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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH (CDER)

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Tuesday, April 12, 2011

Morning Session

8:00 a.m. to 12:00 p.m.

FDA White Oak Campus
Building 31, The Great Room
White Oak Conference Center
10903 New Hampshire Avenue
Silver Spring, Maryland

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P R O C E E D I N G S

(8:00 a.m.)

Call to Order and

Introduction of Committee Members

1 DR. WILSON: I'd like to call the meeting to
2 order and welcome all the members, FDA, and the
3 sponsors. And to start with, let's go around the
4 room. We'll start over here on the end with
5 Dr. Curt. If you could please state your name,
6 what your specialty is, and where you're from.
7
8

9 DR. CURT: Gregory Curt, medical oncology
10 and industry representative to ODAC.
11

12 DR. CHOYKE: Pete Choyke. I'm a radiologist
13 at the NCI.
14

15 DR. FOJO: Tito Fojo, medical oncologist,
16 Medicine Branch, National Cancer Institute.

17 DR. KELSEN: Dave Kelsen, medical oncology,
18 Sloan Kettering.

19 DR. LOGAN: Brent Logan, biostatistician,
20 Medical College of Wisconsin.

21 DR. GREM: Jean Grem, medical oncologist,
22 University of Nebraska Medical Center.

1 DR. SEKERES: Mikkael Sekeres, medical
2 oncologist, Cleveland Clinic.

3 DR. WILSON: Wyndham Wilson, medical
4 oncologist, NCI.

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

7 DR. FREEDMAN: Ralph Freedman, gynecologic
8 oncology, M.D. Anderson Cancer Center.

9 MR. EPPERLEIN: Jim Epperlein, FDA patient
10 representative for pancreatic cancer.

11 DR. ISON: Gwen Ison, medical officer, FDA.

12 DR. SNYDER: Kristen Snyder, medical
13 officer, FDA.

14 DR. MAHER: Ellen Maher, FDA.

15 DR. PAZDUR: Richard Pazdur, office
16 director.

17 DR. WILSON: Okay. Thank you. Welcome. We
18 will now have a conflict of interest statement
19 read.

20 **Conflict of Interest Statement**

21 DR. BRIGGS: The Food and Drug
22 Administration, FDA, is convening today's meeting

1 of the Oncologic Drugs Advisory Committee, ODAC,
2 under the authority of the Federal Advisory
3 Committee Act, FACA, of 1972.

4 With the exception of the industry
5 representative, all members and temporary voting
6 members of the committee are special government
7 employees, SGEs, or regular federal employees from
8 other agencies and are subject to federal conflict
9 of interest laws and regulations.

10 The following information on the status of
11 this committee's compliance with federal ethics and
12 conflict of interest laws, covered by, but not
13 limited to, those found at 18 USC Section 208 and
14 Section 712 of the Federal Food, Drug, and Cosmetic
15 Act, FD&C Act, is being provided to participants in
16 today's meeting and to the public.

17 FDA has determined that members and
18 temporary voting members of this committee are in
19 compliance with federal ethics and conflict of
20 interest laws. Under 18 USC Section 208, Congress
21 has authorized FDA to grant waivers to special
22 government employees and regular federal employees

1 who have potential financial conflicts when it is
2 determined that the agency's need for a particular
3 individual's services outweighs his or her
4 potential financial conflict of interest.

5 Under Section 712 of the FD&C Act, Congress
6 has authorized FDA to grant waivers to special
7 government employees and regular federal employees
8 with potential financial conflicts when necessary
9 to afford the committee essential expertise.

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

21 This morning's agenda involves discussion of
22 supplemental new drug application sNDA

1 022334/S-009, trade name Afinitor, everolimus,
2 tablets, application submitted by Novartis
3 Pharmaceuticals Corporation. The proposed
4 indication or use for this product is for the
5 treatment of patients with advanced neuroendocrine
6 tumors, NET, of gastrointestinal, lung, or
7 pancreatic origin.

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

19 With respect to FDA's invited industry
20 representative, we would like to disclose that
21 Dr. Gregory Curt is participating in this meeting
22 as a nonvoting industry representative, acting on

1 behalf of regulated industry. Dr. Curt's role at
2 this meeting is to represent industry in general
3 and not any particular company. Dr. Curt is an
4 employee of AstraZeneca.

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

16 Thank you, and good morning. I would like
17 to first remind everyone to please silence your
18 cell phones, if you have not already done so. I
19 would also like to identify the FDA press contact,
20 Erica Jefferson. If you are here and present,
21 please stand. Thank you.

22 DR. WILSON: For topics such as those being

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

10 In the spirit of the Federal Advisory
11 Committee Act and the Government in the Sunshine
12 Act, we ask that the advisory committee members
13 take care that their conversations about the topic
14 at hand take place in the open forum of the
15 meeting.

16 We are aware that members of the media are
17 anxious to speak with the FDA about these
18 proceedings. However, FDA will refrain from
19 discussing the details of this meeting with the
20 media until its conclusion. Also, the committee is
21 reminded to please refrain from discussing the
22 meeting topic during breaks or lunch. Thank you.

1 I also would like to, before the sponsor
2 meeting, read the following.

3 Both the Food and Drug Administration and
4 the public believe in a transparent process for
5 information-gathering and decision-making. To
6 assure such transparency at the advisory committee
7 meeting, FDA believes that it is important to
8 understand the context of an individual's
9 presentation.

10 For this reason, FDA encourages all
11 participants, including the sponsor's nonemployee
12 presenters, to advise the committee of any
13 financial relationships that they may have with the
14 firm at issue, such as consulting fees, travel
15 expenses, honoraria, and interests in the sponsor,
16 including equity interests and those based on the
17 outcome of the meeting.

18 Likewise, FDA encourages you, at the
19 beginning of your presentation, to advise the
20 committee if you do not have any such financial
21 relationships. If you choose not to address this
22 issue of financial relationships at the beginning

1 of your presentation, it will not preclude you from
2 speaking.

3 So with that, I would like to invite the
4 sponsor to begin their presentation.

5 **Sponsor Presentation - Lynne McGrath**

6 DR. MCGRATH: Mr. Chairman, committee
7 members, FDA and guests, good morning. My name is
8 Lynne McGrath, and I am the U.S. head of drug
9 regulatory affairs for Novartis Oncology. We are
10 here today to discuss the supplemental new drug
11 application for Afinitor for the treatment of
12 advanced neuroendocrine tumors of pancreatic
13 origin.

14 Afinitor is an mTOR inhibitor. It was
15 approved in the U.S. for the treatment of renal
16 cell carcinoma in 2009. Subsequently, it was
17 approved for the treatment of subependymal giant
18 cell astrocytomas, or SEGAs. Since approval, there
19 have been over 3,400 patient years of experience in
20 21 months of post-marketing surveillance.

21 Neuroendocrine tumors, or NETs, are rare
22 cancers with different biologic characteristics and

1 limited treatment options. Our development program
2 in NET tumors focused on two distinct tumor types:
3 advanced NET tumors of pancreatic origin and
4 carcinoid tumors, which are NET tumors of GI or
5 lung origin.

6 Each distinct tumor type was studied in a
7 large Phase III randomized clinical trial. The
8 benefits seen in these trials led us to seek an
9 indication for the treatment of patients with
10 advanced NET of pancreatic, gastrointestinal or
11 lung origin.

12 As you can see from this slide, the
13 indication we proposed in our briefing material to
14 ODAC has changed. Upon review of FDA's briefing
15 document, we recognized the difficulties in
16 interpreting the carcinoid data to support an
17 approval.

18 We, therefore, amended the indication to
19 focus our application solely on patients with
20 advanced neuroendocrine tumors of pancreatic
21 origin. We recognize the unmet need in carcinoid
22 patients and will continue to investigate therapies

1 that can benefit these patients. The presentation
2 today will be reflective of our changes in
3 indication and focus on our results in pancreatic
4 NET.

5 We've had multiple discussions with FDA. In
6 2006, the agency advised us that the natural
7 history and chemosensitivity of patients with
8 pancreatic NET and GI NET are different. They
9 recommended that we conduct a separate study in
10 each of these two distinct tumor types.

11 We followed FDA's advice and designed a
12 Phase III study in pancreatic neuroendocrine tumors
13 and a separate study in carcinoid tumors. The key
14 design features of these studies were agreed to by
15 the FDA. They included the primary efficacy
16 endpoint of progression-free survival. In
17 addition, agreement was reached on the patient
18 population, sample size, and the comparators.

19 During the course of the Phase III study in
20 advanced pancreatic NET, the protocol was amended.
21 The primary efficacy endpoint of PFS as assessed by
22 central review was changed to PFS as assessed by

1 investigator based on concerns of informative
2 censoring from the carcinoid trial. PFS by central
3 review became a key secondary endpoint. This was
4 done prior to any unblinding of the PFS data. Due
5 to this amendment, the special protocol assessment
6 is no longer in effect.

7 We submitted this supplemental NDA in
8 November 2010. The data in our application
9 included two studies in pancreatic NET patients.
10 Results of the pivotal Phase III study in
11 pancreatic NET met its primary endpoint.

12 These results were consistent across three
13 measures: the investigator, central, and
14 adjudicated review. The results demonstrated that
15 PFS was improved in the everolimus arm by more than
16 twofold that of the control arm. These data
17 support the indication that will be the focus of
18 our discussion today. The results of the carcinoid
19 study also showed patient benefit and were included
20 in the submission.

21 Based on these study results and in
22 recognition of the unmet need in these patients,

1 priority review was granted. The results of the
2 pivotal trial represent a clinically meaningful
3 benefit for patients with advanced pancreatic
4 neuroendocrine tumors.

5 Afinitor is an approved drug, and the safety
6 profile observed in the trials discussed today is
7 consistent with the approved label. Finally, we
8 believe that the data in pancreatic neuroendocrine
9 tumors demonstrate that everolimus fulfills an
10 unmet need in this population. Everolimus
11 represents an important therapeutic option in
12 patients with neuroendocrine tumors.

13 Now, I would like to introduce our
14 presenters for today. Dr. Larry Kvols from Moffitt
15 Cancer Center is a leading expert in the study of
16 neuroendocrine tumors. He will provide an overview
17 of pancreatic neuroendocrine tumors and discuss the
18 need for medical treatment in this disease.

19 Dr. David Lebwohl, development head of the
20 Afinitor program, will then present the efficacy
21 and safety results from the pivotal study in
22 pancreatic NET patients and discuss briefly the

1 carcinoid trial.

2 Finally, we will hear from Dr. James Yao,
3 who led the study steering committees. He's a
4 medical oncologist and deputy chair of the
5 Department of GI Oncology at M.D. Anderson Cancer
6 Center. He will provide a clinician's perspective
7 on treating patients with pancreatic NETs and how
8 Afinitor can be an important treatment option to
9 patients with pancreatic NETs, patients he treats
10 every day.

11 After the presentation, Dr. Lebwohl will
12 return to respond to committee questions. We have
13 several consultants with us to offer their
14 perspective.

15 I thank FDA and members of ODAC for your
16 efforts in reviewing this application. We look
17 forward to the committee discussion and
18 deliberations.

19 At this point, I would like to introduce Dr.
20 Kvols, who will describe the patients that are
21 subject of this application.

22 Dr. Kvols?

1 **Sponsor Presentation - Larry Kvols**

2 DR. KVOLS: Thank you, Dr. McGrath. My name
3 is Larry Kvols. I'm from the Moffitt Cancer Center
4 in Tampa, Florida. I would like to disclose that I
5 have received consultation fees and honoraria from
6 the sponsor, as well as reimbursement of travel and
7 accommodation expenses. I'm also an investigator
8 on everolimus clinical trials for pancreatic and
9 carcinoid tumors.

10 I'm a practicing oncologist and have been
11 treating patients with neuroendocrine tumors for
12 over 30 years. Today, I will provide some
13 background information on pancreatic neuroendocrine
14 tumors and highlight the differences between this
15 disease and carcinoid tumors. I will also review
16 the currently approved treatments for pancreatic
17 neuroendocrine tumors.

18 Pancreatic neuroendocrine tumors, also
19 called islet cell tumors, are rare tumors with an
20 annual incidence of approximately three per
21 million. Patients with advanced metastatic disease
22 often have symptoms associated with tumor bulk,

1 including pain and obstruction. Approximately
2 30 percent of pancreatic neuroendocrine tumors are
3 referred to as functional tumors because they
4 produce hormones that give rise to clinical
5 symptoms. The most common of these is gastrinoma,
6 where gastrin production causes reflux disease,
7 ulcers, and diarrhea. Octreotide LAR is only
8 approved for hormonal syndrome control in VIP-
9 producing pancreatic neuroendocrine tumors.

10 While there is a perception that pancreatic
11 neuroendocrine tumors represent an indolent
12 disease, this is likely related to the favorable
13 prognosis of patients with newly diagnosed local or
14 regionally advanced disease. Median overall
15 survival in this group is 69 to 100 months, as can
16 be seen on this slide, which describes median
17 survival by stage. However, in patients with
18 previously treated metastatic disease, the median
19 overall survival is only 17 months. This latter
20 group is similar to the subjects of the study that
21 will be presented to you today.

22 Treatment options for patients with

1 pancreatic neuroendocrine tumors are limited. In
2 part, as a result of the rarity of the disease,
3 there has been a paucity of large, well controlled,
4 randomized clinical trials to date. The only agent
5 approved for oncologic control of pancreatic
6 neuroendocrine tumors is streptozocin.

7 Streptozocin was approved nearly 30 years ago using
8 different efficacy standards, and its use today is
9 fairly limited because of toxicity and sporadic
10 availability. There is, therefore, a clear unmet
11 need for new effective therapies.

12 Now, I would like to highlight the
13 differences between two diseases included in the
14 broad category of neuroendocrine tumors. Although
15 both carcinoid tumors and pancreatic neuroendocrine
16 tumors arise from enterochromaffin cells, they are
17 biologically and genetically different.

18 Carcinoid tumors can be either functional or
19 nonfunctional. When functional, they release
20 serotonin, which can be detected in the urine as
21 5-HIAA. Serotonin is responsible for the carcinoid
22 syndrome characterized by flushing, diarrhea, and,

1 in some cases, cardiac complications.

2 Advanced carcinoid tumors are resistant to
3 most cytotoxic therapies, and the median overall
4 survival, as shown in the ECOG Study E1281, is
5 short, ranging from 15 to 24 months. There are no
6 approved agents for tumor control of carcinoid
7 tumors.

8 In summary, the key points to remember about
9 pancreatic neuroendocrine tumors, our discussion
10 today, are the following.

11 This is a rare disease, and median survival
12 in advanced metastatic disease is short. There are
13 very limited treatment options for these patients.
14 Streptozocin is approved, but its use is limited.
15 Therefore, effective new therapies are needed.
16 This has spurred interest in new targeted agents,
17 and one of the most rational targets in this
18 disease is inhibition of the mTOR pathway. mTOR,
19 shown in the middle of this pathway is a serine
20 threonine kinase, the central regulator of growth,
21 proliferation, cellular metabolism, and
22 angiogenesis. Disregulation of the mTOR pathway is

1 common in pancreatic neuroendocrine tumors.

2 Preclinical data shows activation of the
3 mTOR pathway induces tumor growth and stimulates
4 secretion of peptides and hormones. mTOR
5 inhibition, on the other hand, controls tumor
6 growth in neuroendocrine tumor models.

7 Based on these observations, there's a
8 strong scientific rationale for the development of
9 everolimus for the treatment of pancreatic
10 neuroendocrine tumors.

11 Thank you for your attention. And now I
12 would like to ask Dr. David Lebwohl to come to the
13 podium.

14 **Sponsor Presentation - David Lebwohl**

15 DR. LEBWOHL: Thank you, D. Kvoles. Good
16 morning. My name is David Lebwohl. I'm a medical
17 oncologist and the global development head for
18 Afinitor at Novartis Oncology. I will present the
19 efficacy and safety results for the Phase II and
20 III studies in pancreatic neuroendocrine tumors.

21 We conducted a comprehensive clinical
22 program in 570 patients with advanced pancreatic

1 NET. The Phase III trial is the largest ever
2 conducted in this population.

3 Study 24 randomized 410 patients with
4 advanced pancreatic NET. Its results are supported
5 by those from the open label Phase II Study 39,
6 which included 160 patients.

7 I would like to describe the results of the
8 Phase III study in pancreatic NET. The study was a
9 double-blind, randomized trial. Enrolled patients
10 had advanced pancreatic NET. A key requirement in
11 the trial was that all patients had radiologic
12 progression due to their disease within 12 months
13 of being randomized.

14 Patients were stratified by WHO performance
15 status and whether or not they had received prior
16 cytotoxic chemotherapy. The primary endpoint was
17 progression-free survival, and secondary endpoints
18 included objective response rate, overall survival,
19 changes in biomarkers, and safety. The study was
20 well conducted, with oversight from an IDMC and a
21 steering committee. We discussed and agreed to
22 key design elements with the FDA, which included

1 the PFS endpoint and the patient population.

2 Here we show the study conduct. 410
3 patients were randomized to either everolimus plus
4 best supportive care or placebo plus best
5 supportive care. Crossover was allowed from
6 placebo to open label everolimus at the time of
7 disease progression. 148 patients crossed over
8 from the placebo arm, which represents more than 90
9 percent of the patients who discontinued due to
10 disease progression on placebo. Of note,
11 progression was assessed until new antitumor
12 therapy was started.

13 The primary analysis was amended from
14 progression-free survival based on central review
15 to progression-free survival based on investigator
16 assessment. This was triggered by informatory
17 censoring observed in the carcinoid trial, a trial
18 with a similar design. It was done prior to any
19 unblinding of PFS data in this study. A blinded
20 adjudication was implemented prior to the final
21 analysis to review potential discrepancies between
22 the investigator and central radiology review.

1 Patient baseline characteristics were well
2 balanced between the two arms. Almost all patients
3 had distant metastatic disease at study entry and
4 more than 90 percent had liver metastases. The
5 patients enrolled in the study were heavily
6 pretreated.

7 A few things I'd like to call to your
8 attention. Twenty-three percent of the patients
9 received prior embolization. Approximately 50
10 percent of patients had received prior somatostatin
11 analogs before entering the trial. Fifty percent
12 of the patients on each arm had received systemic
13 cytotoxic chemotherapy with a variety of different
14 agents.

15 Treatment disposition is shown here. The
16 most common reason for discontinuation was disease
17 progression, which was much higher in the placebo
18 arm, 80 percent in the placebo arm and 44 percent
19 in the everolimus arm.

20 More patients in the everolimus arm
21 discontinued due to adverse events, 17 percent
22 compared to 3 percent in the placebo arm. It's

1 important to note the median exposure was 38 weeks
2 in the everolimus arm and 16 weeks in the placebo
3 arm, which may explain, in part, the higher rate of
4 discontinuation due to adverse events in the
5 everolimus arm.

6 The progression-free survival results were
7 consistent across data sources. P-values were less
8 than .001. The original primary analysis,
9 according to central review, demonstrated a hazard
10 ratio of 0.38. The amended primary analysis by
11 investigator assessment yielded a hazard ratio of
12 0.35. You can see the magnitude of improvement in
13 median progression-free survival is large. The
14 difference in medians ranged from six to eight
15 months. These results demonstrate a statistically
16 significant and clinically meaningful improvement
17 in progression-free survival.

18 Patients treated with everolimus experienced
19 a 65 percent reduction in the risk of disease
20 progression compared with placebo. This translated
21 into a 6.4-month improvement in the median,
22 increasing from 4.6 months for placebo patients to

1 11 months for everolimus patients. This was a 2.4-
2 fold increase in progression-free survival. In
3 addition, 34 percent of the patients in the
4 everolimus arm were estimated to be progression-
5 free at 18 months. This represents a durable
6 benefit.

7 Importantly, the progression-free benefit
8 was consistent across all subgroups, including
9 prior chemotherapy, WHO performance status, and
10 age, with hazard ratios ranging from 0.2 to 0.5.
11 These subgroup analyses were preplanned and they
12 demonstrate a homogenous treatment effect.

13 In addition to the survival data noted in
14 our briefing book, we also have some more mature
15 data we'd like to share today. While we recognize
16 that the FDA may not have had time to review these
17 data, they agree that this may be helpful for
18 today's discussion.

19 Here you can see the updated overall
20 survival data, which show that the median overall
21 survival has not yet been reached. In the
22 everolimus arm, now after three years, the hazard

1 ratio of 0.89 favors everolimus.

