FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC) MEETING

Morning Session

THURSDAY, DECEMBER 7, 2011

8:00 a.m. to 11:30 a.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

ACTING DESIGNATED FEDERAL OFFICER (Non-Voting)

Yvette Waples, Pharm.D.

Division of Advisory Committee and Consultant Management

Office of Executive Programs, CDER, FDA

ONCOLOGIC DRUGS ADVISORY COMMITTEE MEMBERS (Voting)

Deborah K. Armstrong, M.D.

Associate Professor of Oncology

The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

The Johns Hopkins University School of Medicine

Baltimore, Maryland

Ralph Freedman, M.D., Ph.D.

Clinical Professor

Department of Gynecologic Oncology

The University of Texas

M.D. Anderson Cancer Center

Houston, Texas

Wm Kevin Kelly, D.O.
Professor, Medical Oncology and Urology
Director, Division of Solid Tumor Oncology
Associate Director, Translational Research
Thomas Jefferson University
Philadelphia, Pennsylvania

Brent Logan, Ph.D.
Professor of Biostatistics
Division of Biostatistics
Medical College of Wisconsin
Milwaukee, Wisconsin

Mikkael Sekeres, M.D., M.S.
Associate Professor of Medicine
Staff, Cleveland Clinic Taussig Cancer Institute
Department of Hematologic Oncology and Blood
Disorders Cleveland, Ohio

Julie M. Vose, M.D., M.B.A.
Neumann M. and Mildred E. Harris Professor
Chief, Division of Hematology/Oncology
Professor of Medicine
Nebraska Medical Center
Omaha, Nebraska

Wyndham Wilson, M.D., Ph.D. (Chair)
Chief, Lymphoma Therapeutics Section
Metabolism Branch
Center for Cancer Research
National Cancer Institute (NCI)
National Institutes of Health (NIH)
Rockville, Maryland

TEMPORARY MEMBERS (Voting)

Aman U. Buzdar, M.D.
VP Clinical Research and Interim
Professor of Medicine
UT M.D. Anderson Cancer Center
Dept. of Breast Medical Oncology
Houston, Texas

Louis F. Diehl, M.D.
Professor of Medicine
Duke University Medical Center
Durham, North Carolina

Tito Fojo, M.D., Ph.D.
Senior Investigator and Director
Medical Oncology Fellowship Program, NCI, NIH
Bethesda, Maryland

Marc Garnick, M.D. *(Morning Session Only)*
Beth Israel Deaconess Medical Center
Clinical Professor of Medicine
Harvard Medical School
Boston, Massachusetts

Mary Meyer *(Morning Session Only)*
(Patient Representative)
South Salem, New York

TEMPORARY MEMBERS (Voting)

Jane Zones, Ph.D.

(Acting Consumer Representative)

Medical Sociologist (retired)

Breast Cancer Action

National Women's Health Network

San Francisco, California

ACTING INDUSTRY REPRESENTATIVE TO THE COMMITTEE

(Non-Voting)

Gregory Curt, M.D.

(Acting Industry Representative)

U.S. Medical Science Lead, Emerging Products

AstraZeneca Oncology

Wilmington, Delaware

FDA PARTICIPANTS (Non-Voting)

Richard Pazdur, M.D.

Director, Office of Hematology & Oncology Products (OHOP)

Office of New Drugs (OND), CDER, FDA

Amna Ibrahim, M.D. *(Morning Session Only)*
Deputy Director
Division of Oncology Products 1 (DOP1)
OHOP, OND, CDER, FDA

John Johnson, M.D. *(Morning Session Only)*
Medical Team Leader
DOP1, OHOP, OND, CDER, FDA

Amy McKee, M.D. *(Morning Session Only)*
Medical Officer
DOP1, OHOP, OND, CDER, FDA

Somesh Chattopadhyay, Ph.D. *(Morning Session Only)*
Statistical Reviewer
Division of Biostatistics V (DBV)
Office of Biostatistics (OB)
Office of Translational Science (OTS)
CDER, FDA

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(7:58 a.m.)

Call to Order

Introduction of Committee

DR. WILSON: Okay. Let's go ahead and get started.

Yvette?

DR. WAPLES: Good morning. I would first like to remind everyone present to please silence your cell phones, BlackBerrys, and other devices if you have not done so. I would like to identify the FDA press contact, Ms. Erica Jefferson.

If you are here, please stand. Thank you.

DR. WILSON: Good morning. My name is Wyndham Wilson, and I'm the chair of the Oncologic Drugs Advisory Committee, and I would now like to call the meeting to order. I'd like to have us go around the room and state our name and where we're from into the record, and I'll start on the right with Dr. Curt.

DR. CURT: Gregory Curt, medical oncologist, acting industry representative to the ODAC.

DR. BUZDAR: Aman Buzdar from MD Anderson Cancer Center, Houston.

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

DR. DIEHL: Lou Diehl, Duke University, lymphoma branch.

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

DR. VOSE: Julie Vose, University of Nebraska, hematology oncology.

DR. ZONES: Jane Zones, I'm the acting consumer rep, and I'm a medical sociologist.

DR. WAPLES: Yvette Waples. I'm the DFO for this meeting. Thank you.

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

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

DR. FREEDMAN: Ralph Freedman, gynecologic oncology, MD Anderson Cancer Center.

DR. KELLY: William Kelly, medical oncologist, Thomas Jefferson University.

DR. GARNICK: Marc Garnick, medical oncologist, Beth Israel Deaconess Medical Center in Boston.

MS. MEYER: I'm Mary Meyer. I'm the patient representative.

DR. CHATTOPADHYAY: Somesh Chattapadhyay, FDA statistics and reviewer for this application.

