasone remains now a standard of care. But
we do know that bortezomib can be given
subcutaneously with equivalent efficacy and reduced
toxicity. We can also further reduce side effects
with weekly bortezomib.

    This is of particular interest because we
saw in the second phase of the phase 3 trial that
when bortezomib was administered weekly, it was
associated with much better tolerability. Another
encouraging aspect is that the management of
bortezomib associated adverse events has improved
over time as hematologists have become familiar
with the early identification and effective
management strategies for side effects.

    Let's touch on older patients. In the older
population where we see greater vulnerability to
side effects from all available therapies, as well
as comorbidities, the use of weekly subcutaneous
bortezomib for one example in this population has
been especially beneficial.

    In addition, as clinicians, we now have
comprehensive guidance for monitoring and managing
older patients with myeloma. These consensus
guidelines recommend more frequent monitoring for
potential adverse events with early intervention, including dose adjustments, schedule change, and supportive care at the first sign of an adverse event. Furthermore, we have developed effective strategies for managing diarrhea in such patients as one example, which of course is highly applicable to treatment in this setting.

In conclusion, in my opinion, there is clinically relevant benefit with the combination of panobinostat, bortezomib, and dexamethasone, and this is reflected by higher quality responses, a 37 percent reduction in risk of progression or death. And this translates into a clinically meaningful progression-free survival advantage as well as a trend in survival.

Very importantly, there is clear evidence of activity in high-risk and genetically unstable refractory disease. Thus, I believe there is a positive benefit/risk profile in favor of the panobinostat combination. I think primarily there is an urgent clinical need for a new drug class with a novel mechanism of action, which can act
synergistically with our current regimens and overcome resistance.

With panobinostat, there is, in my view, robust and consistent evidence for clinical benefit. The safety profile is clearly important. But I think it's important to also recognize to us as hemato-oncologists that we are familiar with these, and side effects proved generally manageable with best supportive care, appropriate dose reduction, and schedule change. Moreover, I would argue that the use of subcutaneous bortezomib on a weekly schedule is now a standard of care. And in my experience, when used as part of panobinostat combinations, reduces the incidence of adverse events and improves tolerability.

So in conclusion, panobinostat offers a new treatment option for patients with relapsed and refractory disease who have received at least one prior line of therapy and extends most importantly to those who have received multiple treatments. And I thank you very much for your kind attention, and I will now turn the podium over to
Dr. Capdeville to answer your questions.

DR. ARMSTRONG: Excuse me. We're going to have the FDA presentation, and then we'll have questions afterward. Thank you.

We'll now proceed with the presentation from FDA.

**FDA Presentation - Barry Miller**

MR. MILLER: Good morning. I'm Barry Miller, an FDA clinical reviewer for the Farydak new drug application 205353. Dr. Gormley and I will highlight relevant findings from our analysis of this application that make the risk versus benefit determination for market approval challenging. Included here are the many FDA colleagues who contributed to analysis and review of the Farydak application. Our presentation also includes statistical analyses by Drs. Ko and Nie.

The primary issue for which you are seeking the committee's advice is whether the magnitude of benefit of treatment with Farydak in combination with bortezomib and dexamethasone outweigh the risk for patients with relapsed multiple myeloma. Our
review and presentation is principally based on the pivotal trial submitted for review, trial 2308. This was the randomized, placebo-controlled, double-blind trial with an add-on treatment design using bortezomib and dexamethasone as a backbone therapy.

Prior to 2003, treatment of patients with multiple myeloma was based on alkylating agents such as melphalan and carmustine and corticosteroids. Bortezomib was first approved in 2003 for relapsed myeloma, based on a single-arm trial of 202 patients, with an overall response rate of 28 percent, which included a 3 percent complete response rate. Other agents for myeloma have since been approved and are listed here with their primary efficacy endpoints.

Overall response rates from single-arm trials ranged from 23 to 29 percent with median durations of response from 7 to 12 months. For the randomized trials, the difference in time to progression compared to the control arm was an improvement of 3 to 16 months. Keep in mind that
prior FDA approvals in myeloma were based on trials conducted in treatment context that differs from available therapy today such that direct comparisons cannot be made across trials.

The primary endpoint of the trial was progression-free survival as assessed by investigators. Randomization was stratified by the number of prior therapies and by prior use of bortezomib. The trial was sized to detect a median progression-free survival difference of only 2.7 months. This trial was not conducted under an FDA agreed special protocol assessment.

The key secondary endpoint was overall survival. An interim analysis was planned at the time of the final PFS analysis, and an additional interim analysis was recently added. The final analysis of overall survival will be based on the occurrence of 415 events, which would test a 5.4 month difference between arms with their hazard ratio of 0.73.

Missing data is one of the major deficiencies of this trial. The large amount of
missing data in this trial is more than what is typically seen in drug applications reviewed by our office. The missing data limits our confidence in the results and is one of the primary reasons for which we are seeking advisory committee input.

The missing data consisted of a key measure of disease response and progression, namely protein electrophoresis with quantification of M-protein spike. This was a protocol-defined measurement required at baseline and at response intervals. This was missing for 193 patients at one or more time points. Instead of M-protein quantification by PEP, some patients were evaluated with measurements of total globulin or by nephelometric or turbidimetric methods. These methods are generally not used in disease-response assessments.

To mitigate this, the protocol was amended to add an assessment of PFS by an independent review committee while the trial was ongoing. This did not replace the primary analysis, but was done as a sensitivity analysis.

The Independent Review Committee was
comprised of three myeloma specialists from
different major academic cancer centers and an
independent statistician familiar with multiple
myeloma responses. They were chartered to conduct
an assessment of response using the same modified
EBMT criteria as the investigators.

The IRC was blinded to treatment arm and to
the investigator assessments. Consistent with the
modified EBMT criteria, confirmation of response
was to be repeated after at least six weeks, and
confirmation of progressive disease was to be
repeated as soon as possible.

In this trial, the demographic
characteristics of the 768 patients enrolled and
randomized are partly listed here. Overall, the
arms are fairly well balanced. The median age of
63 years, though, is younger than the median age of
69 years for patients diagnosed with myeloma in the
United States. Also in the U.S., twice as many
black patients are diagnosed with myeloma compared
to other races and are underrepresented in this
trial.
The trial enrolled a population fairly consistent with currently observed characteristics of patients with relapsed myeloma. The majority of patients had gamma or alpha immunoglobulin involvement, and the majority of light chain involvement was kappa compared to lambda. Few patients had disease involving light chains only. Overall, disease features and the common prior treatments listed here were well balanced between arms.

Analysis of the primary endpoint of progression-free survival resulted in a median time to progression of 12 months on the panobinostat arm and 8.1 months on the placebo arm, giving a difference of 3.9 months between arms. Notable in this analysis is this large amount of censored data. Forty-seven percent of patients in the panobinostat arm were censored and 32 percent of patients on the placebo arm were censored.

The majority of censoring was due to inadequate response assessments or to missing data. In the analysis of the primary endpoint, this
occurred for 32 percent of patients on the
panobinostat arm and 22 percent of patients on the
placebo arm. Of note, 19 percent of these patients
were censored for withdrawal of consent on the
panobinostat arm compared to 12 percent on the
placebo arm.

The protocol-defined sensitivity analysis of
progression-free survival as assessed by the
independent review committee resulted in a median
time to progression of 9.9 months in the
panobinostat arm and 7.7 months in the placebo arm,
giving a difference of 2.2 months between arms.
Note the increased percentage of evaluable patient
data and reduced censoring.

On October 7th, during preparation for this
advisory committee meeting, the applicant submitted
a revised IRC analysis. This revised analysis was
presented by the applicant earlier. The IRC
analysis presented here by the FDA will reflect the
analysis conducted on the data submitted at the
time of the NDA submission. The FDA has not
verified the applicant's revised IRC analysis.
However, in the next slide, I'll present the critical issues pertaining to the revised IRC analysis.

In the revised IRC analysis conducted by the applicant, disease progression status was changed in a total of 120 PFS observations. In 70 of these 120 observations, the event status was changed from a PD event to a censored observation due to lack of data in subsequent visits. For example, for a given patient, if progression occurred in visit 8, and there was no further follow-up for disease progression, the observation was censored at visit 8 in the revised IRC analysis. This is informative censoring and will lead to biased PFS estimates.

Now, in the remaining 50 of the 120 observations, the PFS time was changed to a later time for lack of confirmation on the earlier PD determination, thus increasing the PFS time in these 50 patients.

A sensitivity analysis of progression-free survival performed by the applicant and confirmed
by the FDA was a so-called dropout analysis by the sponsor. In this analysis, the following were considered events: 1, death; 2, disease progression; 3, initiation of another anti-neoplastic therapy; 4, discontinuation of treatment for disease progression; and 5, disease progression documented after two or more missing assessments.

This analysis resulted in a median time to progression of 9.5 months on the panobinostat arm and 7.6 months on the placebo arm, giving a difference of 1.9 months between arms. Note that in this analysis, the amount of censored data has been substantially reduced.

A comparison of the amount of censored data between the investigator's assessment and the following sensitivity analyses are listed here. Note the censoring differences between the two treatment arms and the differences between the investigators, the IRC analyses, and the dropout sensitivity analysis. The dropout sensitivity analysis addresses censoring when patients require
additional anti-cancer treatment prior to meeting the criteria for protocol-defined progression of disease. While all these analyses show a statistically significant PFS difference between the treatment and placebo arms, the magnitude of effect ranges from a median PFS of 1.9 months to 3.9 months. There is uncertainty with a magnitude of the PFS.

Data for overall survival observed at the time of PFS analysis was submitted for FDA analysis as part of the NDA. During review of the application, the sponsor amended the protocol to add a second interim analysis of overall survival and submitted this data. At the August 2014 data cutoff, 87 percent of the 415 events needed to test the hypothesis had occurred. At this point, there is no overall survival difference.

Our statistician, Dr. Ko, conducted an analysis to evaluate how likely the trial is demonstrate an overall survival benefit for panobinostat at the protocol-specified final OS analysis. Based on the observed hazard ratio and
OS status so far, if we assume that the trend of an event occurrence continues, the projected likelihood of having a positive OS result at final analysis would be only 7 percent. Even if we assume an event-occurrence trend towards the prespecified hazard ratio of 0.73 for events after this interim analysis, then the projected likelihood of a positive result of final analysis would be 20 percent. Thus, a likelihood of demonstrating a survival benefit for panobinostat at the final analysis is only 7 to 20 percent.

Assessments of overall responses were fairly concordant between the investigators and the IRC. For both assessments, the differences between arms are not very impressive. Bortezomib and dexamethasone demonstrate a robust treatment effect, and there appears to be a modest benefit with the addition of panobinostat.

There were a couple of differences between the investigators and the IRC assessments: 1, the IRC determined that none of the patients achieved a near-complete response; and 2, the IRC determined a
median duration of response that was about one month shorter in both arms compared to the investigators.

I want to highlight from the briefing document that single-agent panobinostat has a very modest treatment effect in this patient population. In an earlier trial, which included 38 patients with relapsed multiple myeloma who were given single-agent panobinostat, only one patient had a response, a partial response.

In summary, the median progression-free survival, based on the primary endpoint, is at best 3.9 months favoring the panobinostat arm over placebo. Large amounts of missing and censored data limited our confidence in these results. Sensitivity analyses for PFS demonstrated much shorter differences.

FDA Presentation – Nicole Gormley

DR. GORMLEY: I'm Dr. Nicole Gormley, and I will present the safety findings of panobinostat from the data submitted to the NDA. The safety population consists of 758 patients enrolled on
trial 2308 who received at least one dose of panobinostat. On-treatment deaths, defined as deaths during treatment and within 30 days of the last dose, occurred more frequently in the panobinostat arm compared to the placebo arm, 8 versus 5.1 percent. Deaths due to disease progression occurred in 1 percent of patients in the panobinostat arm compared to 1.6 percent in the placebo arm.

The applicant has shown that the overall percentage of deaths in this trial was similar to that observed in other trials of approved multiple myeloma therapies. It should be pointed out that the information presented by the applicant is the overall percentage of deaths. In most of the multiple myeloma trials, disease progression accounted for the majority of the deaths. In this current trial, most of the deaths were due to causes other than disease progression.

Within the panobinostat arm, 7 percent of the deaths were due to causes other than disease progression, and only 1 percent was due to disease
progression. Twice as many non-progression deaths occurred in the panobinostat arm compared to the placebo arm, 7 versus 3.5 percent. Infection, hemorrhage, and cardiac arrest or failure were the main causes of death not due to disease progression.

Non-fatal serious adverse events occurred in 60 percent of patients in the panobinostat arm and 42 percent in the placebo arm. The most common SAEs that occurred in more than 5 percent of patients in the panobinostat arm were thrombocytopenia, diarrhea, fatigue, pneumonia, and sepsis.

Adverse events occurred in both arms, however, there was a higher rate of grade 3-4 adverse events in the panobinostat arm. Grade 3-4 events occurred in 95 percent of patients in the panobinostat arm compared with 83 percent in the placebo arm. Grade 3-4 adverse events that occurred in more than 10 percent of patients and had a 5 percent higher incidence in the panobinostat arm compared to the placebo arm.
include thrombocytopenia, neutropenia, diarrhea, fatigue, and hypokalemia. Note that for most of these, the incidence of grade 3-4 adverse events was increased twicefold for patients on the panobinostat arm.

Treatment emergent EKG changes occurred in 64 percent of patients in the panobinostat arm compared with 42 percent in the placebo arm. ST-segment depression was reported in 22 percent of patients in the panobinostat arm compared with 3 percent in the placebo arm. New T-wave changes were reported in 40 percent of patients in the panobinostat arm compared with 18 percent in the placebo arm. The incidence of QT prolongation was similar between treatment arms, 12 percent in the panobinostat arm and 8 percent in the placebo arm.