2 The favorable survival results in the
3 placebo patients may be due to the crossover. Of
4 note, 73 percent of placebo patients crossed over
5 to everolimus at disease progression. The benefit
6 of everolimus is evident in the PFS results of
7 those patients who crossed over. PFS in this group
8 is greater than 11 months.

9 The objective response rate by RECIST was 5
10 percent in the everolimus arm and 2 percent in the
11 placebo arm. This waterfall plot demonstrates the
12 benefit of everolimus in terms of tumor shrinkage.
13 This shows the best percentage change from baseline
14 in the size of target lesions in the individual
15 patients on the study. An upward line reflects
16 growth and a downward line reflects shrinkage.

17 By the investigator assessment, tumor
18 shrinkage was observed in 64 percent of the
19 everolimus patients versus 21 percent of the
20 patients in the placebo arm. This is an important
21 treatment effect from everolimus. These results
22 were similar when plotted based on adjudicated

1 review or by central review.

2 Given that pancreatic NET can produce
3 hormones responsible for clinical symptoms, we also
4 looked at biochemical tumor markers. Among
5 patients with elevated gastrin at study entry,
6 treatment with everolimus resulted in a rapid and
7 sustained decrease in gastrin levels. In contrast,
8 patients in the placebo arm had stable or increased
9 levels. This is consistent with the antitumor
10 effect seen by the waterfall analysis. Similar
11 effects were seen in glucagon levels among patients
12 with elevated glucagon at baseline.

13 Now, let's discuss the safety profile of
14 everolimus in PNET. The most common adverse events
15 were consistent with our prior clinical experience
16 with everolimus. They included stomatitis,
17 infections, rash and diarrhea. It is important
18 here to consider that patients in the everolimus
19 arm were treated on study 2.4-fold longer than
20 patients in the placebo arm. In most cases, the
21 incidence of these common adverse events were
22 higher in the everolimus arm, but the incidence of

1 grade 3 and 4 adverse events was relatively low.
2 These events were generally manageable and
3 reversible.

4 Fifty-nine percent of the patients on the
5 everolimus arm and 28 percent of the patients on
6 the placebo arm required dose modifications. In
7 most cases, this was a temporary dose interruption
8 rather than a dose reduction. Despite dose
9 modifications, the delivered dose intensity
10 remained close to the planned dose intensity of
11 10 milligrams per day.

12 This slide shows deaths that occurred on
13 study treatment or within 28 days of study
14 treatment discontinuation. There were 12 deaths on
15 the everolimus arm compared with four deaths on the
16 placebo arm. This, in the balance, may be due, in
17 part, to the much longer duration of treatment on
18 the everolimus arm. Five deaths on the everolimus
19 arm were due to disease progression and seven were
20 attributed to adverse events.

21 The adverse events leading to death are
22 commonly seen in patients with advanced NET. In

1 three patients, disease progression was also
2 indicated at the cause of death by the
3 investigator. One single case was considered by
4 investigators to be related to study drug. In this
5 case, the patient developed acute respiratory
6 distress syndrome.

7 Before providing an overall summary of the
8 data for everolimus in pancreatic NET, I will
9 briefly review the results of the Phase II study in
10 pancreatic NET. This open label trial enrolled 160
11 patients with advanced pancreatic net who had
12 demonstrated disease progression during or after
13 chemotherapy. Patients were enrolled into one of
14 two strata based on their previous treatment with
15 octreotide. Patients in stratum 1 had not been
16 treated with octreotide within the previous
17 60 days. Patients in stratum 2 had shown
18 progression of disease on octreotide.

19 The primary endpoint was objective response
20 rate by RECIST in stratum 1. Secondary endpoints
21 included objective response rate in stratum 2 and
22 PFS, response duration, overall survival, safety

1 and pharmacokinetics in both strata. Baseline
2 characteristics in Study 39 are shown here. Fifty-
3 eight percent of the patients were WHO-0 in stratum
4 1 and 71 percent in stratum 2. Overall, patient
5 and tumor characteristics are similar to the
6 Phase III study.

7 The treatment disposition is shown here. The
8 most common reason for discontinuation was disease
9 progression in both strata. Thirteen percent of
10 the patients discontinued due to adverse events in
11 stratum 1 and 24 percent in stratum 2.

12 Objective response rate by central review
13 was 10 percent in stratum 1 and 4 percent in
14 stratum 2. Analysis of progression-free survival
15 demonstrated a median of 9.7 months in stratum 1
16 and 16.7 months in stratum 2. In addition,
17 31 percent and 46 percent of patients were
18 estimated to be progression-free at 18 months.

19 The most common grade 3/4 adverse events
20 suspected to be drug-related are summarized on this
21 slide. The most common event in stratum 1 was
22 asthenia and stratum 2 was thrombocytopenia. The

1 safety was consistent with the findings from the
2 Phase III trial.

3 We have shown you today the results of a
4 large international Phase III trial including more
5 than 400 patients. In this trial, patients
6 receiving everolimus experienced a 65 percent
7 reduction in the risk of disease progression
8 compared with patients on placebo. This translates
9 into a 6.4-month improvement in median progression-
10 free survival. These results are statistically
11 significant and clinically meaningful. Results are
12 consistent across supportive and sensitivity
13 analyses.

14 We also see a similar benefit in all
15 subgroups examined. While there's no significant
16 benefit in overall survival, it is important to
17 note that the PFS benefit is further supported by
18 the shrinkage of tumors and decreases in
19 biomarkers. Adverse events in the Phase II and III
20 studies are consistent with previous clinical
21 experience and are addressed in the current label.

22 As discussed earlier, we are no longer

1 seeking an indication for patients with carcinoid
2 tumors. Nevertheless, the carcinoid Phase III
3 trial provides valuable data on the safety of
4 everolimus. I will now describe the results of
5 this study.

6 The study was a double-blind, randomized
7 trial in which everolimus was added to octreotide
8 versus octreotide plus placebo. Patients enrolled
9 in this trial had advanced carcinoid tumors. They
10 had a history of symptoms of flushing and/or
11 diarrhea related to those tumors. Octreotide was
12 the appropriate treatment for managing the
13 symptoms. There is now emerging data that
14 octreotide also has antitumor activity in this
15 setting.

16 The primary endpoint was progression-free
17 survival. Key secondary endpoints were overall
18 response rate, overall survival, and safety. The
19 study was overseen by an IDMC and a steering
20 committee.

21 The study conduct is shown here. In this
22 study, 429 patients were randomized to either

1 everolimus plus depot octreotide or placebo plus
2 depot octreotide. A 123 patients crossed over to
3 receive open label everolimus, representing
4 84 percent of those who discontinued due to disease
5 progression on placebo.

6 This trial included two interim analyses.
7 Following the second interim analysis, assessment
8 of the primary PFS endpoint was amended from
9 central to adjudicated review. Although this is a
10 randomized trial, there were imbalances in several
11 important prognostic factors at baseline that
12 favored the placebo arm. These include WHO
13 performance status, tumor histology, and lung as a
14 primary site. The most important of these factors,
15 patients with WHO performance status 1 or 2, was
16 45 percent in the everolimus arm and 34 percent in
17 the placebo arm.

18 Similar to the PNET study, more patients in
19 the placebo arm discontinued due to disease
20 progression, 69 percent in the placebo arm and
21 44 percent in the everolimus arm. More patients in
22 the everolimus arm discontinued due to adverse

1 events.

2 It is important to understand the actions
3 taken at the time of the second interim analysis.
4 At that time, the IDMC reviewed the data shown here
5 and found a hazard ratio of 0.90 by central review.
6 This crossed the boundary for futility. In
7 contrast the investigator assessment yielded a
8 hazard ratio of 0.69 in favor of everolimus. This
9 crossed the boundary for efficacy. If accepted,
10 the trial would have been stopped for overwhelming
11 efficacy.

12 This posed an unusual and difficult
13 challenge for the IDMC. They approached the chair
14 of the steering committee and the global head of
15 development at Novartis to discuss the next steps.
16 Here is what they decided.

17 First, they recognized the importance of
18 determining which result most closely reflected the
19 actual treatment effect. An expert independent
20 adjudication committee reviewed the cases with
21 discrepant results. When the investigator and
22 central review did not agree, the adjudicators

1 determined which of the two assessments better
2 represented reality for that patient.

3 The other important observation at the
4 interim analysis was the loss of events in the
5 central assessment; 220 events were identified by
6 investigators, but only 174 events were identified
7 by the central review. To better understand this
8 issue, an inverse probability of censoring weights
9 or IPCW analysis was planned to determine if
10 informative censoring affected the central review.

11 Now, let's review the final results of the
12 carcinoid trial. The progression-free survival
13 result based on central review did not meet the
14 primary endpoint. There was a hazard ratio of
15 0.93. This result was affected by informative
16 censoring. In contrast, the analysis according to
17 the investigator demonstrated a hazard ratio of
18 0.78 and a p-value of .018. The increase in median
19 progression-free survival was 3.4 months. The
20 independent adjudication committee supported the
21 investigators' results. It demonstrated a hazard
22 ratio of 0.77 and an improvement in median

1 progression-free survival of 5.1 months.

2 With respect to overall survival, the
3 unadjusted analysis shows a hazard ratio of 1.17.
4 You will recall that there were imbalances in
5 baseline characteristics that favored placebo.
6 When we adjust the overall survival based on the
7 pre-specified baseline prognostic factors using a
8 Cox model, the hazard ratio for survival is 1.05,
9 showing no difference in survival between the two
10 arms.

11 Dr. Kvols described the short survival in
12 carcinoid patients from 15 months for previously
13 treated patients to 24 months for treatment naïve
14 patients. It's important to note that the survival
15 shown here appears favorable in both arms relative
16 to these historical controls.

17 Now, I will review the safety profile of
18 everolimus in the study. The pattern of treatment-
19 related adverse events in the carcinoid trial were
20 similar to that in the pancreatic NET trial and in
21 our renal cell cancer experience. However, the
22 rate of events in the placebo arm was higher than

1 we have previously seen. This likely reflects the
2 severity of the underlying disease in this
3 carcinoid patients.

4 The most common adverse events were
5 stomatitis, infections, and diarrhea. The majority
6 of adverse events were grade 1 and 2. In general,
7 the frequency of adverse events was higher in the
8 everolimus arm than in the placebo arm.

9 There were 18 deaths on the everolimus arm
10 compared with 11 deaths on the placebo arm. Six
11 deaths on the everolimus arm were due to disease
12 progression and 12 were attributed to adverse
13 events. None of the on-treatment deaths were
14 considered by investigators to be due to study
15 drug. The imbalance in deaths here may be due, in
16 part, to the poor prognosis of patients who had
17 been randomized to the everolimus arm.

18 We recognize that the central review results
19 are challenging. The PFS endpoint based on the
20 original primary analysis was not met. However,
21 informative censoring affected the outcome of this
22 analysis. Everolimus delayed the progression of

1 disease. This was shown by the investigators'
2 assessment and was supported by the results of the
3 independent adjudication.

4 No benefit was observed in overall survival.
5 Finally, the safety profile was consistent with the
6 previous experience with everolimus, as addressed
7 in the current label.

8 Although we are not seeking an indication
9 for carcinoid patients today, we are committed to
10 continuing to study new therapies for these
11 patients. We learned important lessons from the
12 carcinoid trial. Future studies could utilize
13 real-time central review to minimize informative
14 censoring and will be stratified by important
15 baseline prognostic factors.

16 In summary, we've shown you today that
17 everolimus provides an important benefit for
18 patients with pancreatic neuroendocrine tumors.
19 Now, I'd like to invite Dr. Yao to the podium to
20 provide a clinician's perspective on the use of
21 everolimus for patients with pancreatic NET.

22 Dr. Yao?

1 **Sponsor Presentation - James Yao**

2 DR. YAO: Thank you, Dr. Lebwohl. My name
3 is James Yao. I'm a medical oncologist at the
4 University of Texas, M.D. Anderson Cancer Center in
5 Houston. I have one of the largest neuroendocrine
6 practices in the country, log approximately 2,000
7 visits with neuroendocrine patients each year.
8 I also chaired the study steering committee and
9 have served as a paid consultant for Novartis. I
10 am not being paid for my role here today.

11 I know firsthand the frustration of having
12 non-effective therapy to offer these patients. I
13 would like to share with you my clinician's
14 perspective on the design and results of the
15 pancreatic neuroendocrine study that Dr. Lebwohl
16 presented and the importance of these results for
17 patients with pancreatic neuroendocrine tumors.

18 Recent data suggests the mTOR pathway is
19 critical in the development and malignant
20 progression of pancreatic neuroendocrine tumors.
21 First, hereditary cancer syndromes associated with
22 constitutive mTOR activation, such as tuberous

1 sclerosis and neurofibromatosis, have been directly
2 linked to the development of pancreatic
3 neuroendocrine tumors. More recently, in a
4 manuscript published in the March issue of Science,
5 a study using a whole genome sequencing approach
6 also identified somatic mutations in pancreatic
7 neuroendocrine tumors.

8 Additionally, on a protein level, low
9 expression of inhibitory proteins in the pathway,
10 such as TSC2 and PTEN, are linked to shorter
11 progression-free survival and overall survival
12 among patients with pancreatic neuroendocrine
13 tumors. Therefore, the treatment of pancreatic
14 neuroendocrine tumors with everolimus is based on
15 strong scientific rationale.

16 Most of the patients who come to see me know
17 they have an incurable illness. They come to my
18 practice looking for options. They want to control
19 tumor growth, any secretive hormones, if present,
20 and they want to delay the onset of other disease-
21 related symptoms. They also want to prolong their
22 life while remaining active and productive.

1 To date, only streptozocin is approved in
2 this setting. It is an alkylating agent that was
3 approved almost three decades ago based on response
4 rate using criteria that would not be accepted
5 today. It is generally given in combination with
6 5-FU or doxorubicin, and this regimen is cumbersome
7 and toxic. Major toxicities include nausea,
8 vomiting, diarrhea, diabetes, heart failure, liver
9 dysfunction, and renal failure. These toxicities
10 associated with the streptozocin-based regimens can
11 certainly keep the patients from being active and
12 productive.

13 As I discussed earlier, there is strong
14 scientific rationale to study everolimus in
15 patients with pancreatic neuroendocrine tumors.
16 The Phase III study that Dr. Lebwohl summarized is
17 the largest well controlled clinical trial in this
18 rare disease. It was an international study that
19 included recognized centers of excellence and had a
20 clearly defined eligible patient population.

21 Assessment of the primary endpoint was based
22 on established criteria and were rigorously

1 applied. The study results were consistent in
2 multiple sensitivity analyses. Results were also
3 consistent with a Phase II study conducted at M.D.
4 Anderson, as well as a large supportive multicenter
5 Phase II study in patients with progression after
6 prior chemotherapy.

7 So what do the data mean to my patients with
8 pancreatic neuroendocrine tumors? The study showed
9 a clinically meaningful 6.4 months improvement in
10 median progression-free survival. Six months in
11 this indication is a substantial portion of the
12 patient's expected life span. Additionally, this
13 represents a 2.4-fold improvement compared to
14 placebo. The benefit with everolimus was
15 consistent across all patient subgroups. Not only
16 is tumor shrinkage observed in a majority of the
17 patients, but rapid and sustained decreases in
18 tumor secreted hormones which are associated with
19 disease symptoms were also observed.

20 Everolimus was shown to have an acceptable
21 safety profile. Consistent with previous clinical
22 experience, adverse events were generally

1 manageable and reversible.

2 As mentioned by Dr. Kvols earlier,
3 pancreatic neuroendocrine tumor is a rare disease
4 with a lack of effective available therapy and a
5 paucity of contemporary research. For the past 30
6 years, there have been no significant advances in
7 the treatment of this disease. These patients need
8 new treatment options.

9 In the Phase III pancreatic neuroendocrine
10 tumor study, everolimus demonstrated statistically
11 significant and clinically relevant improvement in
12 progression-free survival. I feel privileged to
13 share these results with you today, which I think
14 will enable evidenced-based therapy.

15 As a clinician treating patients with
16 advanced neuroendocrine tumors, I strongly believe
17 that everolimus provides the important and
18 effective treatment option for patients with this
19 devastating malignancy.

20 Thank you.

21 DR. WILSON: Okay. Thank you. That now
22 concludes the sponsor's presentation. I'd like to

1 invite FDA up to the podium.

2 **FDA Presentation - Kristen Snyder**

3 DR. SNYDER: Good morning. My name is
4 Kristen Snyder. And this morning I will be
5 presenting the review of efficacy of everolimus in
6 the treatment of patients with advanced
7 neuroendocrine tumors of gastrointestinal, lung,
8 and pancreatic origin. The review team is included
9 on this slide.

10 Everolimus was originally indicated in
11 advanced renal cell carcinoma after failure of
12 treatment with sunitinib or sorafenib and
13 subsequently approved under the accelerated
14 approval process for patients with subependymal
15 giant cell astrocytoma.

16 The applicant's initial proposed indication
17 was for everolimus in the treatment of patients
18 with advanced neuroendocrine tumors of
19 gastrointestinal, lung, or pancreatic origin.
20 Eight days ago, on April 4th, 2011, the applicant
21 communicated their plan to revise the indication to
22 everolimus in the treatment of patients with

1 advanced neuroendocrine tumors of pancreatic
2 origin. This is a priority review.

3 Neuroendocrine tumors represent a variety of
4 neoplasms which can originate from a number of
5 neuroendocrine cell types, and, therefore, possess
6 a range of biological activities. According to
7 surveillance epidemiology and end results data from
8 2004, the estimated age-adjusted annual incidence
9 of neuroendocrine neoplasms is 5.25 per 100,000
10 adults in the United States. This application
11 studied patients with well differentiated
12 neuroendocrine carcinoma.

13 These diseases can be classified as
14 nonfunctional or functional, causing characteristic
15 clinical symptoms as a result of their secreted
16 peptide. The patients entering these trials have
17 neuroendocrine carcinomas which are slow-growing,
18 with low mitotic activity, but can metastasize to
19 lymph nodes and liver and, less commonly, to the
20 bone, lung and CNS.

21 A recent review of SEER database estimated
22 the 10-year survival for regional pancreatic

1 neuroendocrine tumors to be 46 percent, with a
2 median survival of 111 months. The 10-year
3 survival for those with metastatic disease is 11
4 percent, with a median survival of 27 months.
5 For regional carcinoid tumors, the SEER database
6 estimated 10-year survival as 48 percent, with a
7 median survival of 111 months. The 10-year
8 survival for those with metastatic disease is 17
9 percent, with a median survival of 33 months. Over
10 90 percent of patients entered on the applicant's
11 submitted trials had metastatic disease.

12 Currently, only two products are approved
13 for use in the treatment of neuroendocrine tumors,
14 streptozocin and octreotide. Streptozocin is
15 indicated in the treatment of metastatic islet cell
16 carcinoma of the pancreas and is limited to
17 patients with symptomatic or progressive metastatic
18 disease, while octreotide is indicated in the
19 symptomatic treatment of patients with metastatic
20 carcinoid tumors, where it suppresses or inhibits
21 the severe diarrhea and flushing episodes
22 associated with the disease.

1 Studies were not designed to show an effect
2 on the size, rate of growth, or development of
3 metastases. Liver-directed therapy and systemic
4 therapies have been administered, but neither have
5 been associated with improved survival.

6 In January of 2006, an end-of-Phase II
7 meeting was held. It was determined that the
8 applicant would proceed with development with two
9 Phase III trials in the treatment of neuroendocrine
10 tumors. One trial was designed limited to patients
11 with pancreatic neuroendocrine tumors, while the
12 other included patients whose carcinoid tumors had
13 originated at non-pancreatic sites, such as the
14 cecum or lung.

15 Special protocol assessment agreements were
16 reached in August and September of 2007. The
17 primary endpoint of both trials was progression-
18 free survival by an independent review committee.
19 In the special protocol assessment approval letter
20 for the PNET trial, the FDA stated progression-free
21 survival is acceptable in principle as the primary
22 endpoint for this study. As previously

1 communicated, whether a given PFS result will
2 support approval is a review issue.

3 The PNET trial was to show improvement in
4 progression-free survival from six months, control,
5 to nine months, while the carcinoid trial was to
6 demonstrate progression-free survival improvement
7 from nine months to 13.5 months.

8 In October of 2009, the applicant and FDA
9 met to discuss the results of the second interim
10 analysis of the carcinoid trial. This interim
11 analysis occurred at 60 percent of progression-free
12 survival events and demonstrated unprecedented
13 results.