DR. MCKEE: Amy McKee, medical officer for this application, FDA.

DR. JOHNSON: John Johnson, clinical team leader, FDA.

DR. IBRAHIM: Amna Ibrahim, deputy director at DOP1.

DR. PAZDUR: Richard Pazdur, office director, Office of Hematology Oncology Products.

DR. WILSON: Welcome all.

For the topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without

interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chair. We look forward to a productive meeting.

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

I would like to remind everyone present to please silence your cell phones and other electronic devices if you've not already done so. The committee is also reminded to please refrain from discussing the meeting topic during the breaks or lunch.

We will now have the conflict of interest statement read.

Could I please have Dr. Armstrong introduce herself into the record?

DR. ARMSTRONG: I'm Deborah Armstrong, medical oncologist from Johns Hopkins.

DR. WILSON: Thank you very much.

Conflict of Interest Statement

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to participants in

today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have a potential financial conflict when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest.

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

Related to discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children, and, for purposes

of 18 U.S.C. Section 208, their employers. These interests may include investments, consultant, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties and primary employment.

Today the committee will discuss new drug application NDA 202324 with a proposed trade name Inlyta, axitinib tablets, application submitted by Pfizer. The proposed indication is for treatment of patients with advanced renal cell carcinoma. This is a particular matters meeting during where specific matters related to Pfizer's NDA for Inlyta will be discussed.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript. To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry

representative, we would like to disclose that Dr. Gregory Curt is participating in this meeting as a non-voting industry representative, acting on behalf of regulated industry. Dr. Curt's role at this meeting is to represent industry in general and not any particular company. Dr. Curt is employed by AstraZeneca.

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

DR. WILSON: We will now proceed with the FDA opening remarks. I would like to remind the public observers at this meeting that while this meeting is open for public observation, public

attendees may not participate except at the specific request of the panel.

DR. PAZDUR: We don't --

DR. WILSON: Okay. Just reading off the script. Thank you very much.

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

For this reason, FDA encourages all participants, including the sponsor's non-employee presenters, to advise the committee of any financial relationships that they may have with the firm at issue, such as consulting fees, travel expenses, honoraria and interests in the sponsor, including equity interests and those based upon the outcome of the meeting.

Likewise, FDA encourages you at the beginning of your presentation to advise the

committee if you do not have such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

I would now like to proceed to the sponsor's presentation. I believe Dr. Rothenberg will be giving it.

Sponsor Presentation – Mace Rothenberg

DR. ROTHENBERG: Thank you, Dr. Wilson, and good morning, members of ODAC, Dr. Pazdur, FDA staff, ladies and gentlemen. We are here today to discuss our application for axitinib in the treatment of patients with renal cell carcinoma.

My name is Mace Rothenberg. I'm senior vice president for clinical development and medical affairs at Pfizer.

Glen Andrews is the axitinib team leader from Pfizer and will provide background on the compound.

Dr. Brian Rini from the Cleveland Clinic is the principal investigator of the pivotal phase 3

trial known as A 4061032 or AXIS 1032 and will present rationale for the study's design and a summary of the clinical efficacy of axitinib in advanced RCC.

Dr. Sinil Kim from Pfizer is the global clinical leader for axitinib and will present an overview of clinical safety.

Dr. Robert Motzer from Memorial Sloan Kettering Cancer Center, a physician who sees and treats these patients every day, will provide an overview of treatment options in this disease and share his perspective on how axitinib could contribute to the treatment of patients with advanced renal cell carcinoma.

I will then finish our presentation with concluding remarks.

We're also joined by Dr. David Cella, professor and chair of the department of medical social sciences at Northwestern University's Feinberg School of Medicine. He is an expert in patient-reported outcomes and is a consultant to us for this purpose today.

In 2011, more than 60,000 people will develop renal cell carcinoma in the United States. Approximately 20 percent of them will present with metastatic disease. And in addition, 30 percent of patients who present with local or locally advanced disease will relapse and require systemic treatment. As a result, approximately 13,000 Americans will die of this disease this year.

There are three established targets for the systemic treatment of advanced RCC, the immune system, the mTOR signaling pathway, and the vascular endothelial growth factor pathway. Inhibition of VEGF receptor signaling forms the backbone of advanced RCC therapy. Mechanistically, this pathway is triggered through the inactivation of Von-Hippel Lindau tumor suppressor gene, leading to high levels of VEGF. Signaling by VEGF is key to angiogenesis and a driver of renal cell carcinoma.

There are six targeted therapies that have been FDA approved for the treatment of advanced RCC. As you can see here, the pivotal trials that

led to approval of all by one of them had progression-free survival as the primary endpoint. Please note that three trials used placebo in the control arm, and three trials compared the new agent to interferon alpha. None of these trials used active targeted therapy in the control arm.

Here are the results of those studies. As you can see, the hazard ratio for progression-free survival range from .33 to .66, representing a substantial delay of tumor progression, a clinically meaningful endpoint for this disease. In addition, with the exception of temsirolimus, none of these studies demonstrated a significant improvement in overall survival, likely due to crossover or receipt of subsequent therapies by patients enrolled in these studies.

This is a graphical depiction of those data. While there was a distribution of hazard ratios for PFS, all of which were significantly below 1, there was a much narrower distribution of hazard ratios for overall survival, all of which were close to 1.

How does this relate to today's

presentation? The primary endpoint for the pivotal AXIS 1032 study was progression-free survival. The study design and selection of the primary endpoint were agreed to by the FDA in a special protocol assessment in 2008. The control arm for AXIS 1032 consisted of sorafenib, a drug FDA approved for patients with advanced renal cell carcinoma. This is the first phase 3 trial in advanced RCC to use an active VEGFR TKI comparator in the control arm and the first phase 3 trial to evaluate two VEGFR inhibitors in a head-to-head comparison.