Given the high rate of SAEs and grade 3-4 adverse events attributed to thrombocytopenia, additional analyses were conducted to evaluate the clinical significance of the observed difference in thrombocytopenia. Patients in the panobinostat arm received 20 percent more platelet transfusions than
the placebo arm, 30 percent compared to 10 percent. Additionally, 31 percent of patients in the panobinostat arm required a dose modification or interruption due to thrombocytopenia compared to 11 percent in the placebo arm. Also recall that there were 5 on-treatment deaths due to hemorrhage in the panobinostat arm compared to 1 in the placebo arm.

An analysis of standardized MedDRA queries, or SMQs, was conducted to examine the extent of hemorrhagic complications experienced in the two treatment arms. SMQs are groupings of MedDRA preferred terms of adverse events that relate to a defined medical condition. The included terms may relate to symptoms, diagnoses, physical findings, or laboratory results. For example, the hemorrhage SMQ includes terms such as hematoma, bleeding, ecchymosis, purpura, and rupture of blood vessels. Based on the SMQ analysis, nearly twice as many subjects had a hemorrhagic complication. Twenty-one percent in the panobinostat arm compared to 12 percent in the placebo arm.
Given the differences noted in treatment-emergent EKG changes, a broad SMQ analysis was conducted to evaluate for cardiac complications. Based on the SMQ analysis, terms consistent with cardiac failure occurred in 31 percent of subjects in the panobinostat arm compared with 21 percent in the placebo arm. Arrhythmias occurred in 21 percent of subjects in the panobinostat arm compared with 12 percent in the placebo arm. And ischemic heart disease conditions occurred in 4 percent of subjects in the panobinostat arm compared with 2 percent in the placebo arm.

Overall, 36 percent of patients receiving panobinostat discontinued therapy due to an adverse event compared to 20 percent of patients in the control arm. Diarrhea was the most common reason for treatment discontinuation in the panobinostat arm. Adverse events leading to treatment interruption or dose modification occurred in 89 percent of patients in the panobinostat arm compared to 76 percent of patients in the control arm.
Thrombocytopenia was the most common reason for treatment interruption or dose modification in the panobinostat arm.

Given the significant number of treatment discontinuations due to adverse events, we performed two exploratory analyses that incorporate toxicity as an event. Specifically, we conducted a time-to-treatment failure analysis and a PFS efficacy plus toxicity analysis using the safety population. This approach is also used in other therapeutic areas such as antiretroviral therapy for HIV. For antiretroviral therapies, discontinuations can negate the benefits of treatment and may pose additional risks to subjects. This type of analysis, which includes both efficacy and toxicity, may provide useful information about the overall risk/benefit profile.

In the time-to-treatment failure analysis, the following were considered events: death, disease progression, and any premature discontinuations. In the PFS efficacy plus toxicity analysis, the following were considered
events: death disease progression, and discontinuations due to adverse events.

The time to treatment-failure analysis resulted in a median time to progression of 6.2 months in both the panobinostat and placebo arms. There was no difference between arms with regards to the median time to event, and the hazard ratio did not suggest any difference.

The PFS efficacy plus toxicity analysis resulted in a median time to progression of 6.8 months in the panobinostat arm and 6.9 months in the placebo arm. As seen in this graph, the two curves overlap and there is no apparent difference between the two arms. These exploratory analyses were conducted to allow for further clarification of the safety profile of panobinostat. Specifically, they offer the opportunity to look at both efficacy and toxicity together. In the analyses, the hazard ratios and medians are not different and the curves cross, primarily due to early toxicity, suggesting that the efficacy of the addition of panobinostat to bortezomib and
dexamethasone may be offset by the toxicity.

In summary, there was a higher incidence of deaths not due to disease progression in the panobinostat arm compared to the placebo arm, 7 versus 3.5 percent. Serious toxicities included pneumonia, diarrhea, thrombocytopenia, sepsis, and fatigue. Thirty-six percent of patients in the panobinostat arm discontinued treatment with panobinostat and 89 percent of patients required a dose modification due to adverse events. Efficacy plus toxicity analyses suggest no difference between arms.

The primary endpoint analysis of trial 2308 demonstrated an improvement in median progression-free survival of 3.9 months. However, large amounts of missing and censored data limit our confidence in these results. Sensitivity analyses for PFS show significant variation in the observed PFS difference and underscore the uncertainty in the efficacy results. Also significant was twice the incidence of deaths not due to disease progression and a high incidence of
myelosuppression, hemorrhage, infection, and cardiac toxicity.

The high amount of observed toxicity, treatment discontinuations, and dose modifications required, combined with unreliable efficacy results, make the risk/benefit assessment of panobinostat in combination with bortezomib and dexamethasone challenging.

We seek advice from the committee for the answer to this question. Given this benefit/risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risk for patients with multiple myeloma? Thank you.

Clarifying Questions to the Presenters

DR. ARMSTRONG: Thank you, Dr. Gormley.

We'll now take clarifying questions for the sponsor and for the FDA. Please remember, for committee members, to state your name for the record before you speak. And if you can, please direct your questions to a specific presenter. If you want a question, must indicate to Caleb, and
he'll keep a running list of folks who have questions to ask.

First with their hand up was Dr. Taylor.

DR. TAYLOR: Yes. My name is Dr. Taylor. I'm a patient representative. I have a question for the sponsor. On the number of dosage modifications or changes that were done, was that primarily reduction in bortezomib to weekly or was it a change in the dose of the panobinostat?

DR. CAPDEVILLE: So the protocol provided guidance, very specific guidance, for those reductions for both panobinostat and for bortezomib. Generally, the investigator modified the dose of the two agents at the same time, and I will show you that. So we have an analysis of the relative dose intensity over time, that gives you a sense on really how the dose was delivered. We have -- the dose intensity by cycle, please?

No. I wanted the dose intensity by cycle, please? So this is a slide that displayed the relative dose intensity of the two agents, panobinostat and bortezomib, by cycle, and this is
in the panobinostat arm. As we can see, to support what I just mentioned, the dose of both agents tend to be titrated down at the same time. So we have this initial phase in the first few cycles where the median -- I mean, the bars represent the median relative dose intensity, decreased and then stabilized at roughly 75 percent here.

This is the median relative dose intensity. So does that answer your question?

DR. TAYLOR: Yes.

DR. CAPDEVILLE: Thank you.

DR. ARMSTRONG: Dr. Liebmann?

DR. LIEBMANN: So I have a number of questions about this. And just to boil it down to how I understand what we have so far, I'm willing to believe that there's a progression-free survival that's somewhere in the ballpark of 2 to 4 months. And that didn't translate to a significant overall survival. And if you take the proposed drug, there's twice the chance of dying while you're on treatment from the drug than if you stuck with the standard therapy.
So I'm trying to figure out now who this treatment would be applicable for. So I have a number of questions about the patients. The first is, what do we know about treatment that patients received after their treatment on the study? Do we have any information on that?

DR. CAPDEVILLE: No, we do. We do actually. We called it the first treatment received after discontinuation from the study and after progression. And actually, there were more patients on the placebo arm who received -- we have a record of the subsequent anti-cancer therapy, so that's shown on this slide. So in total, we have 36 percent of patients in the panobinostat versus 47 percent in the placebo. And the difference is driven by higher use of IMiD in the placebo, 27 percent versus 18 on the panobinostat arm.

DR. LIEBMANN: And correct me if I'm wrong. But most of the patients in this study were from outside the United States? Is that correct?

DR. CAPDEVILLE: The study was a global study. Seven percent of the patients have been
randomized in the U.S., and the U.S. was the third largest country. Thirty-four countries were involved.

DR. LIEBMANN: And I ask just because the application here is for the United States. And so, with subsequent treatment, is there any difference in subsequent treatment based on whether or not it was patients in the United States or elsewhere?

DR. CAPDEVILLE: I don't have a slide on the subsequent treatment in the U.S. patients, however, I'd like to point out that the prior therapies that the patients received in the U.S. -- and I think we have a slide on that -- reflect actually the medical practice that Dr. Richardson was referring to, in the sense that the U.S. patients had a higher use of the very active agent bortezomib and lenalidomide.

That's the slide. So we have 22 patients on panobinostat and 32 on placebo. And if you remember, for example, at the global level, 20 percent of the patients that received prior lenalidomide, for the U.S. patients, it was between
50 and 70 percent, so a much higher usage of lenalidomide. And the same is true for bortezomib. At the level of the global study, it was 40 percent. Here it's more between 60 and 70 percent.

DR. LIEBMANN: If I could just change off of the issues of treatment, because the deaths on treatment are kind of a big issue here, is there any analysis of when on treatment? In other words, was there a cumulative toxicity that resulted in an increased number of deaths after X number of cycles or was it just randomly distributed?

DR. CAPDEVILLE: We have a slide on the time to on-treatment deaths. We have a breakdown here of the deaths defined as early deaths. In the myeloma community, early death is defined as was in the first 60 days. So that's the first slide. And received the same pattern that I showed in the main presentation with 10 deaths on panobinostat and 6 on placebo. And this includes infections with similar numbers between the two arms and the hemorrhages that we talked about.
The next slide showed the deaths after 60 days, so we have 60 on panobinostat and 6 on placebo, with the cause as listed here. We retrieved here the infection, and then a variety of all the causes. I'd like to point out something. As it is often the case in myeloma, these patients, it is sometimes difficult to make a clear-cut between what is an adverse event and what is relative to the disease. And Dr. Richardson could comment further on that.

For example, we have here two patients who died because of acute renal failure, but that was also in the context of disease progression.

DR. RICHARDSON: Dr. Liebmann, your point is extremely well taken. And I think that the key point here from this slide is we looked actually at both those patients with acute renal failure, and that was in the context of disease progression, but the investigator had scored it as possibly related. So that was, hence, the reason that it was scored in that setting as not necessarily related to disease progression.
The other thing to your point is my understanding that in the U.S. population, there was only one on-treatment death in the U.S. population enrolled to this trial. And as I mentioned earlier in our phase 2 experience, 55 patients, multicenter, with relapsed refractory disease, with a median of prior 4 lines of therapy -- so a more heavily pretreated population -- we had no attributable treatment-related mortality on that study. We actually had only one death on study related to rapid disease progression.

DR. LIEBMANN: Believe me, I appreciate the difficulty in assigning cause of death. The reality is that the number of deaths are different. And I asked about when it appeared because you did show that once the dose adjustment was made in the second half of the study, that the instance of thrombocytopenia fell markedly. And so the question was, was that also true for the deaths on study? And if so, is the starting dose the wrong dose?
DR. CAPDEVILLE:  Perhaps I can discuss the question of the dose because I think that's quite important. If we could have the slide that I had on the core slides, for the dose selection?

I think the dose was selected based on a rigorously designed phase 1 study. That was a dose escalation study. For this combination, the end point was MTD to identify the dose with prespecified criteria in terms of toxicity, of course. In that case, different dose and combination of panobinostat and bortezomib have been tested. We observed a high rate of response. The dose of 20 milligram and 1.3 milligram per meter squared of bortezomib. And because of the thrombocytopenia, we introduced in the dose expansion phase of the study a week of treatment holiday to a low platelet recovery. And that's the last bar that we see on the right on the graph, which the same dose of 20 and 1.3 give this high rate of response.

In other words, the selection of the dose was based not only MTD, that is a toxicity
indicator, but also on efficacy with the response rate. And what was very important is also the duration of treatment in the phase 1 that is an important marker in phase 1, and I think we have a slide on that, because this duration of treatment was actually highest in the patient treated with 20 milligram and weighs 1.3 milligram per meter squared. Again, the last bar corresponded to the dose expansion cohort, the one with the one week drug holiday, as a duration, corresponds to prior bortezomib studies.

So that was very encouraging. And one of the important factors that encouraged us to move that dosing regimen in the phase 3 study. But of course, we have discussed the toxicity, and that's why the guidelines for individualized dose titration were quite important. I don't know. You may comment on how you have managed that.

DR. RICHARDSON: Yes. And I think, Dr. Liebmann, in that context, dose reduction in our experience has been very helpful in managing side effects going forward, and particularly with
bortezomib as well, as you saw from that data. The other point to make is that in other combination strategies, for example with immunomodulators, we've seen actually the drug perform very well. So I think that this critical issue of toxicity is something that's very much the subject of ongoing trials because obviously it's a critical importance.

The other point I would make is that we did actually have an effort in PANORAMA 1 to look at quality of life, recognizing that that was difficult and such a large international trial. And some of that information is actually quite helpful I think, certainly when you compare it to previous experiences in other trials, where basically the QOL outcome for certain parameters are very similar between both arms. And that's from our perspective is in some ways reassuring as we go forward to try and optimally manage the toxicity concerns.

DR. LEBWOHL: Hello. David Lebwohl. I'd just like to add to that. I'm head of clinical
development at Novartis.

Dr. Liebmann, you started out by talking about the PFS advantage, so I think it's very important to go back to that part of your assumption. The PFS advantage in this trial is based on the intent-to-treat analysis. PFS advantage is 3.9 months. And the sensitivity analyses, as we've talked about, are not a way to judge what is the extent of treatment benefit. We'd like to talk some more about that.

In fact, the FDA talked about two important treatment sensitivity analyses. One is the IRC. This did show a 3.7 month benefit. The analysis they're showing did not use the mEBMT criteria, and we'll go over that in detail now because the question has come up again. We did explain this and talked to the FDA, but they haven't had time to understand that.

The other point --

DR. LIEBMANN: Although, if I could just respond to that since you seem to think that the PFS is a big deal. Believe me, this committee in
other meetings has discussed the relative merits of PFS or not. And of course, in order for PFS to be valid, intention to treat or not, you have to have an accurate way of assessing the progression part of progression-free survival, and that seems to be a problem here.

DR. LEBWOHL: That's exactly what we want to show you. We want to show that the IRC did a very rigorous job of assessing progression in this trial. The FDA did bring up the point that about 23 percent of the patients did not have an M-protein, and we had a prespecified analysis for this as well. And this is called the per-protocol analysis.