14 Discordant evaluations of progression-free
15 survival by the local investigator and the central
16 review found the initial primary endpoint, as
17 assessed by the central review, or IRC, crossed the
18 futility boundary, suggesting the trial be stopped
19 for futility, while the primary endpoint, as
20 assessed by the investigator, or INV, crossed the
21 efficacy boundary, suggesting the trial be stopped
22 for efficacy. This diametrically opposed advice to

1 stop for futility and to stop for efficacy, given
2 the same set of scans, is unprecedented in the
3 setting of an application coming to the Office of
4 Oncology Drug Products.

5 The applicant subsequently made the
6 following amendments to their protocols: changing
7 the primary endpoint of the ongoing study, C2324,
8 the PNET trial, to PFS, as determined by the local
9 investigator. The primary endpoint of Study C2325,
10 the carcinoid trial, was changed to PFS, as
11 determined by a central adjudication committee, or
12 IAC. I will discuss this committee on the next
13 slides. In addition, the final analysis cutoff was
14 changed from 287 progression-free survival events
15 to the calendar date of April 2nd, 2010.

16 These amendments made to each of the
17 protocols invalidated the special protocols
18 assessments, but more so they highlight a major
19 problem with the conduct of these trials and the
20 reliability of the results.

21 As part of these amendments, an adjudicated
22 review of the primary endpoints was conducted for

1 both trials. The investigator and central review
2 could differ in the type of event, in the timing of
3 that event, or in both. Differences in the timing
4 of an event is very straightforward. An example is
5 a patient who has progressive disease by
6 investigator review at cycle 6, but had progressive
7 disease by central review at cycle 2. Remember
8 that the investigator and the central reviewer may
9 be looking at different target lesions.

10 The investigator and the central reviewer
11 can also differ in the type of event. An example
12 is a patient who has progressive disease by the
13 investigator review at cycle 6 and is discontinued
14 from study drug. No further imaging is done. When
15 the central reviewer examines these scans, no
16 progressive disease is detected and instead this
17 patient is censored at the final analysis.

18 The following diagram shows how the
19 adjudication committee handled these differences
20 between investigator and central review. The
21 adjudication committee only considered
22 discordances, in which there was a difference in

1 the type of event or a difference in the timing of
2 an event of greater than or equal to 126 days.
3 This is equal to the time between one and a half
4 tumor assessments or 18 weeks. It is unclear from
5 the applicant's submission package why 126 days was
6 chosen as the time point for determining
7 discordance. However, I would like to remind you
8 that discordant cases were selected post hoc.

9 Here, the middle set of boxes shows a case
10 in which there was a discordance between the
11 investigator and the independent central reviewer.
12 However, because this case did not fulfill the
13 adjudication criteria, in the adjudicated analysis
14 dataset, it will be represented by the central
15 reviewer's analysis.

16 The right boxes represent an event in which
17 there was a discordance in the type of event or a
18 difference in the timing of an event or greater
19 than or equal to 126 days. Here, the adjudication
20 committee would review the scans and any relevant
21 medical history and choose either the investigator
22 or the central reviewer's assessment of the scans.

1 The full adjudicated analysis dataset is,
2 therefore, the combination of results from the
3 adjudication committee's dataset for discordant
4 cases and results of the central review dataset for
5 non-discordant cases.

6 As you can see by the discussion in the
7 previous slides, the primary issues with this
8 application include the following. In C2324, the
9 PNET trial, substantial discordance between the
10 investigator and the central reviews exist.

11 Although the primary endpoint of progression-free
12 survival reached statistical significance, the
13 benefit-risk ratio of everolimus in this disease
14 will need to be weighed carefully.

15 In C2325, the carcinoid trial, the primary
16 endpoint of PFS by adjudication committee did not
17 reach statistical significance. Here, too, there
18 was a substantial rate of discordance between the
19 investigator and central reviews, involving a
20 greater percentage of patients. In addition, the
21 interim analysis of overall survival at 43 percent
22 of events favors placebo by seven months, with a

1 hazard ratio of 1.22. The benefit-risk ratio in
2 this trial must also be questioned.

3 Two trials were included in this submission.
4 Trial C2324 enrolled patients with unresectable or
5 metastatic biopsy-proven pancreatic neuroendocrine
6 tumors. This trial will be referred to as the PNET
7 trial.

8 Patients were stratified by prior
9 chemotherapy and WHO performance status and
10 randomized one-to-one to everolimus 10 milligrams
11 by mouth daily plus best supportive care or
12 identical placebo plus best supportive care. Tumor
13 assessments were to occur every 12 weeks, that is,
14 every three months. The amended primary endpoint
15 was PFS as determined by investigator. Secondary
16 endpoints included overall survival, response rate,
17 and duration of response. Patients randomized to
18 the placebo arm had the option to cross over to
19 open label everolimus after documented progressive
20 disease, and 73 percent of placebo patients did
21 cross over.

22 Key eligibility criteria for the PNET trial

1 included unresectable or metastatic PNET of low or
2 intermediate grade and disease progression within
3 12 months prior to entry.

4 I will now discuss the efficacy results of
5 the PNET trial. The majority of patients in the
6 PNET trial were Caucasian. Baseline demographics
7 were similar between arms. Patients on both arms
8 of the PNET trial were well balanced regarding
9 their median time since diagnosis and prior
10 therapy. Note that while the median time from
11 diagnosis was two to three years, this could be as
12 long as 24 years. Here, chemotherapy included
13 cytotoxic, targeted and immunotherapy.

14 In the PNET trial, nearly all patients had
15 involvement of the pancreas as their primary site,
16 which was expected given the inclusion criteria.
17 The liver was involved in over 90 percent of
18 patients on both arms of the trial. Disease
19 characteristics for both arms were well balanced.

20 In the PNET trial, there were increased
21 numbers of patients with adverse events in the
22 everolimus arm and increased numbers of patients

1 with progressive disease in the placebo arm. In
2 this completed trial, the pre-specified primary
3 endpoint of progression-free survival by central
4 review showed a hazard ratio of 0.38 and conferred
5 an eight-month prolongation in median progression-
6 free survival. The applicant's amended primary
7 endpoint of PFS by local investigator demonstrated
8 a 6.4-month prolongation in median progression-free
9 survival.

10 Cases in which there was a discordance
11 between the investigator and the central review
12 were also adjudicated in the PNET trial. Again,
13 the hazard ratio was similar and all p-values are
14 statistically significant.

15 This slide shows the discordant cases
16 between the investigator and central review and the
17 adjudicated cases of each arm of the PNET trial.
18 Forty-four percent of placebo patients and
19 38 percent of everolimus patients had discordance
20 between the investigator and central reviews. Of
21 those 168 patients, 133 were adjudicated; that is,
22 there was a difference in the type of PFS event or

1 a difference in the timing of a PFS event of at
2 least 126 days in 133 patients.

3 In the PNET trial, slightly more patients on
4 the placebo arm had a discordance. Of both
5 everolimus and placebo discordances, the majority
6 were in the type of progression-free survival event
7 reported. We must first acknowledge the predicted
8 occurrence of discordances in radiologic
9 assessments between local and independent
10 reviewers. However, these discordances should be
11 limited.

12 There were few partial responses in the PNET
13 trial and no complete responses were seen. This
14 curve shows an interim analysis of overall survival
15 and represents only 20 percent of overall survival
16 events. The median survival was not reached for
17 either treatment group at the time of data cutoff.

18 No statistical significance in overall
19 survival for everolimus therapy relative to placebo
20 was seen. Overall survival may be influenced by
21 the 73 percent of patients randomized to placebo
22 who crossed over.

1 The applicant has subsequently submitted two
2 additional unplanned overall survival updates to
3 the PNET trial. These results have already been
4 discussed by the applicant. Dr. Ison will later
5 discuss the numbers of on-treatment death in her
6 review of safety.

7 I would like to remind you that the
8 carcinoid trial, C2325, is a highly problematic
9 trial. Although the applicant communicated their
10 plan to remove the indication of advanced
11 neuroendocrine tumors of gastrointestinal and lung
12 origin, their submission includes both the PNET and
13 carcinoid trials.

14 These trials enrolled patients with similar
15 tumor types, advanced stages of disease, patient
16 population, adverse event profiles, and both trials
17 identified similar difficulties in radiologic
18 review. Further, the findings at the second
19 interim analysis of the carcinoid trial resulted in
20 a change to the primary endpoint of the PNET trial.
21 Thus, the carcinoid trial provides important
22 information regarding clinical trial conduct and,

1 therefore, a review of this trial will be disclosed
2 today.

3 The major issue of the carcinoid trial
4 involves the results of the second interim analysis
5 performed at 60 percent of progression-free
6 survival events, as determined by central review.
7 Here, the pre-specified primary endpoint of PFS by
8 central review crossed the futility boundary,
9 suggesting that the trial should stop for futility,
10 while the investigator determined PFS endpoint
11 crossed the efficacy boundary, suggesting that the
12 trial should stop for efficacy. This is
13 unprecedented and calls into question the
14 reliability of the results of this trial.

15 Trial C2325 enrolled patients with
16 unresectable or metastatic biopsy-proven carcinoid
17 tumor with measurable disease and a history of
18 carcinoid syndrome. C2325 will be referred to as
19 the carcinoid trial. Patients were randomized one-
20 to-one to everolimus 10 milligrams by mouth daily
21 plus octreotide or to identical placebo plus
22 octreotide. The pre-specified primary endpoint of

1 progression-free survival by central review was
2 amended to PFS by adjudication committee after the
3 highly discordant results seen in the second
4 interim analysis of the study.

5 Secondary endpoints included response rate,
6 duration of response, and overall survival. Fifty-
7 eight percent of placebo patients crossed over to
8 everolimus treatment upon investigator-determined
9 progression.

10 Compared to the PNET trial, the key
11 eligibility criteria for the carcinoid trial were
12 identical, with the exceptions of including
13 unresectable or metastatic carcinoid tumor of low
14 or intermediate grade and the requirement that
15 patients have a history of diarrhea, flushing, or
16 both. However, these symptoms were not required at
17 the time of trial entry.

18 The statistical analysis plan for the
19 carcinoid trial included a plan sample size of 287
20 progression-free survival events to detect a hazard
21 ratio of 0.67. Censoring rules were employed for
22 PFS events of progressive disease or death

1 following two or more missing assessments; that is,
2 patients who had no tumor assessments over a six-
3 month period of time were censored at the last
4 adequate tumor assessment prior to the missing
5 scans. This is unusual and is due to the long
6 interval between assessments in this trial.

7 Sensitivity analyses were also conducted.

8 I will now discuss results of the carcinoid
9 trial. Notable discrepancies in baseline
10 demographic status exists on the carcinoid trial,
11 where the distribution of male and female patients
12 and performance status of zero vary between arms.

13 There were more females in the everolimus
14 arm and females tend to have a slightly better
15 prognosis than male patients with carcinoid tumors.
16 More patients had a performance status of zero in
17 the placebo arm. However, if the number of
18 patients with a performance status of zero to 1 is
19 considered, the numbers of patients are similar.

20 Median time since diagnosis was well
21 balanced. Note, in some patients, the time since
22 diagnosis was as long as 38 years. This slide also

1 shows an imbalance in the number of patients who
2 received prior chemotherapy. Here, chemotherapy
3 includes both systemic therapy and chemotherapy
4 used as a component of chemoembolization.

5 In the carcinoid trial, more patients had a
6 tumor originated in the lung in the everolimus arm,
7 which in patients with metastatic disease portends
8 a worse prognosis compared to those with distant
9 metastatic disease whose tumor originated in the
10 intestine, cecum, or thymus. Over 90 percent of
11 both arms had liver involvement.

12 Patients differed in the number of organs
13 involved, where more patients in the everolimus arm
14 had four or more organs involved with tumor. These
15 values are derived from the investigator-determined
16 sites of target and non-target lesions. However,
17 this imbalance is not present if the sites of
18 target and non-target lesions chosen by the central
19 radiology review are used.

20 In the carcinoid trial, there was a greater
21 number of patients with adverse events and death
22 due to adverse event on the everolimus arm, while a

1 greater number of patients on the placebo arm had
2 progressive disease. In the carcinoid trial, over
3 half of the cases were discordant between the
4 investigator and central radiology reviews.
5 Discordance was greater in the placebo arm,
6 occurring in 55 percent of placebo patients. Of
7 the 223 cases with discordance, 169 were
8 adjudicated.

9 The majority of the discordant cases in the
10 carcinoid trial were due to discordance in the type
11 of event.

12 This is an example of discordance by PFS
13 type. The central review results are listed as
14 rows, while the investigator results are listed as
15 columns. If we look down the column at
16 investigator-determined progression disease in the
17 placebo arm, 96 patients were thought to have
18 progressive disease by the investigator. Among
19 those 96 patients, however, 67, that is, 70 percent
20 of placebo patients were not considered to have
21 progressive disease by the central radiology
22 review, and those patients were instead censored.

1 Given the toxicity profile of everolimus therapy,
2 this raises concerns about the introduction of bias
3 in evaluating progression by the investigator.

4 Looking at investigator-determined
5 progression compared to central review for both
6 arms, we see censoring by central review occurred
7 in 67 patients in the placebo arm and 40 patients
8 in the everolimus arm.

9 The amended primary endpoint for the
10 carcinoid trial was progression-free survival by
11 adjudication committee. A five-month prolongation
12 in median progression-free survival, as determined
13 by the adjudication committee, was seen. The
14 applicant's pre-specified primary PFS endpoint was
15 progression-free survival, as determined by central
16 review. Here, you can see the central review, or
17 IRC, prolongation in median progression-free
18 survival of one month. The difference in PFS
19 between arms varies widely, calling its reliability
20 into question. As in the PNET trial, patients in
21 the carcinoid trial had few responses to treatment
22 and no complete responses were seen.

1 Of note, the applicant has subsequently
2 submitted two additional unplanned overall survival
3 updates. Results are similar; thus, I will only
4 discuss the applicant's planned overall survival
5 interim analysis which occurred at the time of the
6 final analysis of PFS, seen here.

7 This curve shows the interim analysis of
8 overall survival at the time of the final analysis
9 of PFS. At this time point, 43 percent of events
10 had occurred. No statistical significance in
11 overall survival for everolimus therapy relative to
12 placebo was seen. However, after the first 16
13 months, overall survival favors the placebo arm.
14 Fifty-eight percent of patients receiving placebo
15 crossed over to open label everolimus plus
16 octreotide.

17 In the applicant's submission package, they
18 attempt to explain this poor survival in everolimus
19 patients by citing imbalances in baseline
20 prognostic factors, as well as crossover of placebo
21 patients. However, this hazard ratio of 1.22 may
22 represent up to a 22 percent greater risk of death

1 in patients receiving everolimus.

2 The chance of observing this decrement in
3 survival due to random error only is 10 percent.
4 These results are worrisome when taking into
5 account the imbalances of death on treatment.
6 These imbalances will be discussed further in the
7 safety analysis by Dr. Ison.

8 **FDA Presentation - Gwynn Ison**

9 DR. ISON: My name is Gwynn Ison, and I will
10 be presenting the results of the safety review of
11 this application.

12 The safety database includes the three
13 trials shown here. Two trials were conducted in
14 patients with pancreatic neuroendocrine tumors, and
15 one was primarily in patients with neuroendocrine
16 tumors of gastrointestinal origin. The safety
17 database is comprised of 858 patients. The safety
18 review has been divided into events occurring
19 during the double-blind portions of each study and
20 events occurring during the open label portions.

21 For the purposes of this presentation, I
22 will focus on the results from the double-blind

1 portions of both studies. So this excludes adverse
2 events from patients on placebo who may have
3 crossed over to everolimus during the open label
4 phase.

5 This slide shows the exposure information
6 for everolimus or placebo in the double-blind phase
7 of both studies reported in weeks. In the PNET
8 study, exposure to everolimus was more than twice
9 that of placebo. In the carcinoid study, there was
10 no difference in exposure between everolimus and
11 placebo, suggesting that patients on the everolimus
12 arm did not have an increase in the time on study
13 drug or an increase in the time to progression.

14 Shown here are the dose delays and
15 reductions in both trials. More than 60 percent of
16 patients on the everolimus arms in both studies
17 underwent a dose delay or reduction. Of note, in
18 the everolimus arm, it was more common for patients
19 to have multiple dose delays and reductions rather
20 than a single delay or reduction. This speaks to
21 the toxicity of everolimus in this patient
22 population.

1 Here is a summary of the major safety
2 categories for both studies. A primary difference
3 between these trials is that patients on the
4 carcinoid study received octreotide in addition to
5 everolimus or placebo.

6 There were generally more adverse events in
7 the placebo arm of the carcinoid trial compared
8 with the placebo arm of the PNET trial. While the
9 patients on the placebo arm of the carcinoid trial
10 did receive octreotide, as you will see in a
11 moment, most of the adverse events in either arm of
12 the carcinoid trial were not among the commonly
13 described side effects of octreotide. Note that in
14 both trials, there was a high percentage of grade 3
15 to 4 adverse events, even in the placebo patients.
16 This speaks to the severity of the patients'
17 underlying illness.

18 I will begin by discussing the safety
19 results from the PNET study.

20 All deaths and discontinuations due to
21 adverse events are depicted on this slide. There
22 were 12 deaths on everolimus and five on placebo

1 during the double-blind portion of the study.
2 Seven everolimus deaths were due to adverse event
3 and five were due to disease progression. On the
4 placebo arm, there was one death due to AE and four
5 deaths due to disease progression. In addition,
6 there were 41 AE-related discontinuations on the
7 everolimus arm compared with 12 on the placebo arm.

8 Shown here is a breakdown of the adverse
9 event-related deaths on each arm of the PNET trial.
10 There was no predominant cause of death in the
11 everolimus patients. The death on the placebo arm
12 was due to a pulmonary embolus. There were also
13 two additional deaths in patients who crossed over
14 to everolimus from placebo during the open label
15 phase of the study. These deaths were due to
16 complications from hypoglycemia and sudden death.

17 Grade 3 to 4 adverse events in at least
18 5 percent of patients are shown here. Sixty-two
19 percent of patients receiving everolimus had a
20 grade 3 or 4 event; however, 40 percent of patients
21 on placebo also experienced a grade 3 or 4 event.
22 The most notable of these, which did occur more

1 frequently in the everolimus arm, included anemia,
2 hyperglycemia, and stomatitis, all of which have
3 been described in association with everolimus.

4 Grade 1 through 4 AEs in greater than or
5 equal to 30 percent of patients are shown here.
6 Stomatitis was seen in almost three-quarters of
7 patients on the everolimus arm, although it was
8 also seen in about 20 percent of patients on
9 placebo. Rash, diarrhea, fatigue, edema, abdominal
10 pain, and nausea were also fairly common, more so
11 in the everolimus patients.

12 Moving on to the carcinoid study. Patients
13 on both arms received octreotide in addition to
14 either placebo or everolimus, and the dose was 30
15 milligrams by IM injection every 28 days.

16 Investigators were allowed to adjust the octreotide
17 dose in order to treat carcinoid symptoms according
18 to their usual practice.

19 The common side effects of octreotide are
20 depicted here. As I mentioned earlier, it is
21 notable that these side effects do not adequately
22 explain the higher incidence of adverse events seen

1 in the placebo arm of this trial when compared to
2 the PNET trial.

3 On the carcinoid trial, there were 19 deaths
4 during double-blind therapy on the everolimus arm,
5 12 due to adverse event and seven due to disease
6 progression. On placebo, there were a total of 12
7 deaths, five due to adverse event and seven due to
8 disease progression. Sixty-one patients
9 discontinued everolimus due to an adverse event,
10 while 44 patients on placebo discontinued due to an
11 AE.

12 I will also point out that there were more
13 AE-related discontinuations in this study than in
14 the PNET study. For example, in the placebo arm of
15 the PNET study, there were 12 discontinuations due
16 to an adverse event compared with 44 on this trial.
17 When the specific adverse events leading to
18 discontinuation are examined, this does not appear
19 to be related to the use of octreotide.

20 Here is a breakdown of the specific adverse
21 events leading to death on each arm of the
22 carcinoid trial. There were 12 deaths on

1 everolimus and five on placebo. It is again
2 worthwhile to mention the higher number of placebo
3 deaths on this trial compared with the PNET trial,
4 including three placebo deaths due to hepatic
5 failure. Hepatic failure was thought to be due to
6 progressive disease, but was reported as an adverse
7 event.

8 Grade 3 to 4 AEs in more than 5 percent of
9 patients are listed here. Three-quarters of
10 patients in the everolimus arm had a grade 3 or 4
11 adverse event. However, one-half of placebo
12 patients also had a grade 3 or 4 adverse event.
13 This speaks to the severity of the underlying
14 disease in this study population.