It's important to recognize that the use of a VEGFR TKI as an active control in the study creates a higher hurdle for the experimental arm to demonstrate superiority than if placebo or best supportive care were used. As has been observed in other phase 3 trials in advanced RCC, the receipt of active therapy after completion of study treatment cannot be controlled and could attenuate any difference in overall survival attributed to the study drug. In addition, we know survival post progression can also have a similar effect.

Keeping these factors in mind during today's discussion will help place the data to be presented today in proper perspective.

I would now like to introduce Glen Andrews, axitinib team leader from Pfizer, who will provide an overview of axitinib.

Sponsor Presentation – Glen Andrews

DR. ANDREWS: Thank you, Dr. Rothenberg, and good morning.

My name is Glen Andrews. I'm the team leader for axitinib at Pfizer, and as we've heard from Dr. Rothenberg, great progress has been made in the treatment of RCC extending overall survival from 12 months in the area of cytokines out to 24 months by targeting the VEGF pathway. But patients still progress on the current treatments, and most agents are multi-targeted TKIs associated with additional toxicities. Consequently, there is a need for new agents with increased efficacy and reduced toxicity.

Axitinib then was specifically designed with that intent using structured base drug design. As

you can see from the co-crystal structure on the right, axitinib in green fits tightly in the deep pocket of the ATP binding site in the kinase domain of the VEGF receptor and interacts with the juxtamembrane domain side-chain, the dash line here. This is a characteristic specific to axitinib, and the tight fit was intended to provide greater selectivity and potency and ultimately, greater efficacy coupled with less toxicity.

Non-clinically, we were able to show that axitinib was more potent and selective than other approved VEGFR TKIs. And on the left-hand side here on the chart, I've shown the potent and specific inhibition of autophosphorylation of VEGF receptors 1, 2 and 3 for axitinib and other TKIs. A lower IC50 indicates greater potency, and in the plot, the dividing line is at 1 nanomolar. Notably, axitinib's IC50 is a sub-nanomolar and tenfold smaller than for other agents, indicating its greater potency for VEGF receptors.

The right-hand side then shows selectivity of these TKIs for VEGF receptor 2 relative to other

related targets. As you can see, axitinib is highly selective for VEGF receptor 2 relative to other targets.

In phase 2 studies, we saw clinical evidence of the activity of axitinib translated from this preclinical work, and we've shown these data here. These are all single-arm studies of axitinib conducted at a starting dose of 5 milligram BID and including a primary endpoint of objective response rate.

In the cytokine refractory study shown in blue, we saw a response rate of 44 to 50 percent, and a median progression-free survival between 11 to 13.7 months. The median overall survival of almost 30 months in phase 2 Study A 4061012 in cytokine refractory patients was also encouraging.

In an even more refractory study, the last study here, Study 1023, a response rate of 23 percent was seen. In fact, in this study, some patients were refractory to both sorafenib, sunitinib, and patients had received a median of three prior treatments. In total then, these data

provided evidence of the antitumor activity of axitinib in refractory patients and provided confidence to start a phase 3 study.

Our principal investigator, Dr. Brian Rini, will describe the design and efficacy data from our phase 3 study, AXIS A 4061032 later. Here, I've just shown the key timelines for this study. I would emphasize that we designed the study in collaboration with the FDA, and in early 2008 reached a SPA agreement, special protocol assessment agreement, on the protocol, including agreement regarding the primary endpoint of progression-free survival and sorafenib as a comparator.

Beyond that, the first subject was dosed in September 2008, and the last subject was recruited in July 2010. Analysis of PFS occurred; final analysis of PFS occurred in November 2010, and submission of the NDA occurred in April 2011.

I would note at the time that we submitted the NDA, there were 223 OS events, and we presented these interim OS results in the briefing document

to the ODAC panel. The statistical analysis plan required 417 events to trigger the final overall survival analysis. We recently passed that milestone and triggered the final OS analysis.

We shared these results with the FDA at the end of November, and although they have not yet received the datasets in order to verify the results and do their own independent analysis, we have agreed to share these results with ODAC today in order to provide that updated information to you. You will hear more about these results from Dr. Rini.

We have an extensive safety database, and in total, there are approximately two and a half thousand subjects treated with axitinib. These then are the key RCC studies with approximately 900 RCC patients, 537 of whom have been treated with axitinib at a starting dose of 5 milligram BID. I've already discussed the three phase 2 studies, and I've highlighted in bold here the phase 3 study A 4061032 where 723 patients were randomized to axitinib or sorafenib with 361 randomized to

axitinib.

The basis then for our NDA is AXIS A 4061032 study in which the primary endpoint was achieved and demonstrated axitinib has greater efficacy compared with sorafenib in approved multi-targeted TKI.

In our comprehensive database, the adverse events seen were expected for the class and manageable with generally similar overall incidents as sorafenib. In total then, this provided, in our opinion, a favorable benefit-risk profile, and we look forward to expanding on this conclusion in the rest of the presentation.

I'd now like to invite Dr. Brian Rini to discuss the efficacy from the pivotal phase 3 study AXIS A 4061032.

Sponsor Presentation – Brian Rini

DR. RINI: Thank you. Good morning, everyone.

My name is Brian Rini. I'm an associate professor of medicine at the Cleveland Clinic in Cleveland, Ohio. I'm a paid consultant for Pfizer

and have received travel expenses for my attendance at this meeting today. However, I hold no personal financial interests in the outcome of this meeting.