In the per-protocol analysis, the 23 percent of patients who did not have that baseline M-protein are shown here, the benefit. The hazard ratio, if anything, is a bit better. So these are the patients who have the more objective way, of course, of assessing progression. So in this patient population, just missing the patients with the non-measurable disease shows a benefit of .60
with an extensive benefit of 4.6 months. So that's the group of patients that the FDA was raising doubt about.

What I'd like to do is ask Dr. Natarajan to take you through the IRC analysis so you understand what happened with the two analyses there.

DR. CAPDEVILLE: Before you address the statistical aspect on this IRC analysis, I think it's important to really understand what's happened and why we have two analysis of the IRC. To do that, I think the best is to take an illustrative example.

Here, there is just an illustrative patient enrolled into the study, where the graph displays the evolution of the M-protein. So the patient achieved first a partial response, and then in July 2011, at the first spike of M-protein that was isolated, and later on in October 2011, this patient had another spike that was confirmed by a second assessment.

So at the bottom, we have the table showing how the investigator assessed the response, and the
investigator assessed PD at the last two visits, as shown in yellow. The investigator did not assess PD in the middle visit in July 2011 because it was not confirmed by a second assessment. In contrast, the IRC did an assessment of response at every visit, and as a corollary indicated a PD on that visit in the middle but obviously not in the subsequent visit, so this has been analyzed in the PFS analysis. On the next slide, we have the same patients on the top and the same table of assessments. In the time of reanalysis by investigator, the PFS event was declared at the time as indicated on this slide because it was confirmed by a subsequent assessment.

In the IRC analysis, we made an assumption that was incorrect that the first evidence of PD in the IRC assessment was always corresponding to the PFS event with a confirmation. And upon further discussion with Dr. Voorhees, the chair of the IRC, when we realized that an error had been made, we conducted the second analysis, but requiring in the statistical analysis the confirmation of the PFS
event. And the second analysis used exactly the same data set of the IRC. The IRC assessment has not changed. It's only the statistical analysis that has changed.

That has taken us to the result at the trial level when -- I mean, we've shown the primary analysis, shown on the top, with promulgation of median PFS of 3.9. So this is Voorhees confirmation of PD according to the EBMT criteria. And the last analysis at the bottom is again with confirmation of PD per EBMT criteria with a delta of 3.7 months. And the median analysis is, as I said, an incorrect analysis because it does not comply with EBMT criteria.

So if we take all of this into account, that takes us to what Dr. Lebwohl showed, that is the sensitivity analysis that all include this very important aspect of the EBMT criteria that is the confirmation of progressive disease, and that is what we wanted to show here. And Dr. Voorhees, the chair of the IRC, is here, who can utter a couple of comments on how this was done.
DR. VOORHEES: Thank you, and thank you for giving me the opportunity to participate in this important meeting. My name is Peter Voorhees. I'm a myeloma physician at the University of North Carolina, the last 10 years a clinical investigator. And I'm the chair of the Independent Review Committee for this particular study. And I just want to reinforce that the Independent Review Committee did use the modified EBMT criteria when assessing responses.

As you can see from the example that was shown previously -- and if you could put that up again that would be useful. But as you can see on the IRC analysis, as we went visit by visit assessing response, we did not stop at that first progression because we did not view that necessarily as progression. We continued to go on and analyze the particular subject that we were looking at until we had two consecutive confirmations of relapse from CR or PD.

The IRC mistakenly thought that that first PD would not get flagged by this statistical
programming when in fact it did. And when that
came to light, we asked that they reanalyze the
data, and the data from both arms were reanalyzed
in the very same manner. Again, we did not change
any of the responses. We did not go back and
change a single thing. So I think it was done in
an unbiased way.

I think that the updated IRC analysis is
definitely the more accurate one. And if you look
at the concordance between the investigators as
well as the IRC, you can see that we were actually
very close to one another with respect to
assessment of responses throughout the course of
the study.

DR. PAZDUR: Could I just bring back the
committee to the central reason why we're bringing
this application? And that is the amount of
censored data here. And I think if you show -- and
I never hear the word "censor" being uttered from
the applicant's mouth here, so to speak. But if
you take a look at the investigator IRC, almost
50 percent of the data is censored here in the
panobinostat plus chemotherapy arm. In the revised IRC, it's 48 percent.

That's of concern to us. And this is the reason why we're bringing this application. Remember, when we're talking about PFS, as was brought up by Dr. Liebmann, we're talking about the magnitude of benefit. We have to have confidence in what is that magnitude of benefit. And when you have this high degree of censoring, no degree of sensitivity analysis, or IRC analysis, is going to address this. It seems like it's a fundamental issue or flaw in the trial here.

So that's the major issue here. It's not if there is a PFS advantage. I'll give that to the applicant here, that there is an advantage in PFS. But that doesn't help us put this in a risk/benefit analysis. One has to have confidence in the magnitude of benefit that one is seeing to weigh it against the toxicity, which is considerable here with the addition of this drug.

So I really would like to emphasize the reason why we're bringing this application. It's
not is there a PFS advantage. It's what is the magnitude of that advantage and how comfortable you are in assessing that magnitude, given the fact of the high degree of censoring that is present here.

DR. ARMSTRONG: Dr. Liebmann, do you have any other questions? Okay.

DR. LEBWOHL: I would like to address the censoring since Dr. Pazdur has brought it up. And we're just looking here for the censoring in various studies that we've talked about today in relapsed myeloma. And I'll show you why this is very common in myeloma studies.

So these are a series of studies -- bortezomib, lenalidomide, the doxorubicin study -- in which PFS was the primary endpoint. And what you see here is the percentage of patients that were censored in the primary analysis of progression-free survival. And what you're seeing here, first, is a very similar pattern, from our study to the other studies, that is that there is more censoring in the experimental arm, and I'll talk about why that is. In addition,
the level of censoring seen in our study is not
distinctly different from these other studies.

Now, I'd like to show you the censoring in
our study with the investigator analysis. And here
you see the censoring. The biggest reason there's
more censoring in the experimental arm is that
there are fewer events in the experimental arm.
This is a very good reason for censoring, of
course. Having more events in the control arm
leads to more censoring in the experimental arm.
In terms of the other things, there's an imbalance
in ongoing patients. This is also a good finding.
You have 35 patients ongoing in panobinostat and
15 patients ongoing in the control arm.

If you look at the reasons for censoring,
they are actually quite balanced in the two arms.
For the patients who are still being censored in
this trial, the reasons are balanced. Some of
these are very good reasons. For new cancer
therapy, the number of patients, 4 patients,
3 patients in each arm, went on to a stem cell
transplantation. Other patients went on to
continue bortezomib. As you know, often patients want to quit a trial because of the requirements of the trial of coming in. And they go on to take the same therapy in order to continue their response.

I'll ask Dr. Natarajan now to address the censoring and the effect of the censoring.

DR. NATARAJAN: Kannan Natarajan, the head of biometrics and data management in Novartis oncology. I would like first actually, iterate the fact that the PFS analysis, the primary PFS analysis that was done was based on methods that is actually been standard across all solid and hematologic tumors and is actually incorporated methods that are applied actually across multiple applications.

That being said, as per the guidance, there is also, actually, the requirement of using multiple sensitivity analyses. And the purpose of these sensitivity analyses is because the statistical assumptions that are being implemented in some of these analyses, how varying it is and what is the impact of these statistical
assumptions. However, these sensitivity analyses are not by means actually to measure the magnitude of the treatment effect, but instead, it's the robustness of the treatment effect because these sensitivity analyses do indeed actually have an impact into the median because of the fact that the varying degree of the assumptions that are being actually implemented, when you start putting more restrictions on the assumptions, it's likely to actually have an impact in terms of the magnitude of the treatment benefit that you observe, which is no different than any other tumor type.

That being said, again, if you look at the hazard ratio -- which is the true assessment of the treatment benefit, which actually gives you the odds of a patient receiving potential benefit of being treated with panobinostat -- in each of those sensitivity analysis, Dr. Capdeville showed -- in each of these sensitivity analyses -- I'm sorry, the other one in the core -- which has the actual event, the back-dating event, as well as the one that FDA has showed with respect to the dropout
analysis, in each, the hazard ratio and the corresponding confidence interval is below 1.

Again, as Dr. Pazdur said, this actually clearly shows the fact that the treatment is indeed effective. The question that we are asking about is in terms of the magnitude of the benefit. The magnitude of the benefit is measured as per the original intent-to-treat analysis as specified in the protocol.

Now, let me actually go in and look at the individual censoring reasons and why it may actually or may not have an issue. Can I go back to the censoring reasons and give you a perspective in terms of what happened to these patients prior to the withdrawal or at least informed consent, for example?

If you look at the reasons for censoring, as Dr. Lebwohl pointed out, withdrew informed consent is one of the key areas where panobinostat has had a higher number of patients who withdrew informed consent as part of the analysis for the PFS. If you could look into what happened to these patients
prior to the withdrawal informed consent, that is
critical as well in terms of whether they're losing
response, and thereby suggesting some sort of a
censoring that is occurring in these patients.

If you look at this slide, this looks at the
last adequate response assessment of patients
censored due to the greater -- with two missing
assessments. And if you look at the number of
patients who had a CR -- obviously, the CR and NCR
is higher, 3 patients versus 1 patient in the
placebo. Partial response is equal, 33 percent
versus 31 percent. And if you look at the number
of patients who had this impact, it's 36 patients
in the panobinostat versus 28 patients. The median
time from the last response to an actual event in
these patients, with a greater than two missing
assessments is about 107 days versus 116 days. And
in fact, there are more panobinostat patients than
placebo patients.

If you look at the withdrawal of informed
consent, this is the last response prior to the
withdrawal of informed consent. The patients who
had CR in the panobinostat, there are 3 patients versus 2 in placebo, and the near-complete response is 8 versus 4. And the partial response is higher, 31 patients versus 16 patients.

So again, showing the fact that these patients are not actually rapidly deteriorating and therefore withdrawing informed consent, therefore potentially having an impact on the magnitude of the treatment benefit that is observed.

Any of these sensitivity analyses with the stringent criteria of these statistical assumptions are likely to decrease the median. In fact, I would like to actually point out the contrary is if the sensitivity analysis had shown -- because of the relaxation of the assumptions -- had shown a six-month improvement of PFS, that truly is not a benefit of the treatment effect of the sixth month. In fact, the ITT analysis is the right assessment that's based on a sensitivity analysis, is only to assess the robustness of the treatment benefit.

DR. ARMSTRONG: Dr. Fojo?

DR. FOJO: I totally agree with the point
that Dr. Pazdur made, that it's all about censoring, and I'm not sure that the company has addressed it adequately. So the first question I have was that the FDA showed the time-to-treatment failure, essentially, their graph.

Does the company agree with that or do they have a graph that is different than that, the 1.9 months survival advantage?

DR. NATARAJAN: Again, Kannan Natarajan, the head of biometrics and data management oncology. The time-to-treatment failure analysis, while though it's widely used in other therapeutic areas, it is not actually a method that is widely used in oncology. And clearly, actually, the health authority guidances, including the Food and Drug Administration guidances, calls for actually an assessment of the time-to-treatment failure as not a valid endpoint because it actually combines two things, one, the efficacy, and safety. It does not distinguish the efficacy from the drug toxicity.

DR. FOJO: Yes. But I think when you're talking about a drug that has as much added
toxicity as this, in combination, that becomes an important point.

    DR. NATARAJAN: Very true.

    DR. FOJO: I think you can argue whatever you want, but I think certainly from a patient's point of view, they want to know that they can tolerate the drug and get benefit from it. So I think a TTF, in fact, is very valid in this situation. You sort of made it a requisite for the committee and for the FDA the moment you came with such a high degree of censoring.

    Actually, could we have CE-13 that you showed? I may have missed it. You can certainly miss something reading, and I'm not sure Barry Miller alluded to it. But what was the interval for assessment for patients? Was it 2 months, 4 months, 6 months?

    DR. CAPDEVILLE: Patients were assessed every 3 weeks during the treatment, and after treatment, every 6 weeks.

    DR. FOJO: I'm sorry? Every 3 weeks during treatment. But here, the patients at risk are
shown at every 2 months. One of the reasons that I ask that -- and this was alluded to -- when you look at a Kaplan-Meier curve or PFS, you can usually guess when assessments are being done because of the stair steps that you see. There are no stair step to be found here, which is consistent with what was alluded to, a lot of ascertainment bias, which is of concern.

If you look at this, though -- since we're talking about censoring -- you can do a back-of-the-envelope calculation. And what's interesting is that at the 2-month period, the number at risk has dropped dramatically for both arms. If you do a back-of-the-envelope calculation for the panobinostat arm, 72 patients have been censored at that point in time.

Now, I gather that the study -- I meant to ask when the study was terminated and when the assessment was done, but I imagine it was at least 2 months. So I don't think that any of those fit into the "ongoing category" that so very few fit into. So 72 patients by month 2 have been censored
in the PBO arm versus about 42 or 43 in the placebo arm. Why are these patients being censored so rapidly? How many of those -- I can only think that a fair number of these are due to toxicity.

Do you have information on those 72, give or take, patients that were censored and how they compare to the rest of the patient population, for example? That's a lot of censoring in the first 2 months. And you know what it does, that it alters the curves in an artificial manner at the beginning. I think, in fact, when you look at this curve, it supports the FDA TTF analysis because if you look past about 4 months, the two curves are identical. You could take that blue curve and move it up after 4 months, and it would fit right on the green curve.

So a lot of what's driving the difference between these two curves, and which also drives the hazard ratio, is what's happening in those first 4 months. And in the first 2 months, there's a lot of censoring occurring, and much more so, almost twice as much, for the panobinostat arm. So what
about those patients that were censored early?
What was their characteristics?

DR. NATARAJAN: Let me first answer this
question, and then go back to the TTF analysis, if
you don't mind. The censoring, the reason for
patients censored at day 1, you're correct there
are 50 patients who are censored on day 1 in the
panobinostat arm versus 37 patients of which one of
them are ongoing, but then actually these patients
didn't have an assessment that would qualify as an
event.