15 Severe diarrhea was almost twice as common
16 on everolimus despite octreotide. Hypokalemia,
17 fatigue, abdominal pain, and hyperglycemia were
18 also among the common severe AEs in this trial.
19 Abdominal pain was the only specific AE that
20 occurred more frequently in the placebo patients.

21 Grade 1 through 4 AEs in greater than or
22 equal to 30 percent of patients are summarized

1 here. As in the PNET trial, stomatitis was the
2 most common AE in the everolimus patients,
3 occurring in two-thirds of them. The development
4 of stomatitis in patients on everolimus could have
5 led to unblinding of the trial. Other AEs included
6 diarrhea, fatigue, and rash.

7 As mentioned earlier, you will note that
8 patients in the placebo arm of this trial had an
9 overall higher incidence of adverse events than in
10 the PNET trial. However, it is also notable that
11 adverse events such as diarrhea and nausea, which
12 can be associated with carcinoid tumors as part of
13 the carcinoid syndrome, still occurred more
14 commonly in the everolimus patients, suggesting
15 that everolimus may have made these symptoms worse.

16 I'd like to now briefly address three
17 adverse events of interest in this application:
18 pneumonitis, opportunistic infections, and renal
19 failure.

20 In both studies, cases of pneumonitis were
21 identified in three ways, by adverse event reports,
22 by chest CTs done every 12 weeks, and infrequently

1 by information captured on bronchoscopies. I will
2 first talk about the incidence of pneumonitis in
3 terms of adverse events. This will be followed by
4 a discussion of the detection of pneumonitis on
5 imaging.

6 We found that the number of patients in the
7 PNET and carcinoid studies who were reported to
8 have the adverse event pneumonitis was
9 10.8 percent. For a frame of reference, in
10 patients with renal cell cancer treated with
11 everolimus, the overall incidence of pneumonitis
12 was reported to be 14 percent, while grade 3 events
13 occurred in 4 percent of those patients, and there
14 were no grade 4 events.

15 We then examined the adverse event
16 pneumonitis further to see if we could identify any
17 risk factors for the development of pneumonitis.
18 Note that the median duration of pneumonitis was
19 calculated to be 59.5 days, but this is based on
20 information available in only 54 of the 103
21 reported adverse events.

22 There were many events that seemed to have

1 much longer durations, but that had no definitive
2 end date recorded. Therefore, the real median
3 duration for pneumonitis is likely to be longer
4 than 59.5 days.

5 The median age for pneumonitis was 61 years.
6 Fourteen percent of patients with pneumonitis were
7 Asian, while only 8 percent of the total population
8 in both trials was Asian. There was no difference
9 in incidence between males and females. Fifty-
10 eight patients of the 93 were on 10 milligrams of
11 everolimus or placebo at the time of onset of
12 pneumonitis, meaning that 35 patients were already
13 on a reduced dose at the time of onset.

14 We were surprised to find almost 6 percent
15 of all patients at baseline, as well as
16 14.2 percent of patients on placebo, were reported
17 to have pneumonitis by imaging. Between the two
18 studies, there were 135 patients reported to have
19 pneumonitis on imaging, and the numbers were
20 increased in the everolimus patients compared with
21 placebo. Among these 135 patients with imaging
22 changes, pneumonitis was reported as an adverse

1 event in only 39 of them. This indicates that
2 imaging overestimates the incidence of clinical
3 pneumonitis.

4 Since everolimus is immunosuppressive, we
5 looked at opportunistic infections to see if there
6 was a higher incidence of certain infections
7 diagnosed in patients treated with everolimus
8 compared with placebo. We were able to identify
9 the following infections.

10 In the PNET study, there was one case of
11 hepatitis B reactivation, which led to hepatic
12 failure and death. There were also three cases of
13 mycobacterial infection in the PNET study, all in
14 everolimus patients. There was one case of
15 invasive aspergillus in each of the studies, both
16 in everolimus patients. Thus, there is a small,
17 but increased risk of opportunistic infections in
18 patients receiving everolimus, including those with
19 prior exposure to hepatitis. Therefore, patients
20 should be followed closely for these potential
21 infections.

22 Finally, we noted an imbalance in the number

1 of cases of grade 3 to 4 renal failure in both
2 studies, particularly in the carcinoid study. So
3 we investigated this further. We found that many
4 cases were related to dehydration in patients with
5 stomatitis or diarrhea or were due to multi-organ
6 failure.

7 In conclusion, in the PNET study, the median
8 PFS improvement ranged from six to eight months in
9 the everolimus arm. The hazard ratio was
10 consistent despite the various assessments of PFS.
11 The safety profile in the PNET study was in line
12 with the known toxicity of everolimus, although
13 there were seven deaths due to adverse event on
14 everolimus in the PNET study compared with only one
15 on placebo. Therefore, the improvement in PFS
16 afforded by everolimus should be considered in
17 light of the prognosis in this indolent disease.

18 Unlike the PNET study, the carcinoid study
19 results revealed inconsistent hazard ratios with
20 the various assessments of PFS. Of greater concern
21 is that an interim analysis of overall survival
22 favored the placebo arm.

1 Although the safety profile in the carcinoid
2 study was consistent with the toxicity profile of
3 everolimus, adverse events, in general, were
4 reported more frequently in the carcinoid study
5 compared with the PNET study.

6 There were 12 deaths attributable to adverse
7 event in the everolimus arm compared with five on
8 the placebo arm of this trial. The uncertainty
9 about the effect of everolimus on PFS should be
10 considered in light of the prognosis in this
11 indolent disease.

12 DR. WILSON: Okay. I would like to thank
13 the FDA and sponsors for their presentations.
14 We're now going to take a 15-minute break. Let's
15 meet back here at 9:45. And may I remind members
16 of the committee to please not discuss this
17 application. Thank you.

18 (Whereupon, a recess was taken.)

19 **Questions to Presenters**

20 DR. WILSON: So let's go ahead and reconvene
21 the meeting, and I think we'll start out with
22 questions to the sponsors and the FDA. So we will

1 keep track of the people who want to speak and we
2 will keep a list here. But let me start with a
3 couple of questions to the sponsor.

4 My first question is, what constituted best
5 supportive care? Were somatostatins allowed or
6 were any other -- if the sponsor could please
7 address that, and address that if there were,
8 whether or not there were major differences in the
9 types of supportive care between the two arms.

10 DR. LEBWOHL: Yes, thank you, Mr. Chairman.
11 The best supportive care in this study did include
12 somatostatin analogs. About 40 percent, in a
13 balanced way, of the patients in the trial received
14 somatostatin in the trial. All agents that were
15 allowed included everything except antitumor
16 agents, known antitumor agents.

17 DR. WILSON: So maybe you could comment on
18 the fact that one of the studies that you showed
19 was everolimus alone versus one with somatostatin,
20 where there was a significant prolongation.

21 So are we possibly seeing an enhancement of
22 the effect of everolimus in terms of synergy with

1 the somatostatin?

2 DR. LEBWOHL: Let me show you the results
3 of -- in the pancreatic NET trial, the patients who
4 did or did not receive concomitant somatostatin
5 analogs, it is shown here. Patients who did not
6 receive somatostatin analogs had a hazard ratio of
7 0.34. Patients who did receive them had a hazard
8 ratio of 0.43.

9 To your point, there was a somewhat better
10 progression-free survival, absolute progression-
11 free survival, in the group of patients that
12 received concomitant somatostatin analogs, as you
13 see here, placebo arm 4.5 to 5, 10 to 13. Of
14 course, this is not a randomized comparison. So to
15 judge the effect of somatostatin analogs is not
16 possible here.

17 DR. WILSON: And my second question regards
18 the on-study criteria. The on-study criteria
19 required that patients have progressive disease
20 within six months, and I think that one of the
21 questions that comes up with a more indolent
22 disease such as this, and keeping in mind I think

1 there is a clear signal that the everolimus arm has
2 more side effects than the placebo arm.

3 So I would like to understand why the median
4 time to progression for the patients that came on
5 study was 1.7 months in both arms, and yet the
6 progression-free survival for the placebo arms was
7 4.6 months. Hence, there seemed to be an over-call
8 among patients that came on study, because I don't
9 understand why suddenly the tumor would slow down.

10 DR. LEBWOHL: Let me try to make that clear.
11 The 1.7 months is the period from when progression
12 had been noted until they entered the trial and
13 were randomized. We do not and did not look for
14 the period in which they had progressed previously;
15 in other words, over what period did that
16 progression occur before their progression, which
17 was required for entry to the trial.

18 DR. WILSON: I'm sorry. Could you say that
19 one more time? I thought that that was the time
20 between -- oh, that was the time between
21 progression and when they entered on the study.

22 DR. LEBWOHL: Exactly.

1 DR. WILSON: Okay. Thank you.

2 I would like to recognize Dr. Curt.

3 DR. CURT: First, I'd like to congratulate
4 the sponsor on undertaking such well designed
5 studies in rare diseases. But I'd like to get a
6 point of clarification.

7 In the agency's presentation, we heard that
8 the magnitude of improvement in PFS should be
9 considered in the context of the overall clinical
10 benefit in this indolent disease. But I got from
11 the sponsor's presentation the idea that the
12 patients that were selected for study here had
13 anything but an indolent prognosis. So maybe that
14 question should go to the sponsor.

15 DR. LEBWOHL: Thank you, Dr. Curt. I think
16 it is very important here to realize this is not an
17 indolent disease. As Dr. Kvols mentioned, the
18 recognition of this as being indolent are the
19 patients with more regional or local disease that
20 he showed who do live a very long time. Looking
21 specifically at the patients who come onto our
22 trial, I want to show you some of their

1 characteristics.

2 More than 70 percent of these patients had
3 two or more organs involved with metastatic
4 lesions. Over 90 percent had liver metastases.
5 Many of the patients had lung and bone metastases.

6 The figure that Dr. Kvols gave was
7 17 months. The FDA gave an expected survival from
8 the time of initial diagnosis of 27 months. These
9 numbers are actually fairly compatible. Of course,
10 these patients had progressed and had other
11 treatments for their metastatic disease before
12 coming onto this trial. Those therapies are shown
13 here. More than 20 percent had embolization,
14 localized embolization. They had a variety of very
15 toxic chemotherapy, shown here, doxorubicin,
16 fluorouracil platinum, many of which do not have a
17 defined role in this disease.

18 Now, what was their experience on the trial?
19 Their experience on the trial is that they
20 progressed in four months, four and a half months,
21 after coming into the trial. I think by any
22 measure of a disease, this is not indolence. These

1 patients have a short survival. They have a very
2 short period to progression.

3 I'd like to ask Dr. Haller to put this into
4 perspective from the clinician's point of view.

5 DR. HALLER: Thank you. Dr. Lebowhl.

6 Thank you. I'm Dan Haller. I'm a medical
7 oncologist at the University of Pennsylvania, and
8 I've been seeing neuroendocrine tumors for
9 35 years. I think I'd like to underscore -- first
10 of all, I'm being paid as a consultant, as is my
11 housing and travel being reimbursed.

12 I'd like to underscore what you've heard
13 this morning, is that, unfortunately, many people
14 have the misperception that these tumors are
15 indolent. But frequently, the data includes
16 patients with completely localized or regional
17 disease, which weights the long survival toward the
18 direction of indolence. The patients we're talking
19 about today are at the end of that period of time.
20 As Dr. Lebowhl pointed out, they progressed about
21 four months after they were assigned to placebo.

22 When you look at that, we call that

1 sometimes a treatment holiday, which means you can
2 pay me now or you can pay me later, and you can
3 just start the drug four months later. Well, if
4 that's a treatment holiday, it's not very long, is
5 it? So I would say that it's pretty irrelevant.

6 I think one of the big points that David
7 just showed you is that, unfortunately, most
8 patients are subjected to drugs that are not well
9 studied, not approved, ineffective, and highly
10 toxic. And so I think we all look to the day when
11 we take care of patients who already have effective
12 drugs that keeps them off bad treatments for
13 prolonged periods of time.

14 DR. WILSON: I would like to recognize
15 Dr. Kelsen.

16 DR. KELSEN: Thank you. Could you look at
17 table 31 of the sponsor's presentation? It's also
18 one of your slides.

19 You were concerned in the Study 25 about a
20 potential imbalance between the experimental arm
21 and the placebo arm for carcinoid tumors. In this
22 analysis, the entrance criteria were well

1 differentiated, low or intermediate grade
2 pancreatic neuroendocrine tumors.

3 What is shown on this slide is well
4 differentiated or moderately differentiated. I'm
5 wondering if there wasn't any central pathology
6 review. How do you know that you didn't have more
7 low grade, well differentiated, good prognosis
8 patients in the experimental arm and not in the
9 placebo arm?

10 DR. LEBWOHL: First, in terms of the
11 differentiated status, this was determined by the
12 investigator. To show you that, though, the
13 prognostic factors were worse in the everolimus
14 arm, you need to look at the survival curve. There
15 was a pre-planned Cox model that was performed.
16 First, to show you the core slide for the survival
17 in the carcinoid trial.

18 DR. KELSEN: Could I clarify my question,
19 Mr. Chairman? I'm actually asking -- I don't think
20 it was the investigator who determined if it was
21 well differentiated, intermediate grade or low
22 grade. I suspect it was his pathologist. I gather

1 this is a multicenter trial. I wonder if you could
2 first maybe show us how many patients were admitted
3 from each center in the study. That will give us
4 an idea as to how many pathologists were looking at
5 these slides on these uncommon patients.

6 DR. LEBWOHL: I'd ask Dr. Yao to address
7 that. Please come up. And then I'll show you the
8 survival after that.

9 DR. YAO: I think some of this is due to
10 changes in terminology. The neuroendocrine tumor
11 had previously been defined by grade, as well as by
12 differentiation.

13 At the time the trial started, the AJCC's
14 grading system has not been publicly acknowledged
15 or available. At the current time, both low and
16 intermediate grade neuroendocrine tumors are
17 considered in the well differentiate category.

18 So I think the moderate differentiated
19 really is just intermediate grade, and it would,
20 under current AJCC and WHO definition, fall under
21 the well differentiated category.

22 DR. KELSEN: Well, A, I'm not sure how we

1 know that, but my question specifically was how
2 many patients were entered from each center to give
3 us a surrogate for how many different pathologists
4 were looking at the slides on this uncommon tumor.

5 DR. LEBWOHL: I'll ask Dr. Cagnoni, head of
6 clinical for Novartis Oncology, to address this.

7 DR. CAGNONI: If we can have the enrollment
8 by country and site, please?

9 As Dr. Lebowhl mentioned -- and you're
10 correct. Histology was determined by the local
11 investigators. And let me show you, in one second,
12 what those sites were.

13 Many of the centers that enrolled patients
14 in this study were recognized NET centers of
15 excellence, and there was a large concentration of
16 patients enrolled in the United States, as I will
17 show you in a minute. Approximately 190 patients
18 were enrolled, 165 patients were enrolled in the
19 U.S., as you can see here.

20 DR. KELSEN: There are about 400 patients
21 enrolled.

22 DR. CAGNONI: It's correct. You're

1 absolutely correct. There were an average
2 of -- when you look at the average, there's about
3 five patients per site, as you can see here.
4 However, there was more concentration in certain
5 sites, such as the U.S. They averaged about eight
6 patients per site in the U.S.

7 When you look at places like Japan, there
8 was an average of about 13 patients per site. So
9 overall, you're absolutely correct. However, they
10 tended to be concentrating in certain centers that
11 see more neuroendocrine tumors than others.

12 DR. KELSEN: So how are you confident that
13 there wasn't an imbalance in the two arms, in the
14 number of patients who had well differentiated low
15 grade tumors and more in the experimental arm than
16 in the placebo arm?

17 DR. LEBWOHL: We did include this in the Cox
18 regression model.

19 DR. KELSEN: But who reviewed the slides to
20 say that those patients really indeed had low grade
21 rather than intermediate grade?

22 DR. LEBWOHL: Your question, Dr. Kelsen,

1 then, is that this was done by sites of excellence
2 and the pathologists at those sites would have
3 determined it.

4 DR. WILSON: Thank you. I'd like to
5 recognize Dr. Freedman.

6 DR. FREEDMAN: Thank you, Mr. Chairman.

7 I'd like to ask the applicant two questions,
8 and the second may be related to the first. You
9 have a disease that basically has a low rate of
10 response. So a lot of your event determination is
11 dependent upon the assessment of stable disease and
12 the accuracy of stable disease radiologically.

13 We already have heard that there's a lot of
14 discrepancy between radiology in reviewing these
15 data. So my question is what steps did you take to
16 standardize the radiological studies that were
17 being done at the different sites?

18 Did you only use CT with contrast or did you
19 include PET scanning with CTs? And this is
20 critically important that you accurately assess the
21 duration of stable disease, because your PFS events
22 are going to be influenced by that.

1 My second question relates to your data on
2 the biomarkers, which looks quite impressive when
3 you have the two groups separated in that way. But
4 did you have any correlation between the biomarker
5 response and either response or stable disease?
6 Because I've heard mention, I think Dr. Yao
7 mentioned it, that an objective in this disease is
8 to try to control the symptoms.

9 My question is, what evidence do you have
10 that the treatment that you've given controls the
11 symptoms?

12 Thank you.

13 DR. LEBWOHL: First, let me address your
14 question about discrepancies, because the FDA did
15 express concern about the percentage of the
16 discrepancies.

17 What we saw in this trial is actually
18 explained in the FDA briefing book, as well. The
19 rate of discrepancies is very similar to what's
20 been seen in the literature. Of course, this body
21 has discussed that there's very frequent
22 discrepancy between central and investigator

1 reviews.

2 So, first, to show you the rate of
3 discrepancies as done in general in the literature,
4 which is to look at differences in events. What
5 you see in terms of discordance rates, everolimus
6 23 percent, placebo 34 percent, 29 percent
7 discrepancy in terms of type, which is what you've
8 seen in general reported in the literature.

9 Despite these discrepancies, what's been
10 very powerful about central reviews is that the
11 hazard ratio is almost always the same between
12 investigator and the central review. In the case
13 of the pancreatic NET trial, this was very true.
14 You get precisely the same hazard ratio whether you
15 look at the radiology results by the original
16 primary, which is a blinded central review, knowing
17 nothing about the patients, or you do it based on
18 the investigator. This is true in the literature,
19 as well. There's never been shown to be bias in the
20 investigator assessment of PFS in the literature.

21 In terms of the supportive study, the
22 adjudicated review, we took this one step further.

1 We wanted to understand the discrepancies between
2 the investigators and the central review, and,
3 again, precisely the same hazard ratio, 0.34.

4 So despite these discrepancies, we have a
5 very reliable estimate of the effect of everolimus
6 on progression-free survival, which is a 65 percent
7 reduction in the risk of progression.

8 DR. FREEDMAN: Let me make a point to
9 clarify something. All three groups, the
10 investigator assessments, the independent
11 radiologic review, and the subsequent adjudicated
12 review, could be exposed to the same risks
13 basically if you have inadequate radiology studies,
14 because they all utilize radiologic studies to some
15 degree.

16 As I mentioned, assessment accurately of
17 stable disease, because that's a major endpoint for
18 assessing at least the event of PFAs, is critical.

19 DR. LEBWOHL: You're making an important
20 point. The quality is very important. We did use
21 tri-phasic CT scans as part of the assessment of
22 progression. And just to make the point in terms

1 of the criteria for progression by the
2 investigator, these were RECIST criteria. Clinical
3 progression was not part of this.

4 So the radiologic progression, which is
5 forming the primary endpoint, is based on RECIST.
6 You can see only three cases had progression not
7 based on RECIST within the whole group of
8 investigator progressions. So this we feel is
9 rigorous and reliable.

10 DR. FREEDMAN: I don't mean to harp on this,
11 but the quality of the radiology is critical. So
12 going back to my original question, what steps did
13 you take to ascertain quality and comparability of
14 the radiologic studies that were done at the
15 different sites?

16 DR. LEBWOHL: Thank you for that question.
17 The central radiology review does an assessment of
18 the quality when they come in, and the FDA mentions
19 this in their briefing book, that if there are
20 small changes in contrast, other things that make
21 it more difficult to read, the central radiologist
22 would mark this down.

1 He found, despite there being scans that
2 were of lower quality, that all of them were
3 readable. We took one step further and looked at
4 the progression-free survival, excluding the scans
5 that the FDA was concerned about.

6 So they were concerned that some of the
7 scans had issues. We excluded them from the
8 progression-free survival analysis and this is the
9 result. By the central review, the hazard ratio is
10 .39; by the investigator, .34; and, by the
11 adjudicated, .35. So I don't think the quality of
12 the scans has any effect on the quality of the
13 reliability of the assessment of the primary
14 endpoint.