I've been treating patients with advanced kidney cancer for approximately 13 years and studying axitinib for approximately eight years since the early phase 2 trials. I was the lead investigator on both of the phase 2 axitinib studies in the United States and was the principal investigator for the pivotal study AXIS 1032. Today, I'll be presenting a summary of clinical efficacy from that pivotal study.

As you heard from Dr. Andrews, there was rather robust activity of this drug in a refractory setting, demonstrated in single-arm phase 2 studies, and on that basis, a prospective phase 3 trial was conducted, the schema of which is shown here. These were metastatic kidney cancer patients who had progressive disease after one prior systemic first-line regimen, one of the four regimens that you see listed there.

Patients were stratified by ECOG performance

status and type of prior therapy and then randomized with equal probability to receive either axitinib at a dose of 5 milligrams twice daily or sorafenib at a standard dose in schedule of 400 milligrams twice daily.

There are two points about trial design that deserve further comment before I talk about the actual study results. The first is the patient population. As noted, one of several prior systemic regimens was allowed as frontline therapy. These were agents that were available for use when the study was initiated and are currently used today both in the U.S. and globally for the treatment of initial kidney cancer. This allowed for a global study again reflecting different treatment choices and availability within each of the regions.

The second item is the use of an active drug that is sorafenib as the control arm. As Dr. Rothenberg mentioned, this was the first study to compare one VEGF pathway targeted TKI to another, in fact, the first to compare any active

agents against other active agents.

Sorafenib was FDA approved almost exactly six years ago for the treatment of advanced kidney cancer based on a phase 3 study that was conducted in refractory subjects. Since the time of approval and up until currently, this drug is widely used in refractory patients, and retrospective data and later prospective clinical trials support the activity of this drug in this setting, as you see from the references listed.

The key eligibility for this phase 3 clinical trial included metastatic clear cell RCC with measurable disease. Patients must have had RECIST defined progressive disease after one and only one prior first-line systemic regimen. This prior regimen must have contained one or more of the following, either sunitinib, bevacizumab, interferon, temsirolimus or cytokines. Adequate performance status and adequate end-organ function was also required.

The primary endpoint for this phase 3 trial was progression-free survival for a blinded,

independent review committee or IRC. Secondary endpoints included overall survival, objective response rate, duration of response, safety, and kidney cancer specific symptoms and health status.

The planned sample size was 650 patients powered for the primary endpoint of progression-free survival but also allowing analysis of any overall survival difference. This primary PFS analysis per IRC was conducted using a stratified log rank test with a one-sided alpha of 0.025. This trial had 90 percent power to detect a reduction in the risk of progression or death of 29 percent, corresponding to a target hazard ratio of 0.714. There was one interim analysis for futility planned at 50 percent of the total PFS events.

Here are the results: 723 patients were randomized equally to either axitinib or sorafenib. As you can see, this is a very typical kidney cancer population, median age of approximately 60 with a wide range, male predominant with approximately three-quarters of patients being

male, relatively equal split between ECOG performance status zero and 1 and balance between the arms. This was a global study which accrued across the world, as you see listed there. Twenty-three percent of the patients in the study were accrued from the United States. The MSKCC prognostic risk groups were balanced between the arms.

Continuing with baseline disease characteristics, you see approximately half the patients received prior sunitinib-containing regimens, a third prior cytokines, and a small proportion of patients, prior bevacizumab or prior temsirolimus-containing regimens.

Metastatic sites were typical for kidney cancer as a lung predominant disease. And further, about 90 percent of patients had received prior nephrectomy and 20 percent prior radiation, which again is very typical of phase 3 kidney cancer clinical trials. Of note in the U.S. population, approximately 20 to 25 percent had received prior treatment with cytokines.

Here's the patient disposition at the time of the analysis. As mentioned, 723 patients were randomized equally between the arms. At the time of data analysis, 38 percent of patients were still on axitinib, and 28 percent of patients were still on sorafenib.

The primary endpoint of this phase 3 trial was met as represented here. This is the PFS in the overall population as determined by an independent review committee. As you can see, there was an advantage to axitinib over sorafenib in this refractory kidney cancer population with a hazard ratio of 0.665 representing a 33 percent reduction in the risk of progression or death for patients treated with axitinib. The hazard ratio that the study was designed to achieve, as I mentioned, was 0.714.

This is the forest plot showing major subgroups of patients. As you can see, there are very small sample sizes for the bevacizumab containing, temsirolimus containing and in the bottom row, the other regions, precluding

meaningful analysis of those subsets. However, the other major subsets based on performance status, type of prior therapy, race, gender, age, et cetera, all show a hazard ratio of less than 1 in favor of a progression-free survival advantage to axitinib. This supports a consistent treatment effect of this drug across major patient groups.

In the FDA's briefing document, the agency raised the question on whether the PFS outcome of this study was indeed relevant to a U.S. patient population. As shown in this slide, the U.S. patient population, the hazard ratio was 0.613 with a change in the median progression-free survival of approximately just over three months, similar or even a little bit better than the overall population with a hazard ratio of .665 and a median PFS difference of two months.

These data show the objective tumor response, which was a secondary endpoint. As you can see, the objective partial response for axitinib was approximately double that of sorafenib, 19.4 percent compared to 9.4 percent

with a significant p value that you see listed. Responses were durable in both arms with a median duration of response of approximately 11 months.

An interim analysis of overall survival was undertaken when the final PFS was analyzed in late August 2010. As you see from this graph, overall survival was found to be similar between axitinib and sorafenib. At the time of this data analysis, the overall survival data was immature with about 30 percent of patients having an OS event, which was 50 percent of the total required events and a median follow-up of 11 months.