The withdrawn informed consent was the major
one, which is 46 -- so 23 patients versus 15
patients in the placebo arm. Patients were
followed, but they had more than two missing
assessments, adequate assessments, required for
confirming, and that's about 17 patients versus 14
patients. So these are the number of patients who
are censored on day 1.

DR. FOJO: So they're censored on day 1,
although they may have gone out to day 18? Are you
really saying that they were randomized and showed
up in clinic or didn't show up and said I don't want any drug, that 23 percent of patients said that?

DR. NATARAJAN: Yes, that is correct.

DR. FOJO: You have 46 percent, 23 total patients.

DR. NATARAJAN: Twenty-three was those 15 patients. So let me actually go back --

DR. FOJO: But there still is this imbalance. As I say, my calculations, some 30 to 35 additional patients have been censored in the panobinostat arm between month zero and month 2. Who are those patients? What do we know about them, and why are they being censored at a higher rate?

DR. NATARAJAN: The median duration from randomization to the withdrawal was about 1.4 months, 1.4 months to 2 months, in the placebo arm. These patients actually had -- within the first month or the second month, they had withdrawn informed consent from randomization. So these are the 50 patients in panobinostat and 30 patients in
placebo, 37 patients in placebo.

   DR. FOJO: Okay, still not clear. But you
   said you wanted to say something about the
time-to-treatment failure?

   DR. NATARAJAN: Yes. The trial actually has
three distinct phases. One is the treatment phase,
and then actually -- and the follow-up phase, is
where the patients are followed for
progression-free survival, and then a follow-up
phase for survival. So these are three distinct
phases. Among the patients who discontinued due to
adverse event -- if I could actually have a look at
the slides among the patients who discontinued due
to adverse event and what happened to these
patients followed.

   Number one, I would like to first show the
patients who actually had the response prior to the
adverse -- withdrawal of treatment due to adverse
event. If I could have the slide?

   If the last adequate assessment, again,
among the patients who considered event in the
worst analysis, discontinuation due to AE, among
these patients, 7 patients in the panobinostat arm had actually a complete response versus 1 in placebo. Fourteen of them had a near-complete response versus 5. And the partial response was much higher, again, in panobinostat compared to placebo.

In the time-to-treatment failure analysis, if each of these patients were considered as an event, which is actually an undue disadvantage in terms of putting these patients as having an event at the time when they actually discontinued treatment due to an adverse event -- because the time from the treatment discontinuation, due to an AE, until the disease follow-up, the patients are discontinued due to AE.

In the panobinostat arm, the mean duration of follow-up, following the discontinuation of treatment, in the panobinostat arm was 121 days versus 95 days in the placebo arm.

DR. FOJO: I don't think this is really going where we want to go. But actually, the slide you just showed before this, I was going to ask you
because you're trying to say, oh, look, these
didn't patients that we were taking out because
they were doing poorly, in fact you also had the
patients that were voluntarily withdrawn, or
withdrew consent, a lot of patients are having
their treatment discontinued when they appear to be
doing well. And to me, that happens when there's
toxicity, so that's a concern.

You also stated in one of your presentations
by addressing the very concerning fact that the
patients were treated with panobinostat for an
average of 5 months, for a median duration of
5 months, and the control is 6.1 Really? I mean,
this drug is so great, when we add it to the
combination of bortezomib and dexamethasone, that
it gives greater progression-free survival, even
though we don't treat for as long.

When that happens, that discordance, to
me -- and you see it over and over again -- is an
indication of toxicity-driven censoring because
you're stopping it. And the duration of treatment
is well-defined, but the PFS is an estimate from
the Kaplan-Meier. And what you've done is censored out the patients who couldn't tolerate it and who actually may be poor performance status, and then inflating your PFS advantage, which is again why I think the time-to-treatment failure is the thing that is required here.

Then the last thing, because I think other people want to have a chance, is with regards to the one that you showed that had -- it was CS-8, with a median actual dose intensity of panobinostat and bortezomib. What bothers me about this -- and again, you can see there at the bottom the number going forward. You're rapidly eliminating patients at a faster pace than they were having to cease progression scored. What you're showing us here is what those who remained on treatment can tolerate. And so, you're actually enhancing for those that are tolerating treatment, so I'm not quite sure that this is so helpful.

But in any case, especially the bortezomib dose plateaus there at about .18, which is about three-quarters a dose. And if you go back to your
slide that showed -- it was CS-3. I was actually
impressed here; how good a drug bortezomib is, in
CS-3 -- CE-3. I'm sorry, CE-3. I was actually
impressed here with how good a drug bortezomib is.
In going from 1 to 1.3, the response rate went up
from 29 to 53 percent, which is pretty important.

So one has to be concerned if you have
toxicity and you're reducing the dose of a drug
that we already considered to be effective, how
this might impact overall survival, and even
response, but overall survival in the long run.
And then maybe this is why we're not having the
overall survival benefit that one expected. But in
any case, I think the TTF is an important metric
here, and I think we need to keep that in mind.
Thank you.

DR. LEBWOHL: Tito, I'd like to come back to
your comments about time-to-treatment failure. The
issue with time-to-treatment failure is that
considering discontinuation due to AE as a negative
event is assuming drugs don't have a benefit after
they stop. And what we know, that is true for many
drugs. It's true kinase inhibitors often. It's true often for chemotherapy --

DR. FOJO: But David --

DR. LEBWOHL: Yes?

DR. FOJO: -- drugs don't have a benefit if they can't be administered. So it's an important thing to know whether you can get the drug or not. You can have a cure, and if I can't get it, it doesn't do me any good.

DR. LEBWOHL: Let me just show you the periods that these patients were on the trial for treatment, and then the period where they were treatment-free from the core slides.

A drug can have a benefit after you stop if you achieve a deep remission. And what you've heard in this trial is that the patients are achieving a deep remission, almost twice as often as they are on bortezomib. That's the difference.

Now looking at what this looks like in terms of the patient's experience is shown here. As you mentioned, 5 months on the panobinostat arm, 6 months on the placebo arm. And of course we know
why that's happening. There's a higher degree of toxicity in the panobinostat arm, which is the important thing to balance in the risk/benefit analysis. The toxicity is an appropriate thing. It's not appropriate to incorporate it into a PFS analysis, and the reason is shown here.

Patients after an AE are being followed in this trial. They're being followed to the primary endpoint through to the progression-free survival. In addition, what you see here is after they stop treatment and average, they're going 7.5 months on a panobinostat arm. This is now without any therapy. Presumably, their only adverse events then are due to their disease, in general, and this is a positive. On the placebo arm, they're going about 4 months.

We have this from a large number of studies with bortezomib, where it's quite consistent. And again, bortezomib itself does have a benefit that extends beyond the treatment period. You see in all the trials that have been looked at, the treatment period is about 5 months, as in our
trial, but the benefit extends to about 6 or
7 months. Panobinostat, the benefit extends a much
longer period of time. It extends to 12 months.

DR. FOJO: Yes. But actually, you pointed
out in your slide correctly -- and you might feel
that why are we going to be put to a different
standard -- all of these trials suffer from the
same syndrome, and that is a lot of censoring. So
you're taking a hard number and an estimated number
that is greatly affected by censoring.

DR. LEBWOHL: But Tito, the censoring is due
to the patient's experience. We can't change what
the myeloma patients experience in the trial.
They're not trying to go off the trial. They're
not part of that. And all these trials were
assessed based on how myeloma patients are treated,
so that's very important.

DR. FOJO: And I agree with that.

DR. ARMSTRONG: We've let the discussion
about censoring go on a long time because I think
it's a critical issue, but let's to ahead and move
on. Dr. Roth?
DR. ROTH: I had a couple of questions. The first, as it relates to toxicity, you've shown some nice forest plots about PFS benefit regardless of prior treatment, but I wonder about toxicity based on prior treatment because this is obviously a fairly broad indication of giving this a second or third or fourth-line therapy and trying to get an idea of the magnitude of the differences in toxicity based on either the stratification parameter, one, versus more than one prior therapy, or other factors such as prior stem cell transplant or things like that, meaning, is there a population that clearly should not get this drug? And that's responsible for the bulk of the differences in toxicity, so maybe as fourth-line therapy. And there aren't many differences as second-line therapy. That's my first question.

DR. CAPDEVILLE: To address this question, I mentioned in one of my slides, talking about the elderly patient, that we conducted a multivariate analysis of risk factors for toxicity because we wanted to know if the difference in toxicity in the
elderly was due to the age or to other baseline factors. And in this multivariate analysis, we included a number of variables that are relevant to this, including of course the normal demographics. But we also included whether the patient had received a prior transplant, which is potentially a major confounding effect and also the numbers of prior lines of therapies.

We also included in this analysis some baseline count as indicated on the slide. And out of that analysis, only the age and actually a platelet count below 150 as baseline emerged as an independent factor that predicts toxicity. So here, toxicity was defined with one toxicity index that is an index that takes into account all adverse events, including the on-treatment deaths, including the severe adverse events that are relevant to myeloma. This gives you an overall picture. So in this analysis, the number of prior lines of therapy and prior transplant did not come out as being independently predictive.

DR. ROTH: Thank you. My second question
relates to the way bortezomib is being given in this country and will be given several years from now. I get the sense that we're heading towards more and more subcutaneous administration. And you showed in slide CB-9 that the randomized trial subQ versus intravenous bortezomib, although the overall response rate was no different, the end point of interest here, progression-free survival, was actually 2.2 months greater for subcutaneous bortezomib.

I wondered whether the relevance of this trial, to the way bortezomib is going to be given in this country, and whether that 2.2 months eats into your 3.9 months of benefit on the panobinostat arm, is relevant for treatment in the United States population.

DR. CAPDEVILLE: Here, the subQ formulation has been approved, actually, based on the study shown here, but I'd like Dr. Stewart to comment.

DR. STEWART: This study, I think as I recall, was a noninferiority study, so the PFS's were difficult to assess. But 90 percent of use of
bortezomib in the United States is already subcutaneous. And our interpretation is by moving to subcutaneous use, we will not lose any efficacy, but rather we'll gain less toxicity and improve outcomes and tolerability.

Does that answer your question?

DR. ROTH: Yes, thank you.

DR. ARMSTRONG: Any other questions, Dr. Roth? We had a question from the agency.

DR. FARRELL: I just wanted to state there was a slide shown of the censoring in trials that have been conducted, but the censoring was for different reasons. Some of the randomized control trials in multiple myeloma were stopped early because the interim analyses showed outstanding efficacy, and we felt it was not possible to continue the trials.

So I think we have a different reason for the censoring that occurred in this trial, and we just would like to bring that to the committee's attention.

DR. PAZDUR: The other point I wanted to
mention was about the time-to-treatment failure, in our guidance, which I was one of the authors on, so I know it very well. So people do not have to quote my own words back to me. The issue with regard to time-to-treatment failure was with regard to it as a primary endpoint of this study, and we do not recommend that as a primary endpoint. I think Nicole mentioned probably four times in her presentation that this was an exploratory endpoint, and I just want to make sure that people understand this.

One of the reasons, obviously, that we were very interested in presenting this time-to-treatment failure is that 36 percent of the patients discontinued therapy with this drug due to an adverse event. And therefore, we really need to bring this into some context of trying to tie these two together. It is an exploratory endpoint.

DR. ARMSTRONG: Dr. Cole?

DR. COLE: Following up on that point, I am concerned about the differential censoring that occurred here. In studies I've been involved with,
you might lose consent to continue treating but maintain consent for continued follow-up. Although in this case, perhaps that follow-up would not be able to include the assessment of the M-protein, in which case you would end up with missing data, but then wouldn't it be informative missing data in that case?

So I'm trying to reconcile whether it's possible, really, that the differential censoring becomes informative censoring as a result of that, or were those patients who withdrew consent, could they continue to be followed -- did they withdraw consent to continue to be followed for progression-free survival?

DR. CAPDEVILLE: Do you want to take it?

DR. LEBWOHL: David Lebwohl again. The idea of informative censoring, which I think is a concern of the FDA, is the idea that you have an idea that this patient after being censored is going to do differently from other patients on the trial. So reasons of real informative censoring, for example, a patient is starting to progress, and
then the physician decides to give them anti-neoplastic because of that progression. That certainly is informative censoring.

What Dr. Natarajan showed you with the withdrawal of consent patients, these are all patients who are in response. There was no evidence they were starting to progress. So these patients are like every other patient on the trial. They decided to come off for their own personal reasons. I don't think -- it's a very long treatment-free period, as we showed you. That leads to somewhat more informative censoring. They had a period of 8 and 7 and a half months versus 4 months to come off the trial.

So I think there's no sign that the censoring is informative. There is no sign that these patients were different from any other patient on the trial.

DR. CAPDEVILLE: I would like to add a point, David. Sorry. I think there is good reason to think that the blind was quite robust here because bortezomib and panobinostat are very much
overlapping toxicities in terms of thrombocytopenia, in terms of fatigue, in terms of the diarrhea. So we believe that it was very difficult for them to truly determine -- have some informative censoring on this. So the blinding was very robust.

DR. COLE: Thank you. Although I would think from those reasons you provided that there would not be the differential censoring, it was a blinded study, why was this --

DR. LEBWOHL: We could pull it up again. There was not a differential in the proportion of patients. So if you imagine, you have more patients, the chance of any one of them withdrawing consent -- to just show you the censoring again.

The censoring and investigator analysis, please. So here again, we look at the censoring. As recalled, there are more events, many more events, in the control arm than the panobinostat arm. So there are more patients at risk of being -- there are more patients being censored in the experimental arm.
You see here the proportions of patients. There are 180 patients in the panobinostat arm, 121 in the placebo arm. Withdraw of consent percentages are basically balanced, 41 percent in the panobinostat arm, 37 percent in the placebo arm. So what's happening is equal in the two arms. Among the pool of patients who were censored, the proportion of each reason is basically balanced. However, of course, there's a higher proportion ongoing in the panobinostat arm, again, a measure of benefit there, and there are more patients taking different therapy in the other arm.