15 DR. FREEDMAN: The last question was
16 correlation of the biomarker studies with the
17 progression-free survival or with the survival
18 data.

19 DR. LEBWOHL: We don't have the
20 correlation --

21 DR. FREEDMAN: Actually, not for survival,
22 as specific --

1 DR. LEBWOHL: I'd ask Dr. Yao to address
2 that as a general issue with the use of biomarkers.

3 DR. YAO: Thank you for that question. I
4 think the biomarker is definitely very important to
5 us, and I think we'll continue to investigate both
6 from the treated arm and the placebo arm what are
7 the important biomarkers.

8 At this time, we do not have a predictive
9 biomarker, but we do have prognostic biomarkers.
10 As you can see by this slide, the patients who have
11 higher baseline chromogranin A have a worst median
12 PFS compared to those who have a lower baseline
13 CGA, chromogranin A. But nonetheless, regardless
14 of their baseline chromogranin A levels, we saw a
15 benefit for everolimus therapy in terms of the
16 hazard ratio; so showing, again consistent benefit
17 regardless of chromogranin A level.

18 DR. WILSON: So I would actually like to
19 follow up on that within the context of my earlier
20 question, because what we are going to be trying to
21 do here is we are trying to weigh off whether or
22 not the benefit here in terms of progression-free

1 survival is reasonable within the context of the
2 toxicity.

3 Again, you showed an earlier study that
4 there appeared to be a very positive interaction
5 between everolimus and somatostatin. So in terms
6 of these biomarkers have you looked within the
7 group that got everolimus -- looked at these
8 markers individually in people that got everolimus
9 alone versus the ones that got it along with
10 octreotide?

11 DR. LEBWOHL: We have not looked at that in
12 our analyses, no.

13 DR. WILSON: Well, certainly, I think within
14 the context of this, that would be something that
15 would be very useful to look at, because this data
16 has been presented as evidence of the drug working.
17 And, hence, I think that if there is enhanced
18 activity with another drug, that's obviously going
19 to make our ability to evaluate benefit difficult,
20 because we're looking at this drug alone in terms
21 of its indication.

22 DR. LEBWOHL: Something that may be valuable

1 in that line is that in the carcinoid trial, some
2 of the patients were octreotide naïve, and those
3 patients are more likely to have a benefit from
4 octreotide.

5 I'll show you the subgroup analysis for the
6 octreotide naïve patients. What we saw in that is
7 these patients now who are clearly going to be more
8 sensitive to octreotide, that there was greater
9 effect of everolimus, maybe to your point that
10 you're making. So for patients who had prior
11 octreotide, the hazard ratio ranges from .78 to
12 .98. In the patients who were octreotide naïve, the
13 hazard ratio ranges from .6 to .8, and I think that
14 goes to your point.

15 DR. WILSON: Thank you.

16 Dr. Sekeres?

17 DR. SEKERES: Thank you Dr. Wilson. I
18 wanted to follow-up a little bit on some of the
19 points that Dr. Kelsen was making, but I want to
20 take a different approach to it by looking at
21 survival.

22 Now, the sponsor said that about 70 percent

1 of patients enrolled on the study had metastatic
2 disease. Is that correct?

3 DR. LEBWOHL: In which study, please?

4 DR. SEKERES: We're focusing on the
5 pancreatic neuroendocrine tumors.

6 DR. LEBWOHL: No. Almost all the patients
7 did, 98 percent or so.

8 DR. SEKERES: Okay. So the sponsor started
9 the presentation by saying that the median survival
10 of patients with metastatic disease is 17 months.
11 The sponsor then showed updated survival data from
12 the study showing the median survival of 36 months
13 for patients on the placebo arm.

14 Now, if the median survival truly were
15 17 months, we would expect to see some sort of
16 separation of those survival curves for patients
17 treated with the everolimus, if the everolimus was
18 actually prolonging survival. Yet, we're not
19 seeing that.

20 So I'd like some clarification. Is this
21 truly as aggressive a population as the sponsor is
22 saying it is or is this really a more indolent

1 population with a protracted median survival.

2 DR. LEBWOHL: So the placebo arm in our
3 trial does represent a population where 73 percent
4 received everolimus. So that could be a reason why
5 the survival is very good in that arm. To that
6 point, there is now a separation in the curve. You
7 saw early curves. The curves are now separated.
8 The hazard ratio is 0.89 favoring everolimus.

9 The reason we believe this is a possible
10 cause of the improvement in survival , you see here
11 the patients initially on placebo progressed in 4.6
12 months. They're now progressing after that. After
13 that progression they had a progression-free
14 interval of 11 months, and we do think that could
15 be important for their survival.

16 DR. SEKERES: Can you please show your
17 overall survival curve again?

18 DR. LEBWOHL: Yes. So the overall survival
19 was done very recently at the request of the health
20 authority. It's shown here. What you see is the
21 placebo arm is getting close to its median; of
22 course, very few events there, but the median with

1 placebo is around 36 months. Everolimus is at
2 about 60 percent of the patients, extending out
3 beyond 36 months.

4 So the survival experience in this, as you
5 say, is very different from what is expected of
6 this population from the literature.

7 DR. SEKERES: Right. So do you agree that
8 patients who were on the placebo arm crossed over
9 at a median of 16 months on study?

10 DR. LEBWOHL: They crossed over -- you're
11 interested in when they crossed over to everolimus?

12 DR. SEKERES: Yes. So patients on the
13 placebo arm who crossed over to everolimus did so
14 at a median of 16 months. Is that correct?

15 DR. LEBWOHL: I think what you're
16 looking -- I'm not sure where you're getting that
17 from. Do we have a slide?

18 DR. SEKERES: I'm getting that from the
19 exposure data that were shown earlier when we were
20 talking about the toxicities, so patients who were
21 on placebo versus everolimus and what the total
22 exposure was to everolimus.

1 DR. LEBWOHL: So the median time to cross
2 over, as you'd expect, is around the time of
3 progression, 5.6 months on the placebo arm.

4 DR. SEKERES: Okay. Thank you.

5 DR. WILSON: Dr. Choyke?

6 DR. CHOYKE: Thanks. I was struck by this
7 result from the carcinoid study that the
8 independent radiology review showed futility and
9 the independent investigator was wanting stop the
10 trial because of success. And so I'm trying to
11 understand where these discordances came from. It
12 seems -- and I need clarification on this -- that
13 it's not so much that there were differences in the
14 interpretation of the same data, but that they were
15 looking at different datasets because of this
16 informative censoring.

17 Is that correct? Is my understanding
18 correct?

19 DR. LEBWOHL: I want to give you a
20 clinician's understanding of what these many months
21 of looking at it, how I understand it, and then
22 I'll ask a statistician to approach it in that

1 method.

2 In this study, the discrepancy rate is not
3 different from other studies. The difference in
4 the carcinoid study is that we have the crossover,
5 and the second difference is these patients have no
6 other therapy to go to. Then what happened when
7 they progressed is the patients on the placebo arm
8 were censored because they crossed over to
9 everolimus and Sandostatin. The patients on the
10 everolimus arm had often no therapy to go to. They
11 were followed out to an event.

12 As you can imagine the effect of the
13 central -- this is at the central level, censoring
14 the patients because they're not called PDs, if you
15 don't agree with the PD. They're censored. The
16 everolimus patients go to event. That changes the
17 hazard ratio. It harms the everolimus. It shifts
18 from the positive result with the investigator to
19 the negative result by the central review.

20 To understand that better, I'd like to ask
21 Dr. Zuber to explain the issue of informative
22 censoring.

1 DR. ZUBER: Emmanuel Zuber, biostatistics,
2 Novartis Oncology. To again further elaborate on
3 how the informative censoring mechanism may or may
4 not affect the treatment effect estimation, let me
5 just drive you through what a patient experiences
6 there.

7 A patient would be treated on study and
8 would be assessed at a first tumor assessment by
9 the investigator as being stable, as the disease
10 being stable, and this would be confirmed by the
11 central radiologist. And the patient would come to
12 a second assessment when the investigator would
13 determine that the disease is progressing.

14 Then the usual management of the patient
15 would be to be discontinued from study treatment
16 and to go on to further antineoplastic therapy.
17 During that further antineoplastic therapy
18 treatment period, no further assessments would be
19 performed to be made available to the central
20 radiologist.

21 If, at this second scan, the central
22 radiologist does not confirm the investigator-

1 determined progressive disease and, conversely,
2 sees the patient as having stable disease, then the
3 central radiologist would no longer have the
4 possibility to follow up the patient by tumor
5 assessments.

6 However, as suggested by the investigator-
7 determined progressive disease, the prognosis of
8 that patient is likely to be worse. Therefore, the
9 likely upcoming progressive disease that the
10 central radiologist could have seen had tumor
11 assessment been further performed will remain
12 unobserved for the central radiologist.

13 This results in the fact that by
14 investigator, this patient is considered as having
15 an event for the progression-free survival
16 analysis, whereas by the central radiologist, the
17 patient leads only to a censored observation in the
18 progression-free survival analysis.

19 This is typical in any study with a central
20 radiology-based endpoint. However, when this may
21 occur differentially in the two study arms, this is
22 where it may impact the assessment of treatment

1 effect and leads to a bias in the treatment effect
2 estimate.

3 In our studies -- and let me start with the
4 carcinoid trial -- we did observe this differential
5 loss of events from the investigator data to the
6 central radiology data from one group to the other.
7 So you see here an 80 percent loss of event in the
8 everolimus group in the carcinoid study versus a 34
9 percent loss of event in the placebo group in this
10 carcinoid study.

11 I show the same data for the pancreatic
12 study, which showed the same mechanism was playing.

13 DR. LEBWOHL: The important thing that's
14 different about the pancreatic study is because of
15 the extraordinary effect that everolimus had on
16 progression-free survival, it doesn't affect the
17 hazard ratio as it did in the carcinoid trial.

18 DR. CHOYKE: I apologize for taking time to
19 clarify this, but it seems to me that by taking the
20 PFS out, by editing it down, that you would get a
21 better result from the independent radiology
22 review. It's not clear to me why that had a worse

1 result.

2 DR. LEBWOHL: So censoring in the central
3 review for the placebo arm leads to an inflated
4 estimate of progression-free survival. Getting
5 more events on the -- well, not more events on the
6 everolimus arm, because the investigator might have
7 had those events, but getting those same things on
8 the everolimus arm shortens your progression-free
9 survival. So the differential effect, inflating
10 the placebo, shortening the everolimus, leads to a
11 hazard ratio that changes with this informative
12 censoring.

13 DR. WILSON: Dr. Grem?

14 DR. GREM: I have several questions. One is
15 it looked like the patients who discontinued
16 therapy on either arm for any reason other than
17 progressive disease were followed until progressive
18 disease, but then it says PFS assessment until new
19 antitumor therapy started.

20 So I need some clarification of that. That
21 doesn't really make sense. So if they were taken
22 off because they didn't want to do it or for

1 whatever reason, a bad side effect, they stopped
2 therapy, then you were still asking them to undergo
3 scans so you could determine if they had
4 progressive disease.

5 So I would think the definition of
6 progressive disease would be progressive disease,
7 not until they start a new antitumor therapy.

8 DR. LEBWOHL: This is based on agreement
9 with the FDA and other health authorities of how
10 you determine progression-free survival. We do
11 want to follow every patient out as much as
12 possible to a progression event. It's very
13 important in terms of the strength of the analysis.

14 So what we did, even if a patient
15 discontinued due to an adverse event, the
16 investigator was asked to continue to follow them
17 until a progression event. However, of course,
18 when the physicians find the -- local investigator
19 finds progression, they are going to switch their
20 antineoplastic therapy. They're going to add a new
21 antineoplastic therapy often to try to treat them
22 at that point, if it's available.

1 In that case, in the central review, when
2 you start a new therapy, that leads to a censoring
3 event and we did not follow the patient after that
4 censoring event. This is an evolving area. Some
5 people are considering that you should follow them.
6 However, if you think about crossover to everolimus
7 in the pancreatic NET trial, if we did follow them
8 from their starting of everolimus to an event, that
9 event would have occurred 11 months later.

10 So there's caution to be used in doing this
11 because you may get a very inflated result if you
12 follow progression through a new therapy that's
13 effective.

14 DR. GREM: But I thought you made the point
15 that there are no other effective therapies
16 available. So that would make that argument less
17 strong.

18 Then can you please clarify, for the
19 discrepancies in the pancreatic NET trial, were all
20 of those cases reviewed? Because in the carcinoid,
21 only those who there was a discrepancy of more than
22 four months or something like that were reviewed?

1 So can you please clarify what you did for
2 pancreatic NET?

3 DR. LEBWOHL: Now, are you referring to the
4 adjudicated review?

5 DR. GREM: Right.

6 DR. LEBWOHL: Let me show you the
7 adjudication process. What's done here is the
8 cases with the local, the investigator data and the
9 central data are considered, and if they are
10 discrepant, the case is adjudicated by experts.
11 The experts are here today, Dr. Charn from M.D.
12 Anderson and Dr. Haller from U-Penn, who were
13 chosen as the experts for this process.

14 The adjudicated data and then the central
15 data are brought together and that's what you're
16 seeing -- the central data where they agree, and
17 that's what you're seeing as the independent
18 adjudicated committee.

19 In this process, we looked at all
20 discrepancies, but in terms of the time
21 discrepancies -- you've heard of type
22 discrepancies, those were all reviewed. In terms

1 of time discrepancies, it was for a period of
2 greater than 126 days. This is a period of one
3 assessment, and we felt, biologically, medically,
4 one assessment difference in assessment was not
5 necessarily an important difference, because this
6 can happen with any two expert radiologists reading
7 a film.

8 DR. GREM: Right. But if you're looking at
9 improvements in progression-free survival on the
10 order of six months, but you're not looking at the
11 cases where the progression-free discrepancy was
12 three months, I would think you would want to look
13 at everybody.

14 DR. LEBWOHL: Just to bring it back to the
15 pancreatic NET study, whether you did the estimate
16 of treatment by either the investigator, the
17 adjudicator or the central review, you got
18 precisely the same result. You got a hazard ratio
19 of about .35 in all three cases.

20 DR. GREM: Right, but that was only the
21 people when it was the event, not the time. Is
22 that what you said?

1 DR. LEBWOHL: No, no. The adjudication was
2 done -- it was type or if the timing was greater
3 than 126 days.

4 DR. GREM: So you're missing people then.

5 DR. LEBWOHL: Let me come back to this. The
6 central review is done on all patients. So you
7 have the investigator review done first. All the
8 films are sent to a central reviewer.

9 At the central review, you have reader A and
10 reader B reading those films. If those two readers
11 agree, that's considered the right date of
12 progression. If those two readers don't agree, a
13 third reader then determines which of those two is
14 the best assessment.

15 This was done with all patients, and the
16 result you get with the central review is precisely
17 the same result you get with the investigator
18 review.

19 DR. GREM: Okay. And then in terms
20 of -- were there any quality of life assessments
21 built in? So that for things like chromogranin A,
22 a drop in chromogranin A is fine, but that doesn't

1 produce any symptoms in the patient.

2 So I think someone else brought this up, Dr.
3 Freedman. Were the magnitude of the changes that
4 you saw in some of the, like, glucagon or VIP or
5 whatever for the pancreatic NET patients, did that
6 translate into them feeling better or was it just a
7 biochemical improvement or don't we know?

8 DR. LEBWOHL: In terms of quality of life,
9 we did not have an assay for that. There was no
10 validated method that was there when we started it.

11 I'll ask Dr. Yao to address your question.

12 DR. YAO: Thank you for that question. I
13 think the difficulty here is that there was no
14 validated quality of life questionnaire for this
15 group of patients when we started the study.
16 Further, this is complicated by the fact that we're
17 dealing with different syndromes for the different
18 types of patients. For example, the type of
19 symptoms a VIPoma patient gets will be very
20 different than an insulinoma patient gets, and the
21 number of patients with each of the specific
22 hormonal syndromes are not high enough to really do

1 this type of analysis. We don't have the
2 questionnaire for it.

3 DR. GREM: And then the last issue is
4 that -- so it sounded like 22 percent of the
5 patients randomized to placebo did not cross over
6 to everolimus. And so the argument -- and I'm all
7 for allowing people to cross over, but then that's
8 the argument that you don't see a difference in
9 overall survival.

10 But I would think 22 percent, if they were
11 progressing at a median of four months and they did
12 not go on to receive other therapy, they were
13 presumably too sick or they died or their
14 performance status was too poor, still, 22 percent
15 of the placebo, you would think that would make a
16 dent on the overall survival curve.

17 So I don't know what the experience is in
18 other studies where they've looked at crossover,
19 what percent is this, the 22 percent that didn't
20 cross over. Is that about what we see from other
21 studies?

22 DR. LEBWOHL: This actually was an

1 extraordinarily high rate of crossover. Remember,
2 there were also patients ongoing, so it wasn't 22
3 percent necessarily who didn't cross over. You're
4 right. The patients who didn't get additional
5 therapy did very poorly.

6 DR. MAHER: Our statisticians would like to
7 make a comment about discordance.

8 DR. WILSON: Yes.

9 DR. SRIDHARA: I'm Raje Sridhara. I'm not
10 the primary reviewer. The primary reviewer is
11 Dr. Cole, who is sitting here. But I just wanted
12 to bring up the issue of the discordances that were
13 being discussed.

14 There is a differential discordance, as the
15 sponsor showed there, that in the placebo arm,
16 there were double the number of even discordances
17 that were seen between the investigator and the
18 IRC, whether you look at the carcinoid or the PNET
19 trial, in both of them, you are seeing this
20 differential, differences between them.

21 So the question is that there is an
22 evaluation bias and the investigator; rather than

1 looking at it that this was informative censoring.
2 We have to also worry about the investigator bias
3 in this case.

4 DR. LEBWOHL: Mr. Chairman, I think it's an
5 important question that the FDA raises here, is
6 whether investigator bias had any role in the
7 discordance that we see. Even though investigators
8 may have been unmasked in some cases by the
9 toxicities, we see no evidence that there is an
10 investigator bias affecting progression-free
11 survival in either study.

12 First, to recognize what I showed before,
13 that the rate of non-RECIST progressions is
14 basically nil. All the progressions noted by the
15 investigator, shown here, were determined by
16 RECIST. So this is the investigator writing down
17 the measurements of tumor and determining
18 progression. These were all reviewed centrally
19 before any patient was allowed to cross over to
20 make sure that RECIST progression was seen.

21 The stronger evidence has to do with the
22 central review that we see. We looked at the

1 patients -- the investigator progressions. If
2 there was bias, the placebo arm would be calling
3 progressions early. If there was bias in the
4 everolimus arm, they'd be calling them late.
5 That's the only thing that could lead to the type
6 of bias the FDA is talking about. What we see is
7 the number of progressions by the investigator were
8 confirmed at precisely the same rate in both arms.
9 That's shown here.

10 So based on the central review, a blinded
11 central review, there is no evidence of bias in the
12 investigator review. In fact, in the literature,
13 there's been no evidence of bias in investigator
14 review. The reason we may understand this, the
15 investigator, even if they tried to guess the arm,
16 would have a very difficult time.

17 In our study, 70 percent of the patients on
18 placebo were said to have a toxicity associated
19 with the drug use. Therefore, in those placebo
20 patients, 70 percent of the time, the investigators
21 thought their patient was receiving active drug.

22 DR. WILSON: Thank you. I'd like to

1 recognize Dr. Logan.

2 DR. LOGAN: You showed an update of the
3 overall survival curves. Can you tell us what
4 percent of the patients have experienced the event
5 in that update?

6 DR. LEBWOHL: Let's bring up the updated
7 survival curve again. Actually, if someone could
8 give me the numbers of deaths in each arm.
9 Unfortunately, we didn't put it directly on the
10 slide.

11 Dr. Zuber, the number of deaths? Sorry.
12 Here is the slide. Sorry.

13 The new cutoff is shown at the bottom.
14 There have been 78 deaths in the placebo arm and 68
15 deaths in the everolimus arm.

16 DR. LOGAN: So we're still nowhere near the
17 planned analysis update for survival.

18 DR. LEBWOHL: The planned analysis will come
19 at a later date, the planned final analysis, I
20 should say.

21 DR. LOGAN: And do you have an updated
22 survival for the carcinoid study?

1 DR. LEBWOHL: Yes, we do. It looks very
2 similar to the update that was given in the 90-day
3 safety update that we do on a standard basis for
4 the FDA.