As Dr. Andrews mentioned, here are the final overall survival data from a recent analysis. As you can see, the final overall survival remains similar between axitinib and the active comparator arm of sorafenib in this overall population. The hazard ratio is approximately 1. At 0.969, you see overlapping curves. Also of note is the long overall survival in both arms of approximately 20 months in a refractory kidney cancer population.

In conclusion, there is a statistically

significant and clinically meaningful improvement in the efficacy parameters of progression-free survival and objective response rate for axitinib compared to an active comparator, that is sorafenib. The results from this pivotal phase 3 and the supportive phase 2 studies are consistent. The treatment benefit of axitinib was apparent across all major patient groups, and the results in the U.S. population were consistent with the entire study population.

Thank you for your attention. I'd now like to introduce Dr. Sinil Kim, clinical lead for the axitinib development program to discuss safety.

Sponsor Presentation – Sinil Kim

DR. KIM: Thank you, Dr. Rini. I'm Sinil Kim, and I work for Pfizer oncology as the global clinical lead for the axitinib development program, and I will summarize the clinical safety for axitinib.

The total safety database includes over 2,500 patients who received either single agent axitinib or axitinib in combination with

chemotherapy. Among these 2,500 subjects, 699 patients with cancer received axitinib as a single agent of whom 537 had renal cell cancer. The majority of these renal cell carcinoma patients came from the pivotal phase 3 study, A 4061032. The rest received axitinib in phase 2 studies.

The pivotal phase 3 study also included 355 patients who received the active comparator sorafenib. Most of my safety presentation will focus on the findings from the phase 3 study to allow comparison with active comparator sorafenib. Also, the results from the pivotal phase 3 study was consistent with the safety profile for the larger pooled population.

In the pivotal phase 3 study, the duration of exposure was 6.4 months for axitinib versus 5.0 months for sorafenib. Dose modification or treatment delays due to adverse events occurred in 55 percent of axitinib versus 62 percent for sorafenib. About a third of the patients receiving axitinib had their dose increased as allowed by the protocol, and 31 percent in the axitinib arm had

dose reduction versus 52 percent for sorafenib. The median dose intensity was well preserved in both arms of the study.

As expected for patients with advanced RCC, almost every patient had at least one adverse event in the study. About half of these adverse events were grade 3 in either arm, and grade 4 adverse events occurred in 6 percent of patients for axitinib arm and 10 percent for the sorafenib. The treatment discontinuations due to adverse events were 9 percent for axitinib versus 13 percent for sorafenib.

The SAEs were similar in both arms, and also a similar number of patients died in both arms of the study. Ten percent of patients in the axitinib died during the treatment or within 28 days of the last dose versus 7 percent of sorafenib. And most of these deaths were due to disease progression. The treatment-related deaths were 1 percent in each arm.

This slide shows the most common adverse events. Hypertension, dysphonia and hypothyroidism

were numerically more frequent in the axitinib arm, whereas skin toxicity such as hand-foot syndrome, rash and alopecia were numerically more frequent the sorafenib arm.

As mentioned earlier in the safety overview slide, the discontinuation rate due to adverse events were 9 percent for axitinib versus 13 percent for sorafenib. Numerically, more patients discontinued axitinib for general disorders, 4 percent versus 2 percent, and these included asthenia, fatigue and disease progression. On the other hand, fewer patients discontinued axitinib for GI disorders, 0.6 percent for axitinib and 3.1 percent for sorafenib, or skin disorders, 0.3 percent for axitinib versus 3.1 percent for sorafenib.

Among the most common adverse events associated with axitinib, hypertension led to axitinib discontinuation in 1 out of 359 patients, and none of the patients discontinued axitinib because of diarrhea, dysphonia or hypothyroidism.

Looking at the hematology lab results, the

axitinib arm had 35 percent rate of anemia versus 52 percent for sorafenib, and there were low rates of thrombocytopenia or neutropenia in either arm.

For the overall chemistry lab results, most of the abnormalities were of low grade, including elevated creatinine and hypocalcemia. However, on the sorafenib arm, there were 16 percent and 12 percent incidence of grade 3 hypophosphatemia and increased lipase, respectively, and this was consistent with previous sorafenib studies.

The liver function test, alkaline phosphatase, ALT AST and bilirubin elevation were similar in both arms, and hardly any patients had grade 3 or grade 4 elevation in either arm of the study.

Looking at selected adverse events of interest for drugs of this class, there were more venous thromboembolic events on the axitinib arm, including one death from pulmonary embolism. On the other hand, there were more hemorrhagic events on the sorafenib, including three deaths on the sorafenib arm versus one on the axitinib arm.

There are fewer arterial thromboembolic events and fewer other adverse events that are listed on this slide.

In summary, most common adverse events were expected for drugs of this class. Some toxicities such as hypertension, dysphonia, hypothyroidism were more frequent in axitinib than sorafenib. However, dermatological toxicities such as hand-foot syndrome, rash, alopecia was less numerically frequent on the axitinib arm. grade 3 or higher thromboembolic events, hemorrhage, GI perforation, RPLS, and hypothyroidism were uncommon. And grade 3 and 4 lab abnormalities were also uncommon. Most adverse events were manageable with a low rate of discontinuation.

Thank you. Now I'd like to invite Dr. Robert Motzer to the podium.

Sponsor Presentation – Robert Motzer

DR. MOTZER: Good morning. My name is Dr. Robert Motzer. I'm an attending physician at the Memorial Sloan Kettering Cancer Center in New York. I'm a paid consultant for Pfizer and have

received travel expenses for my attendance at the ODAC meeting today. I hold no financial interests based upon the outcome of this meeting.