So it's really where it comes out as being no informative censoring, no difference in the two arms, that would affect the analysis of PFS, which shows a 3.9 months benefit.

DR. COLE: Thank you. I appreciate the clarification. I had also a question about the deaths. CS-04, slide, showing 38 percent on treatment versus 18 on treatment. I'm trying to reconcile the benefit relative to that difference, and whether that difference is actually a real
difference, whether the treatment is in fact 
causing excess deaths. And in the absence of an 
overall survival, clear overall survival benefit, 
if that rate, the difference in rates there, is 
really something you can take to patients and say 
you should take this treatment because it's going 
to delay disease progression, and yet there's this 
elevated risk that you might die and not really 
clear overall survival benefit.

This is primarily I think a question for 
Dr. Richardson, really. I'd like to hear his 
answer on this point.

DR. RICHARDSON: Yes. Thank you very much. 
That's a critical question. And I think from the 
standpoint of U.S. practice, I want to reemphasize 
that we fully recognize the challenge of toxicities 
in this class of drug. We've obviously had 
previous experience with vorinostat and now 
panobinostat.

Going forward, obviously, we're very 
positive about the class of agent. And our main 
goal is how we can make this treatment more
manageable. In that context, I think these data are very helpful. I think they suggest to us that there's a toxicity signal that we need to be very acutely aware of, and we need to finesse dose, schedule, and combinatorial strategies in that context.

But driving back to PANORAMA 1 to the phase 3 trial and what you're looking at here, I'm very struck in U.S. practice -- and remember, we enrolled about 8 percent of the trial overall -- that we had only 1 on-treatment death. And in our own practice, we were actually at Dana-Farber, the lead enroller to this trial, we have no treatment-related mortality. And I think in that context, especially in our phase 2 study, where again we were the lead enroller, 55 patients in a multicenter setting, we were impressed that the toxicities were important but manageable.

I was very struck, actually, by the presentation from the FDA about the EKG changes because we looked at this very comprehensively, and we looked for QT, and that actually was not
different significantly between the two arms. But we obviously were on the look-out for the cardiac signal. Now, in the PANORAMA 2 study, the phase 2, there were 10 percent incidence of cardiac events of grade 1 and 2. There were no grade 3-4.

So I think that this toxicity picture is critical, but I do think it's not manageable? I don't think so. I think it is manageable with appropriate reduction and approaches to supportive care that are appropriate in the U.S. context.

This was a very large international trial, 34 countries, as I recall. And so, I think there were between-country differences in management strategies. So that in no way diminishes it, but it makes it I think perhaps more contextual to what we're discussing this morning.

DR. COLE: But can you comment on the deaths?

DR. RICHARDSON: Sure. So speaking to these deaths as illustrated here, I think I mentioned that the two acute renal failures that we're seeing here were in the context of disease progression.
As you see, the two cardiac events were in both arms. You see across both placebo and the treatment arm. The infection rate does appear marginally higher, but I think that that is an area that obviously is important. And I think Dr. Capdeville went in detail as to what we saw in terms of differences in thrombocytopenia and hemorrhage; again, critical areas, but we need to optimize supportive care.

One question that came up earlier was that there was perhaps a selection process in the phase 2 aspect of the PANORAMA 1 trial, where those patients who went on to the weekly schedule did better, were they just perhaps self-selected. Actually, we didn't see that, that if you looked within a patient, their thrombocytopenia dropped dramatically, and across treatment, their rate of adverse events dropped dramatically when you went to weekly bortezomib. So again, fully recognize the toxicity challenge, but do think with appropriate strategies, they could be manageable.

DR. ARMSTRONG: I'm going to step in here.
The agency has one comment before we take a break.

DR. SRIDHARA: Yes. This is Raji Sridhara. I'm the division director of biometrics, FDA. Just a couple of points to make. Some of the censoring numbers that were being shown, the percentages, were not from the ITT population, what the sponsor was showing. Secondly, the consent withdrawal, 50 percent of them cited that it was either due to AE as reason for withdrawal or discontinued treatment due to AE. So that was what was reported in 50 percent of them who withdrew.

Another point is that many patients left the study after a single PD was observed. So while there were considered PFS events in either the investigator or the first IRC that was done, in the revised IRC, these were considered as censored observations. And that's where we are calling informed censoring, where it was recorded as PD, but later on, the IRC revised one was censored.

DR. ARMSTRONG: Thank you.

We'll now take a 15-minute break. Panel members, please remember there should be no
discussion of the meeting topic during the break, amongst yourselves, or with any members of the audience. And we will resume at 10:40. Thank you.

(Whereupon, a brief recess was taken.)

Open Public Hearing

DR. ARMSTRONG: I think we'd like to go ahead and get started.

Both the Food and Drug Administration and the public believe in a transparent process for informing-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 you, 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 of financial relationships at the beginning of your statement, it will not preclude you from speaking.

    The FDA and this committee place great importance on 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 is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

    Will speaker number 1 step up to the podium
and introduce yourself? Please state your name and any organization you're representing for the record.

MR. CAPONE: Good morning. My name is Walter Capone. I'm the chief executive officer and president of the Multiple Myeloma Research Foundation, and I have no financial relationships or disclosures pertinent to the sponsor of this meeting.

Dr. Pazdur, Dr. Farrell, distinguished members of the FDA and ODAC, thank you very much for the opportunity to address the committee today regarding the panobinostat NDA. On behalf of the entire myeloma community, thank you for your tremendous dedication, commitment, and partnership on behalf of patients and care providers in accelerating new promising medicines that have improved and extended the lives of thousands of patients worldwide over the last decade.

As a patient-founded and driven foundation that conducts research to help exhilarate new promising therapies to help extend and improve the
lives of patients and drive to a cure, meetings like this mean everything to our patients and families that we represent.

As conveyed by some of the most distinguished and leading clinicians and researchers in the field earlier in the meeting, myeloma remains an intractable and fatal blood cancer. Myeloma is complex. Myeloma constantly evolves. Myeloma is different in virtually every person, as some of the data indicated earlier in the meeting has reflected on. This is what makes our mission to eradicate this disease so deeply challenging and our quest for new therapies so urgent.

The newest myeloma therapies used in combination can provide high rates of response for many newly diagnosed patients for prolonged periods of time. This is the work that you've helped us to achieve so far. For relapsed myeloma however, there is no standard treatment. Response rates drop dramatically, often to less than 40 percent. And the duration of response is often less than
12 months and diminishes progressively.

    Worse still are the prospects for
approximately 20 percent of patients or more who
fail to respond to even any initial therapy.
Nothing will work for them, really achieving even
half of the response measures we've just discussed.
Patients like these comprise the majority of the
more than 10,000 patients in the United States who
succumb to this disease each year and are in
desperate need of new therapeutic options and the
opportunity to extend life, new therapies perhaps
like panobinostat.

As the MMRF, and with our MMRC collaborators
and other investigators and research centers, we
have seen in our experience, since 2007, and
working with panobinostat specifically, from
studies with both approved agents as well as novel
drugs in continuing clinical development,
meaningful gains in the quality and length of life
achieved in those patients who received it.

Given the previously described prospects for
patients with relapsing myeloma, the promise of a
new class of drugs that targets the disease in a completely different manner offers hope, hope in the ability to reintroduce or intensify combinations of therapies previously used, and perhaps even more importantly, hope and the potential to combine this agent and this class of agents to enhance the activity of other novel agents in development for patients in the greatest need of new options.

Considering the substantial comprehensive development programs currently in progress and numerous additional late-stage development studies, both planned and ongoing for panobinostat, the sponsor's commitment to the myeloma field and to the patient community are clear.

We encourage the committee to act favorably on behalf of patients who face disease progression and progressive myeloma; who face intense pain, crippling disability, immune system and organ failure, and the risk of death from unchecked progression; offer them the option to potentially benefit and potentially regain hope for the
availability of panobinostat. In so doing, the committee could confer and transform the lives of thousands of patients who would otherwise succumb, and succumb prematurely, to this disease while waiting for other new therapeutic options.

On behalf of the MMRF and the MMRC, and all of our collaborators and the entire myeloma community, we thank you again for your service on behalf of patients, their families, and friends. And we thank you for the opportunity to address the committee today.

DR. ARMSTRONG: Thank you. Will speaker number 2 step up to the podium and introduce yourself? And I'll remind you to please state your name and any organization you're representing for the record. Thank you.

MR. TUOHY: My name is Michael Tuohy. I am a myeloma patient. I have no financial conflicts. My name is Michael Tuohy. I am a myeloma survivor. I was diagnosed with multiple 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 to maybe 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 with a better quality of life. Continued research and approval of drugs is imperative so that 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.

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 here to treat myeloma in sequence and in combination. There is much more hope for our futures. Each new drug approval extends our lives.

There is no cure to date for myeloma, so now
we live from drug-to-drug combination. In the 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.

Facts from a patient's perspective for you to consider. 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. There are patients with a bad high risk of cytogenetics who are responding and living well today on panobinostat, bortezomib, and dex.

Panobinostat is in the key new class of drugs with a new mechanism of action, and sets it apart from the IMiDs and the proteasome inhibitors. Patients even in this highly pretreated population and exposed to both IMiDs and PIs are responding well and reflecting the importance of this new approach.

Side effect management. We know that every treatment comes with its own set of side effects,
but our myeloma specialists and nurses are able to treat us with novel therapies and control side effects so they are tolerable, and we can live with a good quality of life.

I want to be here to watch our children grow up and to be here for my wife. The more options we have, the greater chance I have of living a longer life. A stem cell transplant brought me a three-year remission before I then relapsed. Fortunately, at that time, there was another drug in clinical trials, which I was able to access. I've been on this drug for the past nine years and remain in complete remission. I wish this for all other patients out there in this position.

Side effects don't scare me. I can deal with them. All drugs have side effects, and we need to weigh the risk/benefit ratio. The alternative, quite frankly, is death. I choose life, and I hope you do, too. And I recommend panobinostat as a key new therapeutic option to the FDA for approval in the treatment of relapsed myeloma. The bottom line is more people died on
the placebo than on the treatment. My doctor watches me like a hawk when it comes to side effects. Thank you.

DR. ARMSTRONG: Thank you. Will speaker number 3 step up to the podium and introduce yourself? And again, please state your name and any organization you're representing for the record.

MS. TUOHY: Sure. Good morning. My name is Robin Tuohy. I'm senior director of support groups for the International Myeloma Foundation, and I have no financial conflicts.

I'm caregiver to my husband Michael, who was diagnosed, as you heard, more than 14 years ago in 2000. Wearing both hats gives me a unique perspective on the urgency of having another drug patients can turn to in order to save their lives. I speak as a loving wife and also I speak for thousands of patients and caregivers who are represented and supported by the IMF.

Thanks to new drug treatments, my husband has not only survived well beyond the life
expectancy we were quoted at his diagnosis, Michael has thrived. He has seen our daughter Ally start her senior year of college and Mikey, our son, his junior year of high school. But like all others who are living with myeloma, we are guaranteed two things: one, the disease will return. If a patient is one of the lucky ones who live long enough, it will return time and time again; two, 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 panobinostat literally means life for myeloma patients who have run out of effective drugs in this disease-fighting arsenal.

Myeloma patients like my husband Michael and tens of thousands of others across the U.S. are waiting for you to help save their lives. Some of them cannot wait any longer. I just returned from visiting a myeloma support group in Eastern
Maryland. And while it's great to see the members come together to share experiences and information, in the end, what they are most desperate for is news about promising myeloma treatment. Yes, we've had more drugs in recent years, but, no, it's not enough, and it won't be until this deadly disease is cured.

I'd like to share with you a story of a patient, and Diane has given me permission so you can better understand this patient's journey.

Diane was diagnosed with myeloma in 1997. She was 53 year old. She was not feeling well and went to her primary care doctor. She had a respiratory infection, however, she had a much more devastating diagnosis of multiple myeloma. She's IgG kappa and presented with extensive bony disease, masses on her pelvis and shoulder, L5 plasmyctoma, which resulted in a compression factor. She had lesions to her lumbar and thorax spine, skull, ribs, right and left humerus, and her jaw. Her hemoglobin was 5. Her IgG was 44-50.

Diane had extensive and active myeloma. She
was treated with radiation, high-dose dex and
bisphosphonates, and achieved a durable remission.
When Diane relapsed in 2007, she again had multiple
plasmacytomas. This time her treatment was a novel
therapy combination of lenalidomide based
treatment. Thankfully, the second remission lasted
until 2010, when she relapsed and presented with
aggressive extramedullary disease, including a
grapefruit size mass.

Options were discussed with her myeloma
specialist, Dr. Paul Richardson at Dana-Farber, and they decided together that the best option was the
phase 1 clinical trial of panobinostat, bortezomib,
and dex. I am thrilled to share that by cycle 5,
Diane was in complete remission with this
combination. After completing bortezomib and dex,
Diane is currently going on cycle 83, so almost
five years on panobinostat alone. Talk about a
success story.

In addition, I'd like to share that in 2000,
Diane had developed severe colitis. And I mention
this because although a side effect of
panobinostat, includes GI issues, and despite this underlying GI disease, Diane was still able to tolerate treatment and control side effects without difficulty.

So as a caregiver, I know as well as my husband Michael that each drug has side effects, and patients have to weigh this risk/benefit ratio. But it's our lives, and the choice is always to take the risk and to live. The longer we live, the closer we will be to a cure. Please give us the option to make these well-informed treatment decisions with our hemox by approving this new drug application for panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with relapsed and refractory myeloma. And as Michael said, in the U.S., we do have excellent quality of care for side-effect management, and we choose life, and we hope you do, too. Thank you.

DR. ARMSTRONG: Thank you. Will speaker number 4 step up to the podium and introduce yourself. And again, your name and any organization you're representing. Thank you.
MS. RYAN: Good morning. Thank you for having me here this morning. My name is Kim Ryan, and I am here on behalf of the Cancer Support Community, an international nonprofit organization that provides support, education, and hope to people affected by cancer. The Cancer Support Community believes in fully disclosing all potential conflicts of interest. The Cancer Support Community has received funding for educational activities from Novartis, however, we haven't received any funding for our presence here today.