5 The overall survival in the carcinoid trial,
6 90-day update, which is actually what we
7 showed -- I mean the most recent update. We may
8 not have a slide.

9 So the result, shown here, the hazard ratio
10 is 1.17. Here you can see the events, 117 patients
11 on the everolimus arm, 106 patients on the placebo
12 arm. I have to remind you here that there is an
13 imbalance in the prognostic factors despite the
14 randomization. When the pre-planned Cox analysis
15 was done on this, the hazard ratio was 1.05.

16 DR. WILSON: Dr. Fojo?

17 DR. FOJO: I had a couple of questions, and,
18 obviously, these have already been addressed, in
19 part. But the greatest concern is the amount of
20 censoring, that for the progression-free survival
21 endpoint, which is not as solid as one would like,
22 you end up with nearly 50 percent of the patients

1 censored, which is quite high compared to the
2 majority of studies.

3 So I disagree with some of the things that
4 you have said, because I think it's important not
5 only the percent that are censored -- so you just
6 showed that 59 and 62 percent were disagreements,
7 but it's the time that the censoring occurs.

8 In an indolent disease, early censoring
9 penalizes the arm that suffers early censoring.
10 That's for two reasons. Number one, they can't
11 have the indolent progression-free survival that
12 they normally would. And the other thing is
13 although we censor it, what we do is subtract from
14 the denominator, so that any event then takes a
15 greater significance.

16 So do you have -- and as I look at this, you
17 try to add up tic marks, and it just doesn't work
18 because there are a lot of places I'm sure where
19 they're one on top of the other.

20 Do you have the rate of censoring for the
21 placebo arm versus the everolimus arm? Are they
22 occurring at the same rate or are there more early

1 censorings in the placebo arm than the everolimus
2 arm; which seems to be something that may have
3 happened in the looking at the IRC data.

4 DR. LEBWOHL: So let me just go back.

5 DR. FOJO: Or as an alternate to that --

6 DR. LEBWOHL: You're asking in pancreatic
7 neuroendocrine tumors.

8 DR. FOJO: Correct, yes.

9 DR. LEBWOHL: And I think the first point is
10 that the censoring that we're worried about is
11 informative censoring.

12 DR. FOJO: Correct. So we're worried about
13 censoring in the IRC arm.

14 DR. LEBWOHL: Yes, in the IRC. So just to
15 sort of reassure you that the censoring isn't
16 creating the result, if you look at the
17 investigator, you get the same hazard ratio by the
18 investigator or by the IRC. So the effect of
19 censoring, though, as we showed you, there is some
20 extensive censoring in this trial -- and by the
21 way, every trial where there's a central review, as
22 shown by the FDA in their book, this does not

1 affect the estimate of the hazard ratio. So the
2 hazard ratio is quite reliable despite the
3 censoring that occurs with every central review.

4 DR. FOJO: I'm not quite sure I agree with
5 that, because --

6 DR. LEBWOHL: Let me have Dr. Zuber address
7 this statistically.

8 DR. FOJO: Okay.

9 DR. ZUBER: To further address your question
10 on the impact of censoring on the progression-free
11 survival analysis in the pancreatic study by the
12 central radiologist, here is a depiction of the
13 censoring reasons, either in the investigator-based
14 analysis on the left or by the central radiology,
15 on the right, which, by the way, does illustrate
16 the informative censoring mechanism, where the
17 imbalance occurred here in the new cancer therapy
18 added.

19 We did perform a sensitivity analysis with
20 conservative rules to try to assess the robustness
21 of the treatment effects with respect to the
22 censoring reasons with the central radiology data,

1 and you have it here on the slide. We considered
2 for everolimus patients who were censored for loss
3 to follow-up, adequate assessment no longer
4 available, or even documented up to two or more
5 missing assessments, that an event had occurred
6 instead of a censoring.

7 The second step we took with a conservative
8 approach was to consider patients who were censored
9 for a new anticancer therapy added to have an event
10 which was drawn from a distribution not considering
11 any treatment effect. So we considered they had an
12 event as if there was no treatment effect in the
13 same way in both arms. The results of that
14 analysis are presented at the bottom of the slide,
15 and you see treatment effect estimates being still
16 very robust and consistent, showing a benefit of
17 everolimus.

18 DR. FOJO: So that still doesn't answer my
19 question. Once an investigator scored progression,
20 a penalty has been inflicted on the placebo arm,
21 and the IRC does not have the ability to say, "No,
22 it hasn't progressed, let's let him continue on

1 study."

2 The IRC has only two choices, censor or
3 agree. If they censor, they can't let them
4 continue. So, again, you reduce the number of the
5 denominator, and every event that is a real
6 progression has a greater impact.

7 The other thing is in this case, they could
8 have gone for another three months before they
9 would have been scored as progression. Let's say
10 they were about to progress, but hadn't quite, and
11 they don't get that opportunity.

12 So you don't have the rates of censoring
13 that I would like to see, if there is any
14 difference.

15 Do you have the PFS -- removing all
16 censoring, just let's get rid of that questionable
17 group of patients. How did they compare when we
18 ignore censored patients and just say, okay,
19 anybody who was not censored, what does that give
20 us?

21 DR. LEBWOHL: Well, one way to get
22 at -- tell me if this gets at it for you,

1 Tito -- is whether taking the earliest event by the
2 investigator or the central would avoid -- at least
3 they're agreeing. So let's pull up that analysis
4 for you, the sensitivity analysis.

5 Basically, to give the conclusion before you
6 see it, you get a very similar treatment effect.
7 So if you use the earliest of the investigator or
8 the central review, your hazard ratio is 0.37,
9 similar result to what you get with either the
10 investigator or the central review.

11 DR. FOJO: This is still the same thing.
12 Again, once progression was scored, you can't put
13 the patient back into the mix and let them live
14 longer or let them go longer without progression.
15 You're talking about an indolent disease, where
16 many patients could have gone on for much longer
17 without progression. But I guess that the data
18 that I'm looking for is not quite available.

19 But then related to that, when you look at
20 the curves, either the IRC or the investigator,
21 past that initial evaluation, past the 12-week,
22 they're identical. They decay in an identical

1 manner. In fact, on my computer, I sort of moved
2 them up best as I could, they overlap. So that
3 what is happening is the difference is occurring in
4 the first assessment interval, and then after that
5 there is no difference.

6 It's actually interesting, because if you
7 look at your chromogranin and all of those, you see
8 the same thing, not in the chromogranin as much,
9 but in all the others, there's a drop in that first
10 assessment, and then both of the curves continue at
11 a similar rate. It was alluded to earlier, it
12 almost makes you think that octreotide is managing
13 that manifestation of disease.

14 But I was looking to that and saying, okay,
15 I'm having trouble with the investigator assessment
16 that may have had some bias, and not bias other
17 than what we as humans would do in treating
18 patients with a disease. But in the NFC, in
19 the -- not the chromogranin, the gastrin and the
20 glucagon, there's so much overlap. If you were to
21 consider this to be tumor measurements, there
22 probably would be no hazard ratio there. In the

1 chromogranin, there seems to be some discordance
2 which favors the everolimus.

3 But in any case, I think there's clear
4 evidence that there's tumor shrinkage, there's no
5 doubt about that, and it's supported by your
6 overall response rate. Here, it's over-responded
7 by this. But do you have any thoughts as to why
8 this appears to be occurring and almost confined to
9 that first assessment interval?

10 DR. LEBWOHL: Let me pull up the core slide
11 on the progression-free -- you're talking about the
12 pancreatic NET still, I believe. Right, Dr. Fojo?
13 The pancreatic NET again.

14 DR. FOJO: Yes.

15 DR. LEBWOHL: Let's pull up the core slide
16 for progression-free survival, the Kaplan-Meier
17 curve, of course.

18 Here is the Kaplan-Meier curve. The median
19 is occurring at four months, so that may be after
20 the first assessment, the median for the placebo
21 arm. The median for the treatment arm is occurring
22 at 11 months, so that's really three and a half

1 assessments. So there's actually quite a big
2 difference between those curves. I know Dr. Pazdur
3 would like to say "driving a truck through it"
4 sometimes, but that's a big difference in the
5 curves, by any measure.

6 DR. FOJO: But they're decaying identically.

7 DR. LEBWOHL: Excuse me?

8 DR. FOJO: They're identical past that
9 first -- not identical, but extremely similar past
10 that first.

11 DR. LEBWOHL: Let me have Dr. Wei from
12 Harvard University address this.

13 DR. WEI: I'm L.J. Wei. I'm professor of
14 biostatistics at Harvard. I'm paid by Novartis to
15 come here.

16 Sir, if you notice, the Kaplan-Meier curve,
17 you're absolutely right. In the beginning, they
18 separate rapidly and then they parallel each other.
19 But that doesn't mean the effect has diminished.
20 If the Kaplan-Meier grew together toward the end,
21 we're in trouble. But this one actually still
22 keeps going. I think it's still effective.

1 DR. FOJO: But let's just say that you had a
2 situation where you killed off a fraction of the
3 tumor and set the clock back. And then after that,
4 the indolence of the disease comes into play. You
5 would get this sort of a result.

6 DR. WEI: Well. not quite, because
7 randomization is only balanced in the beginning
8 After that, they're not balanced anymore, and a
9 risk is set, as you know better than everybody
10 else.

11 DR. FOJO: Okay. And then can I make one
12 last point? The last thing was -- so you showed
13 that those who crossed over went from 4.6 to
14 11.1 months or 11.03 months or whatever. So the
15 only thing about that is that it's the investigator
16 assessment, which I think we all agree was probably
17 exaggerated for the 4.6 months. But another way of
18 looking at that, because that's 11.03 and the
19 original everolimus was 11.4, is that there is no
20 difference between getting the everolimus at the
21 outset or getting it six months later.

22 Would you agree with that assessment?

1 DR. LEBWOHL: I believe the patients who are
2 able to cross over are getting the benefit of
3 everolimus. Remember, 90 percent were able to
4 cross over.

5 DR. FOJO: Right.

6 DR. LEBWOHL: Some were never able to get to
7 that point. They became too sick, and that's
8 likely the difference in the two survival curves at
9 this point, with a hazard ratio of .89.

10 DR. FOJO: Okay.

11 DR. WILSON: Let me move on now. We are
12 running late. So there are two more folks on the
13 list, if you could just keep your question short.
14 The first one would be Dr. Kelsen.

15 DR. KELSEN: I'll ask two quick questions.
16 One regards the reliability of the investigator
17 responses or assessments, and you put up the
18 waterfall plot of objective tumor regression for
19 the pancreas trial. It's a little unusual to see a
20 21 percent regression rate, even if it's less than
21 PR in a placebo arm.

22 DR. LEBWOHL: We looked at this very

1 carefully. Of course, you know there's minor
2 variation in many patients. The ones who have a
3 big variation, one was a patient who had started on
4 somatostatin analog. Several of the other patients
5 were patients with very small lesions, 1 to 2
6 centimeter lesions. As you can imagine,
7 measurement of these is more variable, leading to
8 this effect.

9 In almost all trials, you see with waterfall
10 analysis, there is a small percentage of patients
11 with that type of reduction in tumor size.

12 DR. KELSEN: Twenty-one percent is a lot of
13 patients, but putting that to the side. And just
14 to get back to the point I raised earlier, I'm
15 still not 100 percent sure about an unexpected or
16 unanticipated imbalance in favor of the
17 experimental arm, just like you're worried about an
18 unexpected imbalance in the placebo arm in the
19 second trial.

20 I just want to ask one more question about
21 pathology review, which I think is really critical.
22 Did you at least collect data on KI67 or some other

1 measure of low grade versus intermediate grade?
2 Did you at least collect the data or did you just
3 take the pathology report? We're going to hear
4 about KI67 this afternoon.

5 DR. LEBWOHL: For the Cox analysis, the
6 investigator was used. So it was adjusted by those
7 measures.

8 In terms of KI67?

9 DR. KELSEN: Some measure that says that
10 there is some objective thing that told you from
11 all these pathologists, they were sort of in the
12 same ballpark.

13 DR. LEBWOHL: This is KI67. This is in the
14 pancreatic NET study. Whether the patients were
15 low, KI67 less than two points, say, intermediate
16 or greater than 5 percent, there was, again, very
17 small numbers of patients. We weren't able to get
18 KI67 on most of the patients, but looking at these
19 small sets in the subgroup analysis, it all favors
20 treatment with everolimus.

21 DR. KELSEN: I'm just looking at imbalance
22 in the two arms. You took that down real fast, but

1 it looked like there were a few -- maybe I'm
2 reading this --

3 DR. LEBWOHL: You can't get the balance in
4 the three arms. These are the patients who did
5 have samples for KI67, so we can't address it for
6 the whole population.

7 DR. KELSEN: But in this analysis, there's
8 more in the placebo arm that have low grade. Okay.
9 Thank you.

10 DR. WILSON: All right. And the last one
11 will be Dr. Curt.

12 DR. CURT: There's a common theme here from
13 this sponsor, to other sponsors' presentations to
14 ODAC earlier in the year, a trial with an
15 improvement in progression-free survival with no
16 change in overall survival, where you have to
17 balance the PFS benefit against the treatment side
18 effects.

19 One explanation for the higher adverse event
20 rate in this case is the longer median exposure on
21 the treatment versus the placebo arms, 16 months
22 for placebo and 38 for treatment. It's pretty

1 sizable.

2 So the question I have to the sponsor is, in
3 the treatment arm, did the adverse events occur
4 early, did they occur late, or did they occur
5 during that entire 38 months of exposure?

6 DR. LEBWOHL: Thanks. I'd like to have Dr.
7 Cagnoni address this question in terms of duration
8 of treatment and events.

9 DR. CAGNONI: Pablo Cagnoni, Novartis
10 Clinical Development. It really depends on the
11 adverse event; they can occur over time. Now, one
12 thing we did to adjust for that was an annualized
13 rate of the incidence of adverse event. As you
14 point out, the median exposure was nearly two and a
15 half times longer in the everolimus arm than in the
16 placebo arm. As a result of that, the patients are
17 at risk or have been observed for adverse events
18 for a much longer period of time.

19 When you adjust that, in other words, you
20 basically annualize a rate of adverse event, you
21 see that for a grade 3/4 adverse event, the
22 incidence becomes pretty similar, and for those

1 suspected of a drug related, there are still more
2 in the everolimus arm, as you would expect, but the
3 difference is much smaller than without the
4 adjustment for the duration of exposure.

5 DR. WILSON: Actually, let me follow up. I
6 think that the story is told in a more global way
7 that doesn't have issues with how long that people
8 have been on the study.

9 If you look at your slide CE-18, which is
10 the dose modification data, and people don't modify
11 doses unless there is some kind of toxicity. And
12 you can see that there is a doubling in the dose
13 modification on the treatment arm. Hence, I think
14 there is no doubt that there is a much larger
15 degree of toxicity, and this is really -- this is
16 independent of how long they've actually been on
17 drug.

18 So I just wanted to point that out because I
19 think the other analysis is completely confounded
20 by length of time on drug.

21 So with that, let me close this session.
22 And what I would like to do is recognize Ms. Mason,

1 if you could please state your name and your role
2 here into the record.

3 MS. MASON: Thank you. My name is Virginia
4 Mason. I'm with the Inflammatory Breast Cancer
5 Research Foundation and serving as the consumer rep
6 for this meeting. Thank you.

7 **Open Public Hearing**

8 DR. WILSON: Okay. We are now going to move
9 into the open session, and I have some statements.

10 Both the Food and Drug Administration and
11 the public believe in a transparent process for
12 information-gathering and decision-making. To
13 ensure such transparency at the open public hearing
14 session of the advisory committee meeting, FDA
15 believes that it is important to understand the
16 context of an individual's presentation.

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

1 financial information may include the sponsor's
2 payment of your travel, lodging or other expenses
3 in connection with your attendance at this meeting.

4 Likewise, FDA encourages you, at the
5 beginning of your statement, to advise the
6 committee if you do not have any financial
7 relationships. If you choose not to address this
8 issue of financial relationships at the beginning
9 of your statement, it will not preclude you from
10 speaking.

11 The FDA and this committee place great
12 importance in the open public hearing process. The
13 insights and comments provided can help the agency
14 and this committee in their considerations of the
15 issues before them.

16 That said, in many instances and for topics,
17 there will be a variety of opinions. One of our
18 goals today is for this open public hearing to be
19 conducted in a fair and open way, where each
20 participant is listened to carefully and treated
21 with dignity, courtesy and respect. Therefore,
22 please only speak when recognized by the chair.

1 So with that, I would like to invite
2 Ms. Goldstein to the podium.

3 MS. GOLDSTEIN: Good morning. Thank you for
4 the opportunity to speak here today. My name is
5 Grace Goldstein, and I'm the chief operating
6 officer at the Carcinoid Cancer Foundation in New
7 York. We're a nonprofit organization dedicated to
8 the welfare of neuroendocrine cancer patients. For
9 full disclosure, I'm here today at the expense of
10 the Carcinoid Cancer Foundation.

11 I've worked at the foundation for eight
12 years, and during that time, I've spoken with and
13 corresponded with literally thousands of NET cancer
14 patients. I'm not a medical professional, and I'm
15 not here to give you facts and figures that have
16 been covered by physicians, researchers and
17 pharmaceutical personnel. I am a passionate
18 patient advocate who has learned more and more over
19 the years about the difficulties NET patients face.

20 Because these cancers are so rare, over
21 75 percent of the patients go five to seven years
22 after they have symptoms before they are accurately

1 diagnosed, and it's during that time --

2 DR. WILSON: Ms. Goldstein, I'm sorry, we
3 were not able to record the first part of your
4 talk, so we are going to restart the clock, and if
5 you can please start from the start. Sorry.

6 MS. GOLDSTEIN: Thank you.

7 Thank you for the opportunity to speak here
8 today. My name is Grace Goldstein. I'm the chief
9 operating officer at the Carcinoid Cancer
10 Foundation in New York. It's a nonprofit
11 organization dedicated to the welfare of
12 neuroendocrine cancer patients. For full
13 disclosure, I'm here today at the expense of the
14 foundation.

15 I've worked at the foundation for eight
16 years, and during that time, I've spoken with and
17 corresponded with literally thousands of NET cancer
18 patients. I am not a medical person. I'm not here
19 to give you facts and figures. That's been given
20 to you by physicians, researchers and
21 pharmaceutical personnel. I am a passionate
22 patient advocate, and I've learned more and more

1 over the years about the difficulties that NET
2 patients face.

3 Because these cancers are so rare, over
4 75 percent of the patients go five to seven years
5 after symptoms occur to get a proper diagnosis, and
6 that's when symptoms occur. It's during this time
7 that their cancer can grow and metastasize.

8 Frequently, NET patients are misdiagnosed,
9 being treated for diseases they do not have, and,
10 of course, the treatments do not work. When they
11 do get a correct diagnosis, it's a great relief.
12 They can put a name on their disease. And for
13 those who have been told to seek psychiatric or
14 psychological help, they know they're not crazy.

15 On the other hand, they have cancer and it's
16 generally a cancer they've never even heard of.
17 And in the case of the pancreatic NET cancer
18 patients we're talking about today, the cancer has
19 likely grown and spread.

20 When I talk to NET patients, they're scared.
21 They're worried about finding the physicians who
22 can treat them, wondering what medications they can

1 take, what treatments they can pursue, and, very
2 sadly, when are they going to die. It's
3 heartbreaking to be asked that question, and it's a
4 question I really can't answer.

5 They're often in physical pain, as well.
6 They're calling our foundation for support and
7 guidance. If I can tell them there are doctors who
8 specialize in their cancer and medications they can
9 take, it lightens their burden.

10 Right now, there are very few treatment
11 options NET patients can pursue. Medications are
12 limited, and many treatments are only available
13 outside of the United States. To have a new
14 medication they can take is life-affirming. If
15 everolimus can help alleviate symptoms, whether
16 they're from functioning tumors or the result of
17 tumors affecting vital structures, and it can
18 extend their lives, it makes a huge difference for
19 pancreatic NET patients.

20 Most patients do not have the resources and
21 opportunities that are afforded to Steve Jobs.
22 They need a medication they can buy in their local

1 drug store. They need the opportunity to spend
2 more time with their families, spouses, children,
3 other loved ones. They need to enjoy the simple
4 pleasures of life that those of us not affected
5 with metastatic cancer enjoy. And they need hope,
6 hope that comes with knowing there's a medication
7 that can help them, hope that enables them to fight
8 their cancer rather than succumb, hope that buys
9 them time, time during which there may be another
10 medication that becomes available, or a treatment
11 they couldn't have had previously, or a research
12 discovery that can extend their lives further.