I've been treating patients with advanced RCC for over 20 years and do so on a daily basis. I chair the NCCN committee to provide recommendations regarding treatment paradigms in patients with metastatic RCC. I was a co-PI in the pivotal study 1032, and I participated in an earlier phase 2 trial with axitinib. So I have hands-on experience with this agent as well as extensive experience with all the other approved targeted drugs. Today I will be presenting findings from that pivotal study and putting those findings in the context of other approved therapies.

The landscape of RCC has been altered by the emergence of targeted agents. TKIs with activity against VEGFRs have emerged to form the backbone of advanced RCC therapy. Further improvement in patient outcome is needed, including improved efficacy over currently approved therapies and

fewer toxicities that are troublesome to patients.

Axitinib is a new VEGF-targeted TKI with significantly greater potency and selectivity against VEGFR compared with currently approved VEGFR TKIs. All these agents are multi-targeted, and some of the least desirable toxicity comes from off-target inhibition, including skin toxicity and myelosuppression. Axitinib's molecular characteristics were aimed at achieving greater efficacy coupled with less toxicity compared with first generation TKIs.

In the phase 3 study, we choose sorafenib as the comparator. Sorafenib is a widely used compound for the treatment of RCC. It was the first tyrosine kinase inhibitor to be approved by the FDA in 2005. The pivotal study for sorafenib was conducted in mainly cytokine refractory subjects. As the graph shows, sorafenib was associated with a 56 percent improvement in disease progression or death over a placebo control in its pivotal phase 3 study.

Sorafenib is also known to be active in TKI

refractory subjects and is widely used in the community in this setting. Phase 2 data published by Di Lorenzo showed that sorafenib has a PFS of nearly four months in sunitinib refractory patients, and Garcia, et al. showed that sorafenib had a PFS of 4.4 and 3.7 months in sunitinib and bevacizumab refractory patients. This data indicates the activity of sorafenib in TKI refractory patients.

In the phase 3 trial, the primary endpoint of PFS was met, and axitinib demonstrated a greater PFS time compared with sorafenib. This is the first study to show improvement over an active VEGFR-targeted TKI comparator. In all previous phase 3 studies with FDA-approved drugs, comparisons were made to placebo or interferon. The hazard ratio was 0.665, which represents a 33 percent decrease in risk of progression or death for axitinib over an active comparator, sorafenib. These results are both statistically significant and also clinically meaningful.

A question may be raised as to whether the

outcome data for this trial applies to the United States population. Nearly 25 percent of the patients treated on this trial were from the United States. According to country accrual, the United States was the top country in accruing to this study with more than 60 sites open in the United States. A subset analysis of their progression-free survival is shown here. The hazard ratio in this subset in the U.S. population was 0.613, demonstrating a strong benefit in progression-free survival for axitinib over sorafenib.

In cytokine refractory patients, the median progression-free survival for sorafenib in the axitinib phase 3 AXIS study was similar to that obtained in the original sorafenib TARGET registration study in which sorafenib was compared to placebo. In sunitinib refractory patients in the AXIS trial, the median progression-free survival for sorafenib was 3.4 months. In both clinical settings and subsets of patients treated on this trial, I believe sorafenib is active and

was an active comparator in this trial.

Axitinib produced a longer progression-free survival than sorafenib in the phase 3 trial, meeting the primary endpoint of the trial and demonstrating greater activity compared to sorafenib. First-line therapy in this study was heterogeneous, representing the true world population of patients receiving second-line therapy for this disease. PFS was examined according to subsets by prior therapy.

In the cytokine refractory subgroup, axitinib showed a 54 percent improvement in the risk of progression or death. In the sunitinib refractory subgroup, axitinib showed a 26 percent improvement in the risk of progression or death. Both of these results were statistically significant. The two other subgroups, temsirolimus and bevacizumab, were too small for meaningful conclusions to be drawn.

Cross-study comparisons have limitations. However, it is of interest to note that a comparison of axitinib, sunitinib, pazopanib and

sorafenib in cytokine refractory subjects suggest that axitinib is the most effective VEGFR TKI with a median progression-free survival of 12.1 months, longer than that of 8.8 months with sunitinib, 7.4 months for pazopanib, and 5.5 months for sorafenib, based on the data from their phase 3 trial.

These data reflect first TKI patients and patients progressing on cytokines but without resistance or treatment to prior TKI therapy. In this setting, axitinib may be the most effective of any of the TKIs studied or approved to date.

The RECORD-1 was the phase 3 registrational study for everolimus in patients who had progressed after treatment with sunitinib and/or sorafenib and is the only phase 3 trial reported in this population. The comparator arm was placebo rather than an active agent such as sorafenib.

In this study, almost 80 percent of patients had received more than one prior therapy for their metastatic disease. Some had received four or five prior treatments. In other words, this was mainly

a third-line study in a more refractory population. This study was therefore different from the axitinib phase 3 study which only included patients who were refractory to a first-line systemic treatment.

Everolimus showed an improvement in PFS over inactive placebo. In the overall patient population, the median PFS was 4.9 months versus 1.9 months. There was no difference in OS. The main differences between the studies included the patient populations in the comparator. The everolimus trial was mainly third line, and the axitinib trial was only second line. Everolimus was compared to an inactive placebo comparator whereas axitinib was compared to an active comparator, sorafenib. In conclusion, both studies showed benefit for axitinib and for everolimus, but the patient populations are distinctly different.