The Cancer Support Community offers free programs and services to cancer patients and their loved ones, including professionally led support groups, educational seminars, nutritional workshops, exercise and mind and body programs, among others. Our mission is to help people living with cancer to regain a sense of control over their lives, to feel less isolated, and to restore their sense of hope for the future regardless of their cancer diagnosis and regardless of their stage of
disease. Last year, we reached nearly 1 million patients and families, including those living with multiple myeloma.

At the Cancer Support Community, we have learned a great deal from those who we support, and we believe in the importance and value of an educated and empowered patient. In 2014, an estimated 24,000 patients will be diagnosed with multiple myeloma, and an estimated 11,000 deaths are expected to occur in the United States due to multiple myeloma. Although there have been many advances in the treatment of patients with multiple myeloma, for patients whose disease has recurred or for patients whose disease is refractory to other treatment options, those multiple myeloma patients are in great need of improved treatment options and better access to those treatments.

In addition to improved treatment options and better access to treatments, most importantly, we strongly believe that the benefits, risks, and side-effect profile of any treatment should be openly and honestly communicated with patients, and
the decision to move forward with a treatment plan should be done so with a patient's full knowledge and the patient's full engagement.

Today we ask you to carefully consider the plight of people dealing with multiple myeloma and understand the range of both the psychological and psychosocial issues that they face. Please take a leadership role in approving a broader range of treatments, and then encourage patients to be informed, empowered, and optimistic about the possibility of living longer, healthier lives.

Thanks so much for your time today and for your consideration.

DR. ARMSTRONG: Thank you. Will speaker number 5 step up to the podium and introduce yourself? And again, state your name and any organization you represent.

MS. MORAN: Good morning, and thank you for the opportunity of being here. My name is Diane Moran. I am the senior vice president of strategic planning with the International Myeloma Foundation, and I have no financial conflicts. I'm an
experienced nurse with advanced degrees in education, and I have two decades of experience working in the pharmaceutical industry before joining the International Myeloma Foundation.

The IMF is the oldest and largest myeloma organization serving the myeloma community for 23 years, so we speak from experience. In my work, I meet myeloma patients who are living full lives far beyond the 3 to 5 years that was once the prognosis for this disease. Fortunately, for some patients, the disease can be managed with drugs used in combination and in sequence, and they can build back-to-back-to-back long-term remissions.

But as we all know, a string of remissions, it's not a cure, and today, myeloma patients continue to relapse and die. And without a new treatment, their overall survival is a median of 6 months; event-free survival, 1 to 2 months, which means their condition begins to deteriorate almost immediately. Patients desperately need more and newer drug and new drugs combinations like panobinostat.
I witnessed firsthand the unmet needs in my work with the International Myeloma Foundation's nurse leadership board. This board of nurse experts works to improve the day-to-day care of myeloma patients across the country. And although we have made tremendous strides in myeloma treatment over the past few years, it's just not enough. That's why we were so heartened by the results of the PANORAMA 1 trial. This randomized phase 3 trial of panobinostat in combination with bortezomib plus dexamethasone in relapsed refractory myeloma patients showed that panobinostat improved the progression-free survival and the duration of response.

For myeloma patients, news that a next-step drug combination is on the horizon inspires tremendous hope. The IMF's research division would agree. In 2009, the International Myeloma Working Group, our organization of myeloma experts from around the world, undertook a study of patients who were relapsed or refractory to one of the IMiDs, either thalidomide or lenalidomide, as well as to
bortezomib. A total of 300 cases from 8 sites in the U.S., 5 site in Europe and 1 site in Asia, were identified for this study.

The esteemed lead author, Dr. Shaji Kumar at the Mayo Clinic, said of this study, and I quote, "Confirms the poor outcome of patients once they become relapsed and refractory to agents that have become the mainstay of myeloma therapy. The findings highlight the incurable nature of the disease and the urgent need to develop newer, effective therapeutic agents for this group of patients who currently do not have effective treatment options."

Panobinostat is exactly the agent that Dr. Kumar was referring to when he called for effective therapeutic agents in that report. Of course, we are aware that advances in medical treatment are often accompanied by some risks, and this is true of any and all cancer treatments. But as a nurse, I know that side effects can be managed in an approved setting. There is more flexibility to adjust doses once drugs are approved and using
clinical practice. And these dose adjustments can mitigate the side effects reported in the PANORAMA 1 trial.

I submit to this committee that risk has a very different meaning when you are suffering from terminal cancer. Myeloma patients are more than willing to endure the risk if there's a chance that a new drug will be available in their darkest hour when they have no place else to turn. So the most important message I can impart today is that patients must have more and newer drugs, new drug combinations, and new classes of drug for when they're becoming refractory to mainstay treatment. Approval of panobinostat would give them a much needed additional option in their armamentarium. Thank you.

DR. ARMSTRONG: Thank you to all the speakers.

The open public hearing portion of this meeting is now concluded and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the
careful consideration of the data before the committee, as well as the public comments. We'll now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while the meeting is open for public observation, public attendees may not participate, except at the specific request of the panel, and ask the FDA to read the questions to the committee.

**Questions to Committee and Discussion**

DR. GORMLEY: So the question to the committee is, given the benefit/risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?

DR. ARMSTRONG: If there are no questions or comments concerning the wording of the question, we will now open the question to discussion. We did have a request from Novartis to actually respond to the last FDA presentation. You can go ahead and do that now.

DR. NATARAJAN: Thank you, Madam Chair. I would like to actually address the questions that
were actually raised before we broke about the events in the censoring that was shown it was not actually from the intent-to-treat analysis. It was indeed from the intent-to-treat analysis. The number differences between the FDA briefing document and our briefing document shows the ratios or the proportions were calculated based on the proportion of patients who are censored. So I will again go back and provide the same that we actually shared with you before.

The number of patients in each of those categories are identical to what -- my apologies. It's not showing up. The number of patients in each of those categories are identical to what was provided to FDA as part of the submission, as well as actually it is included in our briefing document.

The proportions of patients with the -- the first line, of course, is the proportion of patients who were censored in each of the treatment arms, and then as it's shown, the reasons for those censoring. And the proportions are calculated
based on those patients who are censored. The FDA briefing document calculates it based on the denominator of all patients randomized in each of those treatment arms. That is the difference, and otherwise the numbers are identical.

Then I would actually like to reach out to the second issue that was pointed out. If I could have IRC-32, which pointed out the fact that 50 percent of the patients who withdrew informed consent had due to an AE, I would like to point out the fact that it is indeed similar between the two treatment arms. It was not different in the panobinostat arm. It was similar between the two treatment arms, 48 percent versus 48.9 percent in the panobinostat versus placebo.

Then I would like to actually point out the other issue that was brought up, which is the informative censoring, which the FDA pointed out repeatedly, the presentation as well as in the end. I would like to bring up the fact that 70 patients that are included in the FDA slide who are changed from event to censored, this included 10 percent in
panobinostat versus 8 percent in placebo, well balanced between the two treatment arms. In addition, 33 out of the 70 patients are censored in both the investigator and the IRC analysis, and that needs to be considered as well. Among the 50 patients that changed to a later time point, it was balanced as well. It is 7 percent versus 6 percent in placebo.

DR. LEBWOHL: There was also a question about the cause of the on-treatment deaths. And I think it is very important to realize there are really three things going on here. One is myeloma progression. A second is the side effects of myeloma itself. And you see that, pretty much, most of the events are related to myeloma itself. And there is also the chance that patients could have a side effect of the drugs they're receiving. The best estimate, probably, of the number of patients having an effect of the drugs is the 2.8 percent for panobinostat and 1.8 percent by the placebo that the investigator called.

I also want to point out there's also
another cause of differences in two arms related to on-treatment deaths. Again, it could be due to differences related to the drug, but it also can be due to random differences. As you know, if you take any parameter within a trial, there may be an imbalance due to just random effects.

Just to illustrate this, you saw in our analysis, we cut the data at 28 days. And at 28 days, the difference in the deaths was 30 versus 18. The FDA cuts the data at 30 days, by their standards; again, these early deaths, the difference at 31 versus 19. Just 15 days later if you do a cut, you can see how variable the difference in on-treatment death is. If you go there, now, it's 33 versus 25 or 8.7 versus 6.6.

So another important effect of this is what the FDA has called a random high. When you cut data at multiple points, you may randomly see a difference between the two arms. Thank you.

DR. ARMSTRONG: Thank you. Dr. Liebmann?

DR. LIEBMANN: So actually I wanted to ask a question on something else. But since you just
brought up the whole issue of the deaths on study -- so you showed a slide in which -- for the patients who died on treatment. As I recall, you ascribed 1 percent of the -- or I think you ascribed one-eighth of the deaths, and it worked out to I think 1 percent of the total deaths to progression of disease and the remaining 7 percent. And now you just said, no, it's really 2.8 versus 1.

Could you clarify where your figures from this last comment came from?

DR. LEBWOHL: Let me bring up the core slide. Twenty-eight days afterwards, as mentioned, there were 30 deaths on one arm and 18 on the other arm. And all the causes are delineated underneath there. So some of them were myeloma progression. Other events are infection, hemorrhage, acute renal failure. Again, these are events related often to myeloma as well as could be added to by the drug.

Of course, then, things like myocardial infarction, in this case, the 3 patients who were on the panobinostat arm had severe underlying
disease, and we don't know again how the drug may have affected that. We haven't seen any significant cardiac effect of this drug as we discussed a little bit earlier in our presentation.

Now, the number I was presenting is what the investigator attributed to the drug. So this is a key part of what the investigator does as he sees adverse events in a trial. And what the investigator attributed to the study arm -- again, this could be panobinostat, bortezomib, or dexamethasone, is that 11 patients died due to the study treatment. On the other arm, placebo, bortezomib -- again, two drugs -- this was attributed by the investigator to seven patients.

DR. LIEBMANN: And then the real thing that I wanted to ask about was because I'm still -- again, this is a drug that hasn't shown a survival benefit, there are more deaths on treatment, were any quality of life studies done? Do we have any sense of was there improvement in quality of life in the experimental arm?

DR. LEBWOHL: Let's suggest that. Before I
say that, of course the important thing, there
isn't a significance about it. The study was not
designed to study that -- power to study survival
at the effect level that was seen, .87. Of course,
if a study is larger, you can see smaller effect
size. So it did not make the targeted benefit, but
of course there are more deaths on the placebo arm,
a significant number. Well, not significant, but
for people, the number of people is a substantial
number of people. But we will be glad to look at
the quality of life metrics with you.

DR. CAPDEVILLE: Renaud Capdeville. To add
to what David said, I think on these deaths,
really, the two main things that comes out, that's
infection and hemorrhages. And as we've heard from
Dr. Richardson and Dr. Stewart, these risks are
relatively common with other agents. In myeloma,
that's a common challenge. I think it would be
good also --

DR. LIEBMANN: And I understand that. My
question was really is there a quality of life
study component of this trial --
DR. CAPDEVILLE: Absolutely.

DR. LIEBMANN: -- that can tell us.

DR. CAPDEVILLE: So coming to that, indeed there was a quality of life component of this study. And three instruments have been used in this study. These instruments have been rigorously validated in patients with multiple myeloma. We have the traditional EORTC QLQ-C30 instrument that assessed the global health centers. Then we have myeloma specific model looking at symptoms.

We also had the neurotoxicity assessment instrument for the purpose of assessing the impact of the treatment on the peripheral neuropathy, obviously a major adverse event, with bortezomib. As the FDA correctly pointed out in their briefing document, due to missing data, as patients progress into the study, the results have to be interpreted with some caution.

Do you want to add something?

DR. RICHARDSON: Absolutely. The point is -- show the next slide, please, because this is what I alluded to before, Dr. Liebmann. It's the
picture that gives you -- it's the next figure that shows the two quality of life instruments side by side. That's your question, Dr. Liebmann, isn't that correct?

DR. LIEBMANN: Yes, right.

DR. RICHARDSON: Here we are. This is exactly it. As you can see, we first looked at QOL in the APEX study when we compared bortezomib monotherapy versus dexamethasone. And as you can see on the left screen, you can see the impact on this particular instrument of QOL for the high dose dexamethasone, which deteriorated as you might expect, given the side effects intrinsic to that regimen. And with bortezomib, the decline was not as profound.

What was interesting in PANORAMA 1, to Dr. Capdeville's point, was we saw an initial decline. Things then stabilized. And certainly in treatment phase 1, you saw stability between the two arms. And then moving into treatment phase 2, that improvement actually was sustained. In that regard, my point here -- and this is why I wanted
you to see this slide -- was that the improvement could be attributed obviously to experience in clinical practice, but this I thought was informative.

DR. CAPDEVILLE: Right. And also, if you want to have more details on the interpretation of the quality of life data, we have Dr. Ware with us.

DR. LIEBMANN: So my interpretation looking at this is that there is no difference in quality of life between the experimental arm and the bortezomib-dexamethasone arm. Is that an accurate interpretation?

DR. CAPDEVILLE: I mean, there is a small difference between the arms, panobinostat is in green, bortezomib -- I mean, the placebo arm is in blue. And this difference is attributed to general toxicity. But I'd like first to have Dr. Ware to comment on that because we have to look at the different components. And also, I'd like to start by saying that it was very important to us when we started the study to understand if the triple combination could aggravate the peripheral
neuropathy due to bortezomib. And that's why we had the neurotoxicity quality of life instrument in that study. And the results are identical between the two arms, which was very reassuring. So that was really important.

But let's ask Dr. Ware to comment on the --

DR. WARE: Could we have the next slide?

Thank you.

There are no differences in neurotoxicity. Patient reported no differences in the myeloma specific quality of life questionnaire. Where we really see the differences -- and that's very much what we've been talking about all morning -- is in the general health and quality of life overall global indicator. It declines after baseline more so in the pan arm. It then begins to recover toward baseline after week 18.