13 I ask each of you here today how you would
14 feel if you were in a similar situation and what it
15 would mean to you to have a new drug available for
16 your cancer. I am confident that would be
17 incredibly important to you.

18 Please approve everolimus for pancreatic NET
19 patients. Please give these patients a reason to
20 be hopeful.

21 Thank you.

22 DR. WILSON: Thank you. I would now like to

1 ask Ms. Erb to come up.

2 MS. ERB: Thank you for the opportunity to
3 present here today. I am Lauren Erb, the executive
4 director of the Caring for Carcinoid Foundation.
5 We represent the roughly 100,000 patients in the
6 United States with neuroendocrine cancers. Founded
7 by a metastatic carcinoid cancer patient, Nancy
8 Lindholm, our foundation is dedicated to
9 discovering cures for carcinoid, pancreatic
10 neuroendocrine, and related neuroendocrine cancer
11 patients. We fund research to bring novel
12 treatments to patients. We work with
13 pharmaceutical companies to advance patient care,
14 and we interact directly with these patients.

15 For the purposes of disclosure, I have
16 traveled here unreimbursed and have no financial
17 stake in Novartis or their competitors. The
18 foundation does receive less than 80 percent of
19 revenue from Novartis and competitors.

20 Last year, I had the honor and privilege of
21 addressing the FDA on behalf of these patients to
22 address the specific challenges in bringing drugs

1 to market for these patients. While it's exciting
2 to be here today as two drugs are being considered,
3 I find myself repeating several common themes.
4 First, there are few, if any, treatment options for
5 neuroendocrine tumor patients in the United States
6 and no uniform standards of care.

7 Second, out-of-pocket costs for these
8 diseases are significant and place tremendous
9 financial burden on our patients.

10 Third, among patients on everolimus who
11 experience side effects, many elect to try to
12 remain on the drug to remain without progression.
13 They have no other option.

14 Recently, one of our funded scientists
15 discovered mutations that may prioritize patients
16 for treatment with mTOR-inhibiting drugs. While
17 this is exciting, it does little to address our
18 patients' acute need for effective treatments
19 today.

20 I am not here to present science, but to
21 represent our patients and their loved ones. In
22 preparation for today's hearing, we spoke with

1 about 150 patients with neuroendocrine tumors,
2 including many who had been in everolimus. And
3 while they experienced side effects, they also
4 received benefit. Not a single patient thought
5 that this drug should not be approved. In
6 addition, 83 percent of the patients who were on
7 the drug felt that it had been effective in
8 treatment their neuroendocrine tumor.

9 While we have a lot to learn regarding the
10 biology of these tumors, there are patients that
11 are benefitting today from treatment with
12 everolimus. We ask FDA to consider the data
13 presented here today in the context of the patient
14 population for which it's being considered,
15 patients for which there are no FDA-approved cures,
16 patients for which there are few FDA-approved
17 treatment options, patients with a life-ending
18 disease.

19 The Caring for Carcinoid Foundation supports
20 all drug development for patients with
21 neuroendocrine tumors and encourages FDA and drug
22 companies to evaluate all promising therapies as

1 fast as possible, including things like peptide
2 receptor radiotherapy, everolimus for treatment of
3 carcinoid tumors of the GI tract and lungs, and
4 sunitinib.

5 Furthermore, we encourage the drug companies
6 to track patients to identify predictive markers
7 that may correlate with response to therapy and
8 make use of the placebo datasets to identify
9 prognostic markers and, also, natural history
10 information.

11 While we hope to see everolimus approved
12 here today, we also want to continue learning and
13 fine-tuning our approaches for treating these
14 patients.

15 Thanks very much for your time.

16 **Questions to the ODAC and ODAC Discussion**

17 DR. WILSON: Thank you. The open public
18 hearing portion of this meeting has now concluded,
19 and we will no longer take comments from the
20 audience. The committee will now turn its
21 attention to address the task at hand, the careful
22 consideration of the data before the committee, as

1 well as the public comments.

2 At this point, I would like to invite FDA to
3 frame the question that they would like the
4 committee to discuss.

5 DR. SNYDER: The PNET trial randomized
6 patients with advanced or metastatic pancreatic
7 neuroendocrine tumors to everolimus or placebo plus
8 best supportive care. The amended primary endpoint
9 was progression-free survival, as determined by
10 investigator, while the pre-specified primary
11 endpoint was progression-free survival, as
12 determined by independent central review.

13 By investigator review, the hazard ratio was
14 0.35, representing a difference in median
15 progression-free survival of 6.4 months, while the
16 hazard ratio by central review was 0.38 and
17 conferred a difference in median progression-free
18 survival of eight months. An interim analysis
19 showed no difference in overall survival.

20 Seven patients in the everolimus arm and one
21 patient in the placebo arm died during the
22 treatment period secondary to an adverse event.

1 Grade 3/4 adverse events were seen in 62 percent of
2 patients on the everolimus arm and 40 percent of
3 patients on the placebo arm. Significant adverse
4 events seen in this trial included pneumonitis,
5 opportunistic infections, and renal failure.

6 We ask the Oncology Drug Advisory Committee
7 the following question: Is the benefit-risk
8 analysis favorable in the treatment of patients
9 with advanced pancreatic neuroendocrine tumors,
10 based on the demonstrated efficacy and safety
11 profile of everolimus?

12 DR. WILSON: Okay. So I think that we've
13 had a very good discussion so far regarding the
14 data in terms of whether or not there is evidence
15 of progression-free survival. And I think at this
16 point, we now see that both the investigator and
17 the independent review groups have both shown that
18 there is a delay in disease progression. This is
19 not translated into an overall survival effect.

20 Now, this is something that we're obviously
21 facing when we allow crossover, and I think we
22 particularly face it if we allow crossover to a

1 drug that is actually having some type of
2 biological effect.

3 So I guess what we need to discuss today is,
4 is the benefit adequate to offset the risk; and,
5 clearly, we've seen that the risk is not only
6 increased adverse events, but increased toxic
7 events, as well.

8 I think part of this discussion is, given
9 the indolent nature of this tumor and given the
10 subset analysis showing that the hazard ratio seems
11 to be most beneficial in patients with the high
12 risk tumor, should we consider or at least
13 recommend, if we think that the risk-benefit is
14 adequate here, whether or not there should be more
15 stringent enrollment or more stringent eligibility
16 for approval.

17 Right now, the only eligibility is
18 progressive disease within one year, and we know
19 that this has got a very broad natural history, and
20 there may in fact be folks that progress at one
21 year that are going to be much more indolent, and,
22 therefore, the risk may not be worthwhile.

1 So that's how I want to frame this. And I
2 think that Tito Fojo actually had a concern whether
3 or not the censoring may have actually imparted
4 undue bias and whether or not the progression-free
5 is really that stringent or not.

6 So, anyway, I throw those ideas out.

7 Dr. Choyke?

8 DR. CHOYKE: Before we get started on this,
9 could I ask another naïve question about, if this
10 were approved as a drug, where would it fit in
11 the -- would this be a first line therapy for
12 patients?

13 DR. WILSON: Let me ask FDA.

14 DR. PAZDUR: The indication -- that's why I
15 think this is what Dr. Wilson was framing, is what
16 type of indication or what kind of limitations
17 would you want to put on the indication.

18 The indication that is being sought here is
19 for the treatment of patients with advanced
20 neuroendocrine tumors of pancreatic origin. So
21 that's a huge indication and could be somebody from
22 the very get-go right after surgery that may have

1 very minimal disease.

2 Here, again, with any disease, there is a
3 variation in the natural history. Would you want
4 to put some caveats on which patients would be
5 reasonable to treat with this?

6 You had a very similar discussion with this
7 committee on the medullary thyroid carcinoma drug
8 several months ago, where we did have some
9 restrictions, looking at symptomatic progressive
10 disease in patients in that disease. So here,
11 again, given the toxicity, given the variations in
12 the natural history, we're asking you, also, to
13 opine on potential indications and limitations.

14 DR. WILSON: So let me ask a very specific
15 question, and I would welcome the sponsor's input
16 on this, as well.

17 Is progressive disease within 12 months a
18 very liberal definition for a tumor like this?

19 Dr. Fojo?

20 DR. FOJO: No. I just -- because I think
21 Dr. Lebowhl clarified this. It wasn't that they
22 progressed within 12 months. I mean, it could have

1 taken three years to progress. It's just that that
2 was finally scored in the 12-month period before
3 they enrolled on study. So we don't know how fast
4 or how slow they were growing really.

5 DR. LEBWOHL: That's correct. We do have
6 some data that may help you on this, as the FDA
7 asked us during the analysis, patients who
8 progressed at less than three months or patients
9 who progressed at greater than three months with
10 pancreatic neuroendocrine tumors.

11 DR. WILSON: Right.

12 DR. LEBWOHL: I think it is important to
13 understand the benefit in each of those subsets.

14 DR. WILSON: So if you progressed -- if it
15 took you more than 12 months to progress, you could
16 have gone on the study. I'm confused, because
17 that's not what --

18 DR. FOJO: No. You just have to have
19 progressed in the year before you enrolled. You
20 couldn't have progressed 15 months before and now
21 come and enroll. So in the 12 months before you
22 enroll, there had to be an x-ray that showed

1 progression relative to something in the past, and
2 it could have been the recent past or the distant
3 past.

4 If you were being scanned every two years,
5 two years ago, you may have had 100 percent and now
6 have 121 percent two years later, then you're
7 eligible.

8 DR. LEBWOHL: That's correct. So here is
9 the data here. As you saw, half the patients
10 progressed at 1.7 months, the median. Seventy
11 percent progressed within three months. This is
12 the cut-point that the FDA asked us about at the
13 orientation meeting.

14 What you see is a hazard ratio of .38 if
15 they progressed within three months of
16 randomization. Between three and 12 months, the
17 hazard ratio is .36. So anytime in that period,
18 there is a benefit.

19 What may be interesting to you is there does
20 seem to be a slightly better prognosis of the
21 patients who progressed greater than three months,
22 so they may not have needed to come on therapy as

1 early or they were in shape to come on even though
2 they processed three to 12 months later; six to 14
3 months or an eight-month benefit versus four to 11
4 months or a seven-month benefit, depending on those
5 two periods, but very similar benefit in both
6 populations.

7 DR. FOJO: Yes. But this is not addressing
8 what the pace of the disease was. This is
9 addressing how quickly they went on study. And you
10 have a preponderance of the less than three months,
11 because your median was 1.7 months.

12 I think that's where you were going, and we
13 don't have that.

14 DR. WILSON: So this wouldn't be the kind of
15 wording we would use for our studies. If we say
16 progression within 12 months, it wouldn't be
17 12 months from the time that you were randomized.
18 It would have to be 12 months from the time that
19 you were considered a stable disease.

20 So as I understand it, then, this is wide
21 open. If you have advanced disease, you can go on
22 this drug; even at the time from diagnosis to an

1 advanced disease to progression was 50 years, you
2 could still go on this drug.

3 I really did not understand this, because
4 this isn't the way we actually use eligibility. So
5 this was my error, but I think it's a very good
6 clarification.

7 Yes, sir?

8 DR. KELSEN: Just to follow this up, I
9 suspect that the thing that we don't have is how
10 close the patients are being surveilled, because
11 it's practice among some oncologists in these
12 patients to do imaging studies every six months,
13 some oncologists once a year, depending from the
14 date of diagnosis. If it's recently diagnosed, you
15 don't know what the pace is. You'll do it every
16 three to four months. And unless sponsor can give
17 us that data, it's actually the velocity of
18 progression that we are completely missing.

19 So I don't know if these are totally
20 asymptomatic people who somebody did a scan on, as
21 Tito said, 18 month go, and then they did another
22 scan, and now it's 21, so he's eligible.

1 So I think that would be helpful if sponsor
2 could tell us that. It would affect the label,
3 because one is rapid progression or with the
4 development of symptoms and one is really indolent,
5 they've been around for 28 years, and now a scan
6 looks bad.

7 Do you happen to have velocity data?

8 DR. LEBWOHL: Let's bring up the
9 progression-free survival again, because it gives
10 you a good idea of how placebo patients are doing
11 as they enter this trial.

12 Again, 70 percent had progressed within
13 three months. So it gives you a pretty good idea
14 that at least the detection of progression by their
15 physician was very recent. They're being monitored
16 by their physician.

17 DR. KELSEN: No, I don't think that
18 data -- I don't think that that's --

19 DR. LEBWOHL: What you see here is that
20 80 percent of the patients had progressed by nine
21 months. So 50 percent by four months, 80 percent
22 by nine months. So by any measure, these are

1 patients who are rapidly progressing. Again, the
2 nature of these patients we've reported. These are
3 patients, almost all with metastatic disease and
4 with liver metastases.

5 DR. KELSEN: I don't want to hammer this to
6 death, but rapidly progressing patients with this
7 disease do not live for three years and haven't yet
8 reached the median. It's just they don't. So we
9 don't have the velocity data. We don't have it.
10 That's okay.

11 DR. LEBWOHL: David, in terms of three
12 years, again, you're not counting the fact that the
13 patients may be benefitting from the therapy.
14 Again, we can't show overall survival in the study,
15 but that is a possibility.

16 DR. KELSEN: Sure, but the therapy stops
17 working at a median of, say, 11 months or 12
18 months, or whatever it is, and then they're still
19 alive for two years.

20 DR. WILSON: Dr. Logan?

21 DR. LOGAN: I guess I just want to iterate
22 Dr. Wilson's point about the progression analyses.

1 We have seen a lot of inconsistency between the
2 different progression assessments and a number of
3 different analyses. Each of these has potential
4 bias, unfortunately.

5 The investigator analysis can be biased due
6 to unblinding, as the FDA pointed out, that may
7 occur from the toxicities. The independent review
8 committee analysis may be biased from informative
9 censoring. And, unfortunately, it's very difficult
10 to untangle all those potential biases and, in
11 fact, any attempt to do so basically relies on a
12 number of assumptions.

13 But as Dr. Wilson pointed out, we do see
14 consistency in the PNET study across the analyses
15 of progression-free survival scored according to
16 these different methods. So they do suggest a
17 benefit in terms of the median progression-free
18 survival at about six months, six to eight months.

19 The concern, of course, is how do you weigh
20 that benefit in progression against the increases
21 in toxicity that we're seeing, especially given the
22 fact that we're not seeing a difference in

1 survival. The difference in survival is difficult
2 to -- or the lack of difference in survival is
3 difficult to interpret. There may be an
4 attenuation of the effect from a high crossover,
5 and the survival data are very immature.

6 So I guess one question that I had was about
7 the accelerated approval mechanism. Is this
8 something that should be considered in this context
9 in terms of longer-term follow-up for survival
10 data?

11 DR. PAZDUR: Obviously, we could consider
12 it, but given the crossover and the significant
13 crossover, do you think that is realistic that when
14 you have that amount of crossover, you're really
15 going to see a difference in overall survival?
16 Because both arms are basically getting the same
17 drug.

18 DR. WILSON: I mean, I think it would be
19 nice. However, you point out that if you don't see
20 it, I don't think that necessarily takes away that
21 this may in fact be prolonging overall survival.

22 Dr. Sekeres?

1 DR. SEKERES: Thank you, Dr. Wilson. Just
2 to follow-up again. I think you and I have been
3 beating the same drum, when I discussed the
4 survival curves earlier.

5 I suspect that this is a population that has
6 a more indolent disease than perhaps the median
7 survivals for metastatic pancreatic neuroendocrine
8 tumors presented earlier. That being said, this is
9 also the population where we discussed at an
10 earlier meeting where an interim marker may be
11 actually appropriate. So it may be okay that this
12 is a more indolent disease and that progression-
13 free survival is being used because it may indeed
14 be impossible in a rare disease with a prolonged
15 course to demonstrate an overall survival
16 advantage.

17 So I'm actually surprisingly okay with that,
18 with using PFS in this situation, as long as we all
19 acknowledge that this is a very heterogeneous
20 population that has a more indolent course.

21 I do have one question for the FDA. In
22 looking at the discrepancies, I think it was a

1 41 percent discrepancy between different reviews of
2 CT scans for progression based on type or time.

3 Were there any sensitivity analyses to see
4 if those were in one direction or another? The
5 hazard ratios between investigators and central
6 review and the adjudication would indicate not,
7 that it probably was somewhat random and all evened
8 out at the end. But I'm just curious if those
9 analyses were done.

10 DR. MAHER: We did do sensitivity analyses.

11 DR. PAZDUR: You want to bring down your
12 microphone?

13 DR. MAHER: We did do sensitivity analyses
14 which looked at patients who were censored and
15 those who are not censored, and really showed very
16 similar results in the two.

17 DR. SEKERES: So there didn't appear to be
18 any kind of bias in one direction or another, that
19 patients who were on the treatment arm were
20 censored preferentially or patients who are on
21 placebo were censored preferentially.

22 DR. MAHER: We certainly see a higher

1 percentage of placebo patients who were censored
2 and a higher percentage of placebo patients who
3 were censored due to the type of event.

4 DR. WILSON: Let me just ask the members
5 here who treat this. Given that the indication as
6 it's now -- if we base it on the study, it's really
7 anybody who has advanced disease. And we see that
8 the -- well, there is an impression they are living
9 longer than you might expect. The historical
10 control is 17 percent. I recognize that 70 percent
11 of the placebo crossed over.

12 But what kind of indication would the
13 treating doctors here use to decide when somebody
14 should go on therapy? Is it just the moment you
15 see the disease growing?

16 I would presume, in an indolent disease,
17 like we do with low grade lymphomas, it's not about
18 growth, but as you bring up, Dr. Kelsen, it's about
19 the rate of growth and other indices. But perhaps
20 you and Dr. Fojo and other people who treat this
21 disease might want to comment on what you would
22 consider to be standards of care.

1 DR. KELSEN: I'm sure Dr. Fojo is going to
2 have some comments and probably Dr. Grem. I don't
3 think there is a standard of care to decide when to
4 intervene in these patients. There are several
5 different ways to approach the problem. I don't
6 think that most people or many people would say you
7 really need unequivocal evidence of progression of
8 disease under surveillance.

9 In a patient who has a positive octreoscan,
10 it's common practice to use octreotide as a single
11 agent as initial therapy. It's not universal
12 practice, but it's common practice. And if there's
13 failure of this less toxic therapy and the patient
14 has clearly progressed, at least in our place, on
15 two scans that are at least three to four months
16 apart, we would then say there's a failure and then
17 additional treatment, whether it's regional
18 therapy, which could be embolization, or a systemic
19 treatment would be considered.

20 So it would be unequivocal evidence of
21 progression of disease under surveillance with
22 images at least X period of time. I don't know how

1 you draw that label up, but that would be a way to
2 approach it, or the development of symptoms which
3 are uncontrollable by other methods.

4 DR. WILSON: Drs. Fojo or Grem, do you have
5 any additional thoughts?

6 Dr. FOJO: The only thing that I would point
7 out, which I was trying to point out with my last
8 question, is that it didn't appear to matter that
9 the therapy was delayed in terms of its efficacy.
10 Another way to look at that is that administering
11 it six months earlier didn't help any more. And I
12 would probably argue that administering 12, 18 and
13 24 months earlier wouldn't help any more. And that
14 would be, I think, the concern, based on what you
15 were pointing out, that it's a broad indication, is
16 that there's a lot of these patients that are quite
17 asymptomatic; yes, they have a tumor, oftentimes
18 widely metastatic, but earlier on the course of the
19 disease, when they're asymptomatic, you're going to
20 take and give them a drug that clearly is toxic.
21 You pointed out the dose reductions. I mean, 20
22 percent of the patients were discontinued on the

1 therapy.

2 So that would be my major concern that we
3 don't have any evidence that coming in earlier does
4 it and will do it just because we have it. And
5 we're taking patients in the best part of their
6 remaining life and actually giving them a drug,
7 which is going to make the quality of their life
8 much less than it would be otherwise.

9 So I think it's something that would be
10 prudent to hold off on administering it until there
11 was a clear indication for that.

12 DR. WILSON: So to be helpful to the FDA,
13 how would you, in the real world, frame that?

14 DR. KELSEN: I think we're saying the same
15 thing, but I' just try to say it, and we'll work it
16 out.

17 It would be unequivocal evidence of
18 progression of disease under surveillance of
19 several imaging studies, reasonably placed apart,
20 or the development of symptoms that could not be
21 controlled by other means. That's what I think
22 we're conceptualizing.

1 DR. WILSON: For example, would there be a
2 timeframe clinically? Like, for example, in
3 lymphomas, depending on the settings, we will do
4 six months or something like that. I'm just trying
5 to kind of get your thoughts, because FDA
6 may -- they want to get our advice. I'm just
7 wondering. Is there a little more structure?