One of the most attractive aspects of axitinib is its favorable safety profile when given as outpatient chronic therapy. The most common AEs for axitinib were expected for this class of drugs,

targeting the VEGF pathway, include diarrhea, hypertension and fatigue.

However, axitinib has differences in the incidence of some important toxicities compared to the approved VEGFR TKIs. Hypertension was a predominant adverse event seen with axitinib which we hypothesize is related to its properties as a potent VEGF pathway targeting agent. On the other hand, other toxicities problematic for other TKIs, such as hand-foot syndrome and rash, occurred less frequently with axitinib.

Axitinib has less hand-foot skin reactions compared to several of the other tyrosine kinase inhibitors. In the AXIS trial, more than 50 percent of patients developed hand-foot syndrome with sorafenib compared to only 27 percent with axitinib. The incidence of grade 3 hand-foot syndrome with sorafenib in this study was 16 percent which was triple that of axitinib.

A notable feature of axitinib is its lack of myelosuppression, which is strikingly less than that seen with sunitinib, a TKI which is commonly

used in standard practice.

Liver function test abnormalities have been observed for pazopanib and sunitinib which has resulted in boxed warnings on their labels. Axitinib results demonstrate a very low incidence of severe liver function test abnormalities.

The current NCCN recommended treatment paradigm for patients who have received prior treatment for advanced renal cell cancer are shown on this slide. In my opinion, axitinib has Category 1 evidence, the highest, for its effectiveness following previous treatment with a cytokine or a TKI and provides a valid treatment option for second-line therapy.

In summary, axitinib has superior efficacy compared to sorafenib, a widely used approved TKI. Axitinib has advantages with a lower incidence of some important toxicities compared to approved VEGFR TKIs. The benefit-risk evaluation is favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy.

Thank you for your attention, and I would now like to invite Dr. Mace Rothenberg from Pfizer oncology back to the podium.

Sponsor Presentation – Mace Rothenberg

DR. ROTHENBERG: Thank you, Dr. Motzer.

By way of reintroduction, I'm Mace Rothenberg from Pfizer oncology. The data presented today provides strong support for the safety and efficacy of axitinib in the treatment of patients with advanced RCC. The pivotal study met its primary endpoint by demonstrating a 33 percent reduction in the risk of progression for patients treated with axitinib compared to those treated with sorafenib. This progression-free survival benefit is consistent across patients groups.

This was a robustly designed phase 3 trial incorporating an active control arm, representing a higher hurdle for demonstrating efficacy than previous phase 3 trials where a new agent was compared to placebo or to interferon alpha.

Axitinib succeeded in this rigorous test, conferring a statistically and clinically

meaningful improvement over sorafenib in PFS and a twofold improvement in objective response rate. These benefits were observed across patient subgroups, including patients treated in the United States. The superior efficacy of axitinib was achieved without increased risk for serious adverse events, grade 3 adverse events, or discontinuation due to adverse events.

Taken together, these data establish a favorable benefit-risk profile for axitinib. We believe that axitinib represents an important treatment advance and should be made available for patients with advanced renal cell carcinoma. Thank you.

DR. WILSON: Thank you very much.

We'll now proceed with the FDA presentation.

FDA Presentation – Amy McKee

DR. MCKEE: Good morning, ladies and gentlemen, members of the committee. My name is Amy McKee, and I'll present the FDA analysis of this application for regular approval.

Briefly, this is the core FDA review team

for this product from the Office of Oncology and Hematology Products. NDA 202324 was submitted to FDA with the proposed indication, quote, "Inlyta is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma."

A brief outline of my presentation is as follows. I will discuss background both for advanced renal cell carcinoma as well as the key regulatory milestones for this particular product. I will present FDA's analysis of the key registration trial AXIS, and I then will discuss the primary findings with this application.

Our primary findings with this application, which will be discussed later in greater detail, are as follows. The PFS benefit demonstrated in the AXIS trial was driven by a subset of patients. Second, the PFS difference in this trial was two months, and there was no difference in overall survival compared to sorafenib. Bear in mind, that this is a difference between an experimental arm and an active comparator arm, not a placebo or interferon as for all other drugs approved in

advanced RCC.

All of the products approved since 2005, including all of the VEGF-pathway-targeted agents and mTOR-targeted agents, are approved for the broad indication of advanced RCC with the exception of everolimus, which is specifically labeled for use after progression on either sorafenib or sunitinib. However, what order to use these agents for either first-line or second-line therapy in advanced RCC is not known and has not been studied in a randomized trial.

This table outlines the products that have been approved for advanced RCC since 2005. When the first of these products, sorafenib and sunitinib, were approved, there were few palatable treatment options for patients with renal cell carcinoma. Hence, the agency gave full approval for the broad indication of advanced RCC.

Although many of these trials were powered to show a difference in a secondary endpoint of overall survival, crossover occurred in a majority of patients at the time that a PFS benefit was

demonstrated. Thus, full approval was granted for many of these based on demonstration of a PFS benefit in the absence of an OS benefit.

If you examine the randomized controlled trial column, all of the products with the broad indication were studied in treatment naive patients with the exception of the sorafenib and pazopanib. Sorafenib patients could have received one prior therapy, and the population included patients who had received cytokines and chemotherapy but not prior VEGF receptor inhibitors.

Pazopanib was studied in a mixed population of treatment naive patients and patients who had received one prior cytokine regimen. Sorafenib, everolimus and pazopanib all had placebo-controlled arms whereas sunitinib, temsirolimus and bevacizumab all had interferon alpha control arms.