In parallel with that, the EORTC symptom measure, which happens to have the side effects, patient reported, that we've been talking about: fatigue, diarrhea, loss of appetite. It mirrors that over time. And since we've been talking a lot
about missing data, when we limit the quality of
life assessment to this stale cohort, that makes it
into phase 2. And we go back and look at them at
baseline and throughout. The quality of life
differences between the two arms mirror what's in
the briefing book with full data and a lot of
missing data.

Further, the sponsor's statistician did
associations between these side effects and quality
of life, and at every time point, worst side
effects is associated with worst quality of life,
suggesting that if those side effects could be
managed better, there would be a quality of life
benefit.

DR. LIEBMANN: But again, just to clarify
this if I could, there is no evidence from the data
that you have that quality of life is improved in
the experimental arm. Is that correct? Yes or no?

DR. WARE: That's correct.

DR. LIEBMANN: Okay. That was really what I
was kind of hoping to get at.

DR. ARMSTRONG: Does anyone else have any
other questions?

(No response.)

DR. ARMSTRONG: I had a couple of questions. One, you've previously shown a slide looking at the dose reductions in panobinostat and bortezomib on the experimental arm. And I wonder if you have a similar slide with dose reductions on the placebo arm, which would just be obviously the bortezomib.

DR. CAPDEVILLE: Just one second.

DR. ARMSTRONG: I just wanted to see what the dose reduction ended up being. It looks like you had about 75 percent dose after 3 or 4 cycles on the experimental arm.

DR. CAPDEVILLE: Okay. So I showed --

DR. ARMSTRONG: Is it EF-21?

DR. CAPDEVILLE: Okay. So I showed on one slide the graph on the panobinostat arm. So here, this is the median actual dose intensity of bortezomib in the placebo arm. It's expressed differently. It's actual median dose intensity, but the pattern is actually the same, that you see a decrease in the dose of bortezomib. That occurs
here starting at cycle 4 or so. And then of course we have the treatment phase 2, where you have this [indiscernible] that is induced by the switch to a weekly injection of bortezomib.

DR. ARMSTRONG: EF-21, is that the slide that was a bar graph that showed the percentage of the plan dose that was given?

DR. CAPDEVILLE: No. In fact --

DR. ARMSTRONG: If you have one that's like that for the placebo arm. I don't know if you have that.

DR. CAPDEVILLE: So let me show you the slide. This is, again -- here, relative dose intensity -- no. In fact, there is another slide on that.

DR. ARMSTRONG: That may have shown it.

DR. CAPDEVILLE: So we don't have the same bar chart. What we have, what appears on the screen, this is another way to look at relative dose intensity. This is the proportion of patients who had a relative dose intensity above 90 percent that is considered to be close to the starting
dose. And the first two bars, the red and the
orange, are the panobinostat arm. So the first red
bar is panobinostat. The second orange bar is
bortezomib. And the blue bar is bortezomib in the
placebo arm.

So what it shows is that dose reduction
occurred earlier in the panobinostat arm, but it
also occurred on the placebo arm a bit later, but
they occurred. And as we can see, it's more
happening on cycle 4, 5, 6 or so.

DR. ARMSTRONG: Thank you. So as you said,
you're able to maintain the bortezomib dosing on
the placebo arm a little bit longer than on the
experimental arm. Thank you.

I have another question but a clarification
from the FDA first.

DR. MA: This is Lian Ma. I'm
pharmacometric reviewer, clinical pharmacology. We
have comments on the sponsor's relative dose
intensity analysis. And we wanted to point out to
our -- backup slide CP-8, please.

I'd like to point out that the sponsor's
analysis on the relative dose intensity was based on the patients who are remaining on this trial, that is the patients who dropped out or discontinued the treatment were excluded from the analysis. So the FDA conducted an independent analysis after including the patients who dropped out and discontinued treatment, and the results are showing on this slide.

The left plot with white bars is the panobinostat arm. The plot on the right with blue bars is the placebo arm -- is the control group arm. As we can see from these two plots, the proportion of patients having relative dose intensity higher than 90 percent, in the panobinostat arm, it as actually continuously declining over time instead of stabilizing as presented by the sponsor. And also, as compared to the control group, the magnitude of decline was actually greater over time. Therefore, we feel these results indicate that panobinostat dose 20 milligram was not well tolerated and also did worse in terms of retaining the intended dose as
compared to the control group.

DR. ARMSTRONG: Thank you. Briefly?

DR. CAPDEVILLE: I think we believe that it is more correct to look at the percentage of patients by cycle to just have a sense on what dose the patient received in a given cycle. Actually, when you do that to see how the patient evolved, the patient who made it to the second, to the third, to the fourth, to the fifth cycle, in fact there is a relatively constant proportion of patients, here 40 percent, who were able to receive high relative dose intensity. So this is something that we feel also presents an accurate way on how the dose was delivered.

Dr. Stewart, do you want to add a comment?

DR. ARMSTRONG: Briefly.

DR. STEWART: Very, very briefly. I just think as a clinician, I find this an irrelevant discussion, to be honest. What matters is depth of response, frequency of response, and duration of response for a 3-drug regimen versus a 2-drug regimen. Whether or not you stay on 1.3 of
bortezomib or 1, I don't find clinically relevant.

DR. ARMSTRONG: I have a question for Dr. Richardson. One of the issues that was brought up before is how applicable to this is the population in the United States. We've heard that there is a very small number of African American patients, so they're clearly underrepresented.

In looking at the eligibility criteria, patients were allowed to have 1 to 3 prior lines, and about half of the patients had only one prior therapy. And my question for you is, bortezomib and dexamethasone, today, is that the standard treatment you would give for second-line treatment in the United States? So I'm asking is the control arm a control arm that would be commonly used, that you would use commonly in your practice in the United States.

DR. RICHARDSON: Madam Chairman, I think that's an excellent question. In terms of what we tried to frame earlier was that upfront therapy now in myeloma in the United States is very different to what it was a few years ago. And the
combinations of lenalidomide and bortezomib have
been used early as part of induction,
consolidation, and maintenance.

So consequently, if you're on maintenance
lenalidomide, for example, and your disease
progresses, a proteasome inhibitor platform as a
salvage strategy would be very appropriate. But
what would be particularly attractive is to have
something with a novel mechanism of action that you
could then deploy in that same setting because
obviously the patient would have already been
exposed to both the combination of an
immunomodulator and proteasome inhibitor.

So this construct of relapse after first
line of therapy has changed over time, making
obviously some comparisons of would this have been
an appropriate strategy that we would have used in
the United States, difficult to frame exactly. But
suffice to say that it would be a very reasonable
option in the U.S. in 2014.

I did also want to make one point. In the
PANORAMA 2 study, we actually did have good African
American representation, and a number of patients were mine. I believe the number was 22 percent. And we saw encouraging response rates. Interestingly enough, it's too small a number, so one doesn't want to over-read this, but the response rate in our African American population of those 22 percent was higher than in the Caucasians, just as a point. But obviously, in the global trial it's a more difficult issue because other countries are represented to a greater degree.

DR. ARMSTRONG: Can you comment also -- I think I recall from the overall population that about 45 percent of the patients had previously had bortezomib and that in the U.S., it's more like 70 to 80 percent.

DR. RICHARDSON: Exactly.

DR. ARMSTRONG: In that population, would you be using bortezomib and dexamethasone as a second-line treatment?

DR. RICHARDSON: As long as they were bortezomib sensitive, that's correct. In fact there's, as you may know, been a recent approval
for retreatment with bortezomib by the agency on
the basis of the quality of responses to bortezomib
therapy after previous bortezomib exposure. The
response rate in that population was around
38 percent as I recall.

DR. ARMSTRONG: Thank you. Dr. Taylor?

DR. TAYLOR: Dr. Richardson, my question's
for you. In the experience with the U.S., you had
commented that although there were fewer numbers in
the whole trial, we had experienced fewer
mortality.

DR. RICHARDSON: Yes.

DR. TAYLOR: And I just wanted you comment
on, do you have an explanation for that? Was it
more vigilant monitoring? Was it your dosing that
you adjusted? What's your comment on why you did
so well?

DR. RICHARDSON: Dr. Taylor, I think one has
to be very realistic about cross-country
comparisons. And I know them very well from
running a large number international trials. In
fact, it's very clear that there are differences in
salvage strategies, the differences in supportive care. And so I think one has to really be very aware of those.

In terms of U.S. practices, as you know, I can say so as a British person, I think that U.S. medicine in cancer care is the best in the world. And I say that without bias as someone who trained in Britain and worked in Britain before I got the privilege of coming here. Now that being said, I think supportive care is very important.

The point I was trying to make is I think that in the context of once we establish what an individual patient is tolerating and benefitting from, we can then go forward. To Dr. Liebmann's point about the QOL, my simple point was, if you looked, you are quite right. There's no difference. But if you noted, there was no deterioration. The panobinostat, bortezomib, and dexa didn't deteriorate, it stabilized.

So I think, Dr. Taylor, that gets to your point, that with the appropriate dose reduction schedule changes as indicated, we can manage the
side-effect profile that much better. I think we have to be careful about saying that's why we did better. I'm not sure the trial necessarily tells us that. One of the clues in the trial is the phase 1 versus the phase 2 portion. And what you see is that when you go to the weekly bortezomib, for example, the tolerability improves, and the patients access there within patient controls. Also, there's no major evidence of loss of benefit in those patients.

Then finally, I think another point to share with you, because it's just become available, is that there was a national abstract to the meeting coming in December from actually British colleagues who looked at VTD plus panobinostat, subcutaneous bortezomib. And guess what? The rate of discontinuation, 55-patient trial, zero. So that's hot data. It literally just got on the website this morning, so I can share it with you.

I think there are a number of considerations, but to me, at least -- and it's I think reflected very nicely from the public
statements, not least from Diane Moran with her nursing background, with appropriate support of care management in the U.S. context, I would expect our therapeutic index to be that much more better. And my own experience with it in combination, for example, with lenalidomide, bortezomib, and dexamethasone, has so far in our prospective clinical trial been very favorable.

DR. ARMSTRONG: Dr. Fojo?

DR. FOJO: All right. I can't let this go. I'm surprised she did. The statement was made -- I looked at your face. As a clinician, what I'm interested is depth of response, frequency of response, and duration response, and that everything we're talking about is irrelevant. I strongly disagree. As a clinician, I think toxicity is an incredibly important thing to be talking about, which is why we're talking about it. I think it is trivial to be talking about all these quality of life measures that get better with time; sure, those who tolerate it longer, of course. And they're being measured longer, and
they get better. The bottom line, though, is if you look at the patient disposition, 129 patients, 33 and a half percent of the patients discontinued the drug, the combination, and only 17 percent of those who had -- 67 out of 387 -- discontinued the drug in the control arm. And if you add in those who withdrew consent, that's 40 percent.

So these might all be manageable, but in 30 to 40 percent of the patients, we couldn't manage it well enough so that they discontinued. So I think that we've had all the discussion we need to about the toxicity of this regimen. It's more toxic than the control arm. I mean, 25 percent grade 3-4 toxicity for diarrhea, I've never had grade 3-4 toxicity for diarrhea, thank God, but I don't want it. And a quarter of the patients have, and that is way too many. So then the question is not whether we have toxicity or not. We do. I think we're past that.

The other question, there were two things that Dr. Liebmann brought up, and he sort of didn't follow up on. One that you alluded to is, is this
a relevant population. So we were told by Barry Miller that the median -- age of diagnosis in the United States is 69. The median age in these patients was 63, and they'd had the disease already for 3 years, which means that the median age of diagnosis for these patients was 60.

We're talking about almost a decade difference here. And we all know tolerability has to do with age. So we're talking about a patient population that's far younger than the patient population in the United States that would get it. And if tolerability is a problem in this much younger patient population, what will it be in the older population? So I think that that's an important thing. You brought it up. You didn't pursue it, but I thought it was important.

Then the other thing that you brought up is are deaths a concern. And I'm not quite sure we've answered that. Death is important. I'm not quite sure that this combination is more likely to cause death than not. I don't think the data's there. That to me in the end was not that great a concern.
Then the last thing I think maybe as a committee we want to discuss is, is this combination effective. And I think -- we've certainly heaped a lot of stuff on the sponsor. But it clearly is a drug that in combination -- I mean, there's more near-CRs, there's more CRs. So I'm not quite sure that this is the combination for it, but clearly it's a drug that has activity in myeloma, and maybe we can as a committee also address that because we don't want to approve toxic therapies. We also don't want to miss approving therapies that might be effective as was alluded to by some of the speakers during the open session. But as far as I'm concerned, this is toxic, and we ought to just accept it and move beyond that.

DR. ARMSTRONG: Are there any other comments? Dr. Pazdur?

DR. PAZDUR: I'd just ask the sponsor to present any other randomized trials with this drug in myeloma that are ongoing.

DR. CAPDEVILLE: We have one trial that is ongoing that's our expanded treatment protocol. We
don't have another randomized study. And the expanded treatment protocol is ongoing in the U.S. And this is a study that allows for the use of subQ bortezomib. As we've heard, this is now the standard practice.

DR. ARMSTRONG: I'm sorry. What population is that in?

DR. CAPDEVILLE: It is in the same population as the phase 3 study here.

DR. ARMSTRONG: Any other discussion points?

DR. LEBWOHL: Just to Dr. Pazdur's point about whether there's another study. If you took this study and cut it in half, it would still be statistically significant. So I think that's one of the standards the FDA has used for the question of having more than one study. It is the largest study done for patients with relapsed multiple myeloma.

Also, just on Dr. Fojo's point --

DR. PAZDUR: That is not why I asked the question.

DR. LEBWOHL: Okay. I wasn't sure. But of
course, it would be statistically significant, as you know, if you cut it in half. So it's like the power of two studies.