8 I think symptoms, obviously, yes, but in the
9 absence of symptoms, in the absence of a mass
10 threatening a major organ, disease progression in
11 and of itself is more kind of a future issue than
12 it is a current issue if you don't have the other
13 two.

14 So is there a kinetics that you would be
15 looking for to be concerned about a future problem
16 occurring earlier, and would you put a number on
17 that, six months, 12 months, something like that?

18 DR. KELSEN: I think it's a shame that we
19 don't have that data, which is what you were asking
20 earlier. Right, exactly. And you would think it
21 would have been easy to obtain, because all you
22 needed to obtain was that last scan, Somewhere

1 else, and it was probably in the same center,
2 scored the patient as progression and see what they
3 did between that last scan and the enrollment scan.
4 And you might have been able to discern that, yes,
5 this is helping those with a fast pace to their
6 disease, but not those who have a more indolent
7 pace to their disease.

8 I suspect that also still could possibly be
9 gathered in this day and age of everything
10 digitalized, that we could probably get that
11 information and guide it better. But I think we're
12 both agreeing that you're going to prescribe it to
13 a very large patient population, the majority of
14 which probably don't require it.

15 Then the other thing, Lauren Erb made the
16 point, which was the disappointment that there
17 isn't correlative studies here, that we're looking
18 at even some basic things with regard to the mTOR
19 pathway that may have discerned who might benefit
20 and who might not.

21 DR. FOJO: That they can probably get from
22 the -- pull those slides. I was also wondering why

1 they hadn't pulled those slides.

2 But I think we're saying -- three to four
3 months apart is what we do, at least. I don't
4 think it's much different than what you said when
5 you said four to six months for lymphomas.

6 DR. WILSON: Dr. Grem?

7 DR. GREM: Right. It also has something to
8 do with burden of disease, because for some of
9 these people, they have 20 lesions in the liver,
10 but they're 10 to 15 millimeters in diameter. So
11 if three months later they're now 20 percent
12 bigger, that still really doesn't pose any kind of
13 threat to them. But it would be hard, I think, on
14 a label to specify those issues, and so then you're
15 going to be stuck saying that you need to have
16 evidence of documented disease progression and/or
17 symptomatic or impending symptoms. But I think
18 it's going to be hard to say on a label that you
19 have to have 30 percent involvement of the liver.
20 I think that's just impossible.

21 DR. WILSON: I don't think the label would
22 have to say that, but there probably is something

1 between anything and 30 percent.

2 The other issue I wanted to bring up is we
3 don't usually face trials where you're allowed to
4 use another effective agent, and it's been shown in
5 data that the company presented that that
6 agent -- I'm talking about octreotide -- actually
7 doubled the time to progression when combined with
8 everolimus versus everolimus alone.

9 I guess that's got me a little bit -- that's
10 just, to me, a confounding factor, because we're
11 being asked to evaluate risk-benefit here, and I
12 think we would all agree that there is a clear,
13 consistent signal that everolimus is doing
14 something here. But if it was four weeks and we
15 see the increase in the toxicity, would we have the
16 same -- would we like the data as much.

17 So I just kind of want the committee's
18 thoughts about how they think about the confounding
19 aspect of the fact that there may be synergy
20 between octreotide and everolimus.

21 I think Dr. Grem has a, hopefully, comment
22 on that.

1 DR. GREM: The issue with Sandostatin is
2 there are sort of two levels. One is that for some
3 of these patients, they actually have symptoms
4 because of release of bioactive hormones, and the
5 Sandostatin can definitely decrease the secretion
6 of these bioactive substances, and so you get
7 improvement of symptoms.

8 Now, before we had the PROMID study, there
9 were some people who felt that if the tumor
10 expressed -- took up octreotide, then you must use
11 Sandostatin because it has a definite anti-
12 proliferative effect. The only solid data comes
13 from a small randomized study that was done in
14 Europe, where they took patients who had basically
15 intestinal midgut neuroendocrine tumors that may or
16 may not be symptomatic, and they were randomized to
17 just careful surveillance versus giving them
18 Sandostatin LAR. And in that, they showed a
19 significant improvement in progression-free
20 survival, but it was on the order of a couple of
21 years. And so that was really the first data that
22 showed that there may be a direct anti-

1 proliferative effect of the Sandostatin.

2 So the unresolved issues with the use of
3 Sandostatin, when this is the only drug that we
4 have, clearly if they're having more symptoms
5 because of increasing hormone secretion, the
6 strategy is to go ahead and increase the dose of
7 Sandostatin or give it more often.

8 What we don't know is if they don't have a
9 functioning tumor and they now have disease
10 progression, in the absence of having anything else
11 to use, some clinicians are saying, "Well, let's
12 try giving a higher dose of Sandostatin," even
13 though we really don't have any data that that
14 works. But it sort of just shows you that you're
15 dealing with people who they want treatment, they
16 want something to do. They're not really having
17 symptoms, but things are getting worse on their
18 scan. And so it's one of those things that it's
19 very difficult for patients; if they have
20 functioning tumors, it's hard to tell them they're
21 going to have to stop the Sandostatin.

22 I think it's a different issue if they're

1 just on it for the putative anti-proliferative
2 effect. I think in that case, if the disease is
3 progressing, it's not working, going to quadruple
4 the dose of Sandostatin is probably not going to
5 affect that.

6 DR. WILSON: FDA had a comment.

7 DR. PAZDUR: I think he answered it. As far
8 as the labeling, we will negotiate with the
9 sponsor. And I think when people are answering the
10 question, what we ask them to do when they vote is
11 answer the question as written, and if you feel
12 that there needs to be a further restriction on the
13 population, please mention that when we go around
14 to poll you at the conclusion.

15 DR. WILSON: Dr. Freedman?

16 DR. FREEDMAN: I just have a question for
17 the FDA just to clarify. Does the orphan drug
18 designation affect in any way how this drug is
19 looked at in terms of its indication?

20 DR. PAZDUR: No.

21 DR. WILSON: Let me pose one more question
22 for the specialists here.

1 Would you think that octreotide ought to be
2 used first before going on to a drug like this?

3 It sounds like given the fact that that is
4 commonly used, I think there's very good evidence
5 that it works. Would that be considered standard
6 of care?

7 DR. KELSEN: Well, as Jean said, I'm not
8 sure we can say it's standard of care. There's a
9 second trial that was underway, I don't know if it
10 was ever completed, with lanreotide, a random
11 assignment trial in about three times as many
12 patients as the German study that suggested that in
13 carcinoid tumors, octreotide is useful.

14 I think it's pretty common practice if the
15 octreoscan is positive, so the target is expressed
16 and the tumor is growing, to use octreotide,
17 because it is relatively nontoxic, and at least we
18 have one small study. That's a big difference than
19 saying in the label it should require that they
20 have octreotide first, because I don't think we
21 have any data to address that issue. That's my
22 feeling today anyway.

1 DR. FOJO: I also think the practical thing
2 will be, because it's not curative and it only
3 works so well, to then quickly add the second drug
4 on top of it. So I don't see physicians trying
5 this and let's hunker down and see how far we get
6 with this before we think of adding something. So
7 once this was out there, it would quickly be added.
8 So it's additive or synergistic, well, that's okay.
9 That's a plus, from my point of view.

10 But can I just come back to one thing that I
11 was trying to make before, and it relates to the
12 efficacy and safety issue. And that is that we
13 keep saying, "Oh, yes, the investigator and the
14 independent review came up with similar hazard
15 ratios."

16 Realize that once the investigator scored
17 somebody as progressive disease, then that fixes
18 that patient, of which there are more in the
19 placebo arm, with a bad outcome; that all the IRC
20 can do is reduce the penalty to a censor. It can't
21 say, "Okay, you get to be progression-free for a
22 longer time." So once the investigators introduced

1 that bias into it, then it was never going to
2 disappear altogether, and especially if you
3 introduce a lot of that bias, it's impossible to
4 leave the .3.

5 Having said that, there probably would
6 be -- I wish we would have had data without the
7 censored patients. I think we probably would have
8 found that there was a hazard ratio in favor, but
9 nowhere near this .36, .38 that keeps coming up.
10 That's been driven by that bias that was introduced
11 by the investigators.

12 DR. WILSON: So do you think -- because we
13 can't fix this, do you think that there is
14 compelling evidence, based on this, that the real
15 hazard ratio is less or more, and, therefore, the
16 benefit is not nearly as great. Because, again,
17 what we're looking at here -- I'm just trying to
18 get a sense of what you're really saying here. I
19 think everything you say is right, but the rubber
20 hits the road here.

21 Does it really matter when it comes down to
22 what we're dealing with now, because we have what

1 we have?

2 DR. FOJO: I think the hazard ratio is not
3 as great as is shown, and I actually think you can
4 go to the markers, to the tumor markers, to see
5 that. There is a difference, no doubt about it.
6 But, again, if those were, instead of tumor
7 markers, those were tumor burdens, you would find
8 the hazard ratio, but that wasn't nearly as great.

9 Then the other thing that we all know, the
10 benefit is in a subset of these patients. It's not
11 in the patient as a whole. There are clearly some
12 patients that are probably receiving great benefit
13 from this, but a majority of them are not, and
14 that's hopefully what in the future can be
15 discerned, sorted out.

16 DR. WILSON: I'll get you in, in a second,
17 Dr. Grem. We do know, at least from the subset
18 analysis, with all the caveats around the subset
19 analysis, that those patients that had the more
20 aggressive disease seemed to be the ones that had
21 the greatest benefit. But I think that, again, we
22 have what we have here, and unless we have

1 compelling evidence, that all this censoring is an
2 issue.

3 In fact, we have Dr. Logan here. And maybe,
4 Dr. Logan, you've looked at this data. This is
5 really a statistical issue.

6 Do you feel that the censoring is so
7 imbalanced here that we may not really be getting
8 anywhere near the accuracy that we should be
9 wanting?

10 DR. LOGAN: Well, I think the censoring is
11 not an issue with the investigator analysis.
12 That's the first point. It's the IRC analysis.
13 Certainly, there are concerns there. There are
14 sensitivity analyses that could be done. I don't
15 know the extent that they have been done here to
16 look at that. But any of those sensitivity
17 analyses have assumptions, so it's difficult. I
18 mean, you don't have the data. The data is just
19 not there, and it's difficult to make a real
20 conclusive statement.

21 But the investigator analysis, at a minimum,
22 doesn't have that issue. The investigator analysis

1 may have other issues in terms of the lack of the
2 potential break of the blinding.

3 DR. WILSON: Dr. Grem?

4 DR. GREM: And I would not want to see this
5 restricted to metastatic disease, because with the
6 neuroendocrine tumors and with the pancreatic
7 neuroendocrine tumors, they can have -- they
8 present with unresectable disease with nodal
9 involvement, and it doesn't spread, but over time,
10 things just get more -- they get a lot of scarring
11 around that, and you can end up getting encasement
12 of lymphatics and vessels that, over time, they're
13 not going to die of metastatic disease, but they're
14 going to die of intestinal ischemia or lymphatic
15 obstruction, and they end up getting refractory
16 ascites and that type of thing.

17 DR. WILSON: So you bring up a very good
18 issue here, and I would appreciate FDA's guidance.
19 We have an eligibility that calls for advanced, but
20 the reality is 90 percent-plus had metastatic
21 disease.

22 How do you reconcile the fact that the

1 clinical trial represents a group that has
2 metastatic disease, but the entry criteria were
3 actually more open, such as what Dr. Grem brought
4 up?

5 DR. PAZDUR: Generally, we approve a drug
6 with the population that has been studied in the
7 trial, and it is described therein. There are some
8 different situations recently that we brought on
9 labels, et cetera, but in this situation, we're
10 looking at the population that was studied, so to
11 speak. And here, again, our discussion of whether
12 we want to make it more restrictive is one that
13 we're interested in hearing your comments on.

14 Here, again, there is a point -- and that's
15 why don't want to delve into great detail on this
16 and trying to put numbers on things, et cetera, but
17 we almost broach into the area of the practice of
18 medicine here. We want to give some broad general
19 guidance to clinicians, and then after that, I
20 think one has to take a look at an individual
21 patient and an individual physician making a
22 decision here.

1 The major issue I think we have is just
2 rushing into this with the first diagnosis of
3 neuroendocrine tumors being established in a
4 completely asymptomatic patient and not having any
5 history of how that patient is going to do; just
6 there's a new drug on the market, let's just use
7 it, kind of kneejerk reaction.

8 DR. KELSEN: Do you ever use a phrase like
9 "unequivocal progression of disease" or
10 "uncontrollable symptoms" in a label? Because I
11 agree with you that it's very hard to say --

12 DR. PAZDUR: We could use those phrases.
13 Here, again, there are more nuances here, and, in
14 general, the labeling and the indication is
15 something that we get into with the sponsor in
16 greater detail out of the ODAC meeting venue, so to
17 speak. So I think the issue here is we're looking
18 for more broader guidance from people rather than
19 the specific language of the label.

20 DR. WILSON: Dr. Fojo?

21 DR. FOJO: I think there should be clarity
22 that -- because sometimes people think of PNETs and

1 carcinoids as one continuum. They did withdraw the
2 carcinoid indication, and this would not apply to
3 those tumors. That just would need to be clear.

4 DR. PAZDUR: And we could put even a
5 restriction in the labeling that it's not indicated
6 or has not been demonstrated to have efficacy in
7 carcinoid tumors.

8 DR. WILSON: Any further thoughts?

9 [No response.]

10 DR. WILSON: Okay. Well, then, let's go
11 ahead and move on to the voting. Before I read the
12 vote, I would like to have you all look at your
13 mics there. Your name is on the mic, and there is
14 a yes and a no and an abstain button. And so when
15 I tell you to vote, you will press one of those.
16 Then we will see the results on the screen, and
17 then we will go around the room. If you could, for
18 the voting members, we'll start with Dr. Curt, if
19 you can give your name, how you voted, and why you
20 voted the way you did.

21 So the vote is as follows: Is the benefit-
22 risk analysis favorable in the treatment of

1 patients with advanced pancreatic neuroendocrine
2 tumors based on the demonstrated efficacy and
3 safety profile of everolimus? And let's go ahead
4 and vote.

5 [Voting.]

6 DR. WILSON: So I would like to read the
7 following into the record; yes-10, no-zero,
8 abstain-zero.

9 So starting with Dr. Curt, if you could
10 comment on why you voted, and also if you could
11 perhaps address FDA's further clarification as to
12 whether or not you think there should be some
13 restriction beyond what was the entry criteria for
14 the study.

15 DR. CURT: Just to be clear, Dr. Wilson, as
16 the industry rep, I'm a nonvoting member. Thank
17 you.

18 DR. WILSON: Thank you. Yes, correct.
19 Sorry.

20 Dr. Choyke?

21 DR. CHOYKE: So I voted yes because I think
22 this drug has activity in metastatic disease in

1 pancreatic neuroendocrine tumor, and most
2 convincing, I think is the waterfall plot that
3 clearly shows activity.

4 I'm moved by the argument that there's
5 really nothing else out there in this disease, but
6 I'm also cautious because I do know that the tempo
7 of this disease is extremely variable. It's really
8 a spectrum of diseases, ranging from very indolent
9 to very aggressive, and it seems like the evidence
10 is stronger that the risk-benefit ratio will be
11 better in people with more aggressive disease
12 that's progressive.

13 DR. KELSEN: Dave Kelsen. I voted yes. I
14 think that there is a subgroup of these patients
15 who we will eventually identify who would clearly
16 benefit from this mTOR inhibitor. I don't think
17 it's the entire group, but I think that this will
18 come. And I think that there's been enough
19 discussion that it's clear it will not be widely
20 available -- well, that's a better way of putting
21 it -- that there will be care in drawing up the
22 label so that it will be limited to patients or at

1 least the label will say it is patients who clearly
2 have progressed or who clearly have symptoms and
3 need this, and there will be enough education so
4 that it will not be given to patients right at the
5 time of their first diagnosis.

6 DR. FOJO: Tito Fojo. I voted yes, maybe
7 just barely. I think that there is a fair amount
8 of risk that we didn't discuss in the last
9 45 minutes, and I think that that risk has got to
10 be confined to patients who have a real need for
11 intervention with this drug. And if that's the
12 case, then at that point, there is benefit that
13 might be favorable. But hopefully the FDA and the
14 sponsor, as well as academia, will work very hard
15 to identify the small fraction of patients who
16 benefit from this.

17 DR. LOGAN: Brent Logan. I voted yes, as
18 well. There appeared to be a fairly sizable
19 magnitude of the benefit in the progression-free
20 survival that was robust to a number of different
21 analyses, given the potentials for bias.

22 There were certainly concerns about

1 toxicity, and I share the concerns of the previous
2 comments in terms of a better delineation of the
3 patients that really need the drug given that it
4 is, in many patients, an indolent disease, as we
5 saw in many of the survival curves.

6 DR. GREM: Jean Grem. I voted yes, because
7 I think there is an unmet need and, actually, in
8 terms of the -- there are toxicities with some of
9 the regional therapies that we employ for patients
10 with significant burden to the liver -- has
11 substantial toxicities. And since those are
12 considered devices, there really isn't very strong
13 data, but that's sort of universally -- I shouldn't
14 say universally, but widely employed. You have to
15 share referral centers to treat these patients, and
16 now, even in the community, people have their ads
17 up on their Web page, "Come here to
18 radioembolization" and everything.

19 So I think that this is something where it
20 is a large randomized study. We have concerns
21 about the data interpretation, et cetera, but as
22 our statisticians have pointed out, it did seem to

1 survive the different analyses, and I think it has
2 activity in at least some of these patients.

3 DR. SEKERES: I'm Mikkael Sekeres, and I
4 voted yes. I voted yes because this is precisely
5 the disease and precisely the patient population in
6 whom I think interim markers for survival are
7 appropriate in that the disease is rare, the
8 disease, of course, can be indolent, and there are
9 limited available therapies for patients with
10 pancreatic neuroendocrine tumors.

11 My caution, though, is to avoid this drug in
12 patients with carcinoid tumors in whom certainly no
13 benefit has been demonstrated and in whom the drug
14 may actually do harm.

15 DR. WILSON: Wyndham Wilson. I voted yes.
16 I would just like to echo what we've been
17 discussing, and that is that this is a drug that
18 does have serious side effects. It is also a drug
19 that I think I believe has effectiveness, as well.

20 I think that this is a drug where the risk-
21 benefit is going to be greatest in people who need
22 therapy. And I'm really quite convinced by that if

1 I look at the subgroup analysis, because all of the
2 hazard ratios are more favorable in the patients
3 who have the worst performance status, who are
4 older, who are the ones that have less well
5 differentiated tumor, indicating that it seems to
6 benefit those that are higher risk.

7 So I think that if there was some way to
8 label this so it wasn't quite so open, that we
9 would be enhancing the risk-benefit for patients.

10 DR. FREEDMAN: I'm Ralph Freedman. I voted
11 yes, since there was an improvement in progression-
12 free survival across the board and because this is
13 a rare disease that is certainly deserving of new
14 options at this time.

15 I was, however, concerned about the adverse
16 events, particularly those events where there's
17 confusion as to whether it's related to the drug or
18 whether to the disease, and also the seven deaths
19 that the FDA mentioned that they assessed as being
20 attributable to the drug.

21 I would say that in addition to excluding
22 the carcinoid group for which it's too

1 controversial, and even the company would appear to
2 have admitted that, there should be some monitoring
3 of the long-term effects and maybe the deaths, in
4 particular.

5 MS. MASON: I'm Virginia Mason, and I voted
6 yes and for many of the same reasons you've already
7 heard, with a few reservations regarding the
8 toxicities. But I would hope since this is a
9 disease that doesn't have a lot of treatment
10 options, that this would be used for the
11 appropriate patient population.

12 MR. EPPERLEIN: I'm Jim Epperlein, and I'm a
13 patient survivor. And I'm very proud at this
14 moment, very thankful at this moment for the
15 sponsors, the committee, the FDA, for a tremendous
16 presentation. And I think Carol and the other
17 wonderful lady back there said it best. You've
18 just provided hope for all of us, and that means
19 more than anything. Thank you.

20 **Adjournment**

21 DR. WILSON: Okay. Thank you. It's now
22 just about noontime. We will take a one-hour lunch

1 break. We will start again at 1:00 sharp.

2 May I remind the committee to please not
3 discuss this afternoon's presentations. Thank you.

4 (Whereupon, at 11:52 p.m., the morning
5 session was adjourned.)

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