The other point, Dr. Fojo, the patients were an average of 63 when they entered the trial, about 6 years younger than patients with the disease. The point is that this is the patient that entered clinical trials. It's an important point, and I think you just have to take that into account. This is the age of the people who come on to these trials. Thank you.

DR. ARMSTRONG: So this committee over the years has struggled with approvals when PFS is the only statistically significant endpoint. I think all of us consider overall survival a gold standard, but overall survival, particularly in a population that lives a fair bit of time after they get their experimental treatment, is often something that's difficult to use as an endpoint, although I think even the folks who presented here would say what they want is to live longer.

We'd all like a cure, but if you have to
live longer with your disease, then that's the second issue. And I think we struggle when we don't see an overall survival benefit and we do see a PFS benefit. And I think we've all heard as much as we want to hear about censoring and the issues about how reliable the PFS is. But nonetheless, I think we would agree that there is a PFS benefit with the addition of this agent.

But then, when you don't have a survival benefit, we generally look at something else. And what you want to see is the trend of everything else looking in favor of the agent, at least that's what I do. And so, is the response rate significantly better? Is the quality of life significantly better? Are patients being treated for a longer period of time? And in fact, not only are you not seeing that, but patients are treated on a shorter duration of treatment on the experimental arm here.

Then you look at the issue of -- we've talked about survival issues, but death on treatment and the rate of death on treatment, which
is -- in respect to the multiple causes of death on treatment, presumably if it's death related to disease, and the treatment arm is better, you should have fewer deaths related to disease. So this would argue that those are toxicity related deaths, and that's not an insignificant number. It's 8 percent of patients who had death on treatment.

The problem I see here is that there is a clear PFS benefit, but there is nothing else to hang our hat on in terms of the benefit for this. And we've struggled with PFS alone. So I guess I'd like to get the committee's comments on using PFS alone, particularly when may of the other parameters that we look at aren't favoring the experimental arm.

DR. PAZDUR: I think one of the reasons, as I mentioned before, that we brought this in is not is there a PFS effect. And we've approved other drugs not only in this disease, but in other diseases on PFS. So that's not the question.

We had a very extensive discussion -- for
example, with Avastin and breast cancer, which is not that different from this discussion that we're having here in a big sense -- of what is the magnitude of benefit because you have to put this ultimately in a risk/benefit analysis. What is the magnitude of benefit that would off-weigh this toxicity that you're seeing here?

That's the essential reason why we brought this to the committee; not is there a PFS advantage. What is the magnitude? And because of these censoring issues, there was a lack of clarity on our part of what that benefit is. And that's what we're trying to address here, and that's why I need to hear from the committee.

DR. ARMSTRONG: Any discussion? You never give us the easy questions. Dr. Liebmann?

DR. LIEBMANN: I agree with you completely, and that's why I wanted a clear answer about quality of life because I think that -- like you, I think that survival is a gold standard, and if I can't get survival, I'd like to see patients feeling better. And that didn't seem to be the
case here. And this is now getting into the
philosophy of approving drugs.

It would be nice if you could identify a
patient population that would derive the most
benefit and have the least risk. And we seem to
have one cut here being younger patients. I wonder
if another cut looking -- and you didn't present it
on a slide, but it's a table, figure 7.5 in the
packet that we got, that would suggest that
patients with poor cytogenetics seem to derive a
greater benefit than patients with normal
cytogenetics. So honestly, if there was some way
to say, gee, maybe this ought to be reserved for
younger patients with poor cytogenetics who would
be less likely to have toxicity.

I am concerned, as Dr. Fojo pointed out,
that the average patient diagnosed with myeloma is
in fact almost 10 years older than the average
patient diagnosed with myeloma on this trial
because, again, they would have been 60 when they
were diagnosed, not 63. And those are the patients
that could be harmed.
DR. CAPDEVILLE: I'd like to come back to two aspects in the description. The first is to reemphasize what we said about the fact that there is a long period where the patient treatment-free before there is a progression. If we could have the core slide that shows that again as a starting point. And after that, we have an illustration of this.

So the duration of treatment, as mentioned earlier, is roughly 5 months. And even though it's a little shorter than in the placebo arm, it remains in the range of the duration you would expect with the bortezomib backbone regimen. But with the PFS that we see, there is a longer period where the patient is without treatment before progressing, and this is estimated at 7.5 months here versus 3.9 months. And these data are represented graphically also on the next slide. And I will ask my statistical colleague to comment on the methodology if you want.

So the figure is coming.

DR. ARMSTRONG: I'm sorry. Could you bring
that slide back up? I'm sorry, before you move to
the next one. The reasons for delaying next
treatment can be because there's a benefit from the
treatment you've had. It can also be because you
need time to recover from the toxicities. And
thrombocytopenia, for example, you may not be able
to introduce a new treatment.

If you look at the total amount of time till
next treatment, it's 12 months on the experimental
arm and 10 months on the other arm. So I think
there are things happening during this period of
time that may not be beneficial for patients.

DR. CAPDEVILLE: But I will also come back
and address that point because we have to take into
account the durability of the responses, but I'll
come to that in a second.

If I may, this data, also illustrated
graphically here, this is with that methodology.
So here this is an attempt to represent the period
during which the patient is exposed to toxicity.
So this is the red part of each of the curve. You
have the panobinostat arm on the left; the placebo
on the right. And on the green, you have the period that is free of toxicity in the panobinostat arm and the same in blue on the placebo arm.

So it's really to emphasize that the patient has a longer period of treatment. Now, why is that? I think the main reason for that is probably the durability of the responses. And we talked about achieving a complete response, but in fact achieving a complete response matters, and I'd like, really, to show the data that supports that.

We have conducted a landmark analysis to see what is the impact of achieving a complete response versus a partial response just to have a sense on whether the death of response matters.

So this is coming. So here we have the patient with a landmark at 18 weeks, taking into account the time to response and also the need to have enough patients to make this kind of analysis. So this is a landmark analysis, but despite the limitation of any landmark analysis, there is a clear difference in achieving a complete or near-complete response. And this data in fact
confirms what has been published in other studies with other regimens. So the depth of response matters.

We looked at the same using the exploratory endpoint of the study that is responded by IMWG criteria, where there is a slightly different definition of what is a deep response, and we observed exactly the same results, and actually there is a slide for that.

David, do you want to add?

DR. LEBWOHL: Thank you, Dr. Capdeville. I'd just like to add to that.

You were raising the point of the appropriate reasons to approve a drug. I'd like to go back to the core slide from Dr. Stewart for relapsed disease, about how drugs have been approved. For all the drugs that have been approved in the relapsed setting, PFS has been the primary endpoint. In all these trials except the liposomal doxorubicin's trial, the control arm has been really a fairly weak control arm, dexamethasone, the benefit in these trials being
2.7 months, 3.9 months, 2.8 months.

So in these cases -- sorry. You don't have the trial, the slide yet. Let me show that to you again. So these are the approvals, bortezomib IV, lenalidomide plus dex, liposomal dox, and this is the data coming from the FDA briefing book, that the approval basis was 2.7 months, 3.9, 2.8 months. In only one case was there a survival advantage. You can see the p was less than .05, so it was very close. As I mentioned, in our trial, we did not power it to see survival advantage with the hazard ratio that's been seen, but there are fewer deaths on the active arm.

Now, an important point here -- so all of these were approved based on TPP. And I will ask Dr. Stewart to come up again to show what the effect of these new drugs seems to be for patients with myeloma.

DR. ARMSTRONG: We need to be quick here.

DR. LEBWOHL: Okay. The only thing to mention, it is not just PFS. We have complete responses that are enhanced. They're almost
doubled. As you know, these deep responses are very important to these patients, as well as disease overall response, and the trend, and survival. So all of the efficacy parameters, 3.9 months, the survival of 3 months, are quite consistent. Thank you. And Dr. Stewart?

DR. STEWART: I will be very brief, Chairman. I just wanted to point out that although the approvals for all of these drugs were on the basis for approximately 3 months time to progression advantage, they have revolutionized therapy for multiple myeloma both in terms of their use in earlier stages of disease, depth of response.

I did want to very briefly comment on Dr. Liebmann's point about treating younger high-risk patients, which is very astute. So I think that that is the population that physicians will steer their patients towards. However, as you well know, there are 75 year olds that are just as fit and healthy as 40 year olds, so putting some arbitrary age limit, I think that just doesn't work
DR. SHAH: Just one last comment if that's okay. So just addressing your question of saying what is the real benefit of these PFS events and does it really correlate overall survival, this slide I think says a lot to me because these are the drugs that over the last several years have been approved based on these PFS events. And globally what we see are these approvals or these drugs, based on these PFS events, have led to improvements in overall survival.

Several different centers have demonstrated this, that we do see significant benefits and overall improvements in overall survival for all patients based on these improvements that we see. So I think that this is clinically meaningful, and these do become additive and do impact patients' outcomes.

DR. ARMSTRONG: Thank you. Any further discussion on the panel?

(No response.)

DR. ARMSTRONG: If not, we will now begin
the voting process. We will be using an electronic voting system for the meeting. Once we begin the vote, the buttons will start flashing, the buttons on your microphone, and will continue to flash even after you've entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you 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. The DFO will read the vote from the screen into the record. Next, we will go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you wish to.

If there are no more questions, we'll proceed to the vote process. I'm sorry. Dr. Fojo?

DR. FOJO: Before you had asked for -- does this mean does the benefit of the combination that has been submitted outweigh the risk for patients?
Correct?

    DR. PAZDUR: If there are favorable risk/benefit.

    DR. FOJO: For this regimen? Okay.

    DR. ARMSTRONG: I'll read the question again. Given the benefit/risk profile of the addition of panobinostat to bortezomib and dexamethasone, does the benefit outweigh the risks for patients with relapsed multiple myeloma?

    So please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

    (Vote taken.)

    DR. BRIGGS: The vote is 2 yes, 5 no, zero abstentions.

    DR. ARMSTRONG: Everyone's voted. We're okay? All right.
If we would go around the room starting with you, Jane. And state your name, your vote, and any comments you have. You're non-voting. Correct.

DR. ZONES: I'm Jane Zones, and I voted no. I did not think it was clear that the benefit outweighed the risks. The reasons for that are the missing data, the lack of shown improvement in quality of life, and the toxicity of the added on new drug.

DR. ROTH: Bruce Roth. I voted no for similar reasons. And it's not that I don't think that there's not some potential biologic activity here because I think there is. This just may be the wrong combination or the wrong dose. And as evidence of that, the fact that the quality of life measures that go down in both arms initially and come back to baseline around the time that people get to phase 2 and get lower doses or a less aggressive schedule might indicate that that might be more tolerable to start with. And while I agree that in myeloma centers of excellence, the dose reductions in the majority of patients may be
undertaken appropriately, many of the patients treated will not be treated in centers of excellence. And maybe the more appropriate way to do this is to find the right dose first.

DR. FOJO: Tito Fojo, and I voted no. Dr. Pazdur has said on multiple occasions that the easy ones are not the ones that come here. That the ones that come here are difficult, and this was no exception. Actually, like most recent elections, I was 51 percent no and 49 percent yes. In fact, I almost voted yes because I hope the company continues to pursue it because I think this is a drug that likely has activity in this disease and could bring benefit to these patients, but not in this combination. So it's a no vote, but it's a yes for the drug and activity in the disease, and I'm hoping it's pursued.

DR. COLE: Bernard Cole. I voted yes. I'm sorry. I voted no. Oh, I'm sorry. I voted yes. (Laughter.)

DR. COLE: While the pivotal study has limitations, the PFS benefit to me seemed to be
sufficiently robust. It would also appear to have some possibility, at least in some patients, of translating to an overall survival benefit. While I have concerns about the toxicity of panobinostat, including the possibility of elevated treatment-related deaths, there's clear potential for benefit in a large proportion of patients in terms of PFS.

Given this and in consideration of the challenges in treating multiple myeloma, I was in favor of recommending approval really for the purpose of adding panobinostat to the relatively small arsenal of approved therapies available for use by physicians in treating patients with this difficult disease.

DR. ARMSTRONG: Deborah Armstrong, and I voted no. Like Dr. Fojo, this was a very difficult decision for me. I think this is a drug that has some activity, but progression-free survival alone, particularly when there are issues of missing data and a high rate of censoring, alone is of concern to me.
I think that this drug may be able to be better handled and the toxicities better managed in the U.S., but this study does not show us that. I was particularly concerned about the fact that patients on the experimental arm were treated for a shorter period of time, that the rate of discontinuation was higher and that the on-treatment death rate was also twice as much as it was for patients on the placebo arm.

I believe this also, as Dr. Fojo said, this is a drug that will have a role in the treatment of multiple myeloma, but potentially in a more narrow population of patients because if you can manage the toxicity, you can probably manage a lot of those other issues. But I was quite concerned about those issues in this particular study that was presented.

DR. TAYLOR: I'm Wayne Taylor. I voted yes. I think that panobinostat in this setting of relapsed and refractory myeloma, which is genetically complex in multiclonal diseases, it did show adequate PFS. I think the magnitude, because
of the nature of this challenging international study -- it was small. I think because of the nature of this subpopulation, I believe it was enough to show benefit over risk, and I think we'll see you back here some time.

DR. LIEBMANN: James Liebmann, and I voted no. And I voted no for all the reasons that we've already hear, and I'll echo everyone who said that, first, this was a very difficult decision because I do think that this probably have some activity in this disease and probably can be useful in this disease. But as presented in this trial, I think that the toxicity outweighed the marginal benefit in progression-free survival, which absolutely was there whether it's 2 months or 4 months, but it was there. So I also hope that the drug is not given up on.

Adjournment

DR. ARMSTRONG: I'd like to thank all the panel members. I think for all of us this was a difficult vote. We will now break for lunch. We'll reconvene in this room in one hour, at 1:00,
at which time we'll begin the open public hearing session. Panel members, please remember there should be no discussion of the meeting topic during lunch amongst yourselves or with any members of the audience. Thank you.

(Whereupon, at 11:56 a.m., the morning session was adjourned.)