Next, the endpoint column shows that only temsirolimus has demonstrated a survival advantage. Many of the trials were powered to examine overall survival as a secondary endpoint. However, crossover from placebo arm in the sorafenib,

sunitinib and pazopanib trials may have confounded overall survival results. Finally, the key findings of the trials for median PFS or OS and hazard ratios are listed in the final column.

Moving now to drug development for axitinib, the IND was activated in 2001. At an end to phase 2 meeting in 2007, the sponsor proposed a phase 3 trial in second-line advanced RCC with sorafenib as a comparator arm and a primary endpoint of PFS as assessed by an independent review committee. The sponsor also indicated at that time that they would seek a second-line indication for this product based upon such a trial. An SPA agreement was reached in 2008 on a protocol that became the basis for the AXIS trial.

I will now briefly discuss the key points of the design of the AXIS trial. This schema summarizes the trial design. Patients must have received a single prior systemic therapy, and this therapy must have been one of the following: sunitinib, temsirolimus, bevacizumab or a cytokine. Six hundred and fifty patients were randomized one

to one to axitinib or sorafenib, stratified by ECOG status and prior therapy. Patients were treated until disease progression, death, or unacceptable toxicity. No crossover was permitted from the sorafenib arm to the axitinib arm upon progression.

Disease evaluations were performed every six weeks for the first two evaluations and every eight weeks thereafter. The primary endpoint was PFS as assessed by an independent review committee blinded to treatment arm, and patients also would be followed for survival.

I have summarized the approval of sorafenib for treatment of advanced RCC on this slide. It was the first of the targeted therapies to receive full approval for this indication. The randomized trial in which this full approval was based was a placebo-controlled trial in patients who had received one prior systemic therapy. For 83 percent of the patients enrolled, this prior therapy was a cytokine regimen. For the remaining 17 percent, this included a mélange of chemotherapies and hormonal agents. The median PFS

was 5.5 months in the sorafenib arm versus 2.8 months in the placebo arm with a hazard ratio of 0.44.

There was a 2.1 percent objective response rate in the sorafenib arm compared to zero in the placebo arm. The trial was terminated early based on these PFS results, and the majority of placebo patients crossed over to sorafenib, which complicated the analysis of overall survival.

Sorafenib was selected by the applicant for the control arm in the AXIS trial and was agreed to by the FDA. However, the benefit of sorafenib after sunitinib in RCC is unknown. There are no randomized controlled trials examining the sequence of targeted therapies in advanced RCC. A number of retrospective trials suggest that the sequence may be important, but this has yet to be tested in a perspective trial. With the superiority trial design for AXIS, axitinib had to improve upon any benefit demonstrated by sorafenib in this trial.

The key inclusion criteria included confirmed metastatic RCC, measurable disease,

progressive disease per RECIST criteria after one prior systemic therapy, ECOG performance status of zero or one, and no evidence of uncontrolled hypertension.

The primary endpoint was PFS defined by the time from randomization to first documentation of objective tumor progression or death due to any cause. The trial had 90 percent power to detect a 40 percent improvement in median PFS from five months in the sorafenib arm to seven months in the axitinib arm in the intent-to-treat population.

Key secondary endpoints included overall survival, objective response rate, duration of response and safety evaluations. For overall survival, the trial had 80 percent power to detect a 32 percent improvement in median overall survival from 18 months to 23.7 months at the final analysis. An interim analysis of OS at approximately 50 percent events was to be performed at the time of the final PFS analysis.

The independent review committee would adjudicate all PFS results for the primary efficacy

analysis. The IRC consisted of two radiologists blinded to treatment arm. If there was disagreement between the two, a third radiologist would adjudicate the response.

I will now highlight some of the key patient baseline characteristics from the AXIS trial. As can be seen in this table, patient demographics in terms of age, sex, ECOG performance status, race and MSKCC risk group were well matched between arms. Approximately a quarter of patients were enrolled in North America, half in Europe, 20 percent in Asia, and the small remaining number in other regions.

In terms of prior treatment, slightly over half the patients had received sunitinib as first-line therapy, a third had received a cytokine, and smaller numbers had received either bevacizumab or temsirolimus.

Moving to the efficacy results, for the primary endpoint of PFS as analyzed by FDA, there were a total of 192 events on the axitinib arm and 210 events on the sorafenib arm. Median PFS in the

axitinib arm was 6.7 months and 4.7 months on the sorafenib arm with a hazard ratio of 0.67. The Kaplan-Meier curve for PFS is shown on this slide with axitinib in blue and sorafenib in red.

The applicant provided results from the interim analysis of overall survival that was conducted at the time of the final PFS analysis. There was no crossover permitted from sorafenib to axitinib. This represented approximately 53 percent of the events needed for the final overall survival analysis.

As can be seen here, there were 113 deaths on the axitinib arm and 110 deaths on the sorafenib arm. The hazard ratio was 1.009, indicating no benefit for axitinib over sorafenib in terms of overall survival. The Kaplan-Meier curve shows that for overall survival, the axitinib and sorafenib arms are superimposable and cross several times.

In terms of safety results, axitinib is a small molecule inhibitor of the VEGF receptor. The side effect profile for this class of drugs is

fairly well established, and for the most part, axitinib adheres to this profile. For this reason, I will not go into great detail on FDA's review of safety and will highlight a few of the adverse events particular to axitinib.

The common adverse events for axitinib are noted here as are the serious adverse events. Both of these lists are familiar to oncologists who treat patients with other VEGF pathway inhibitors. However, there are some differences in adverse event rates between the arms in the AXIS trial, which I will highlight in the next several slides.

On these slides, there were several categories of adverse events that had a higher incidence on the axitinib arm than the sorafenib arm. Gastrointestinal adverse events were uniformly higher on the axitinib arms. As shown here, the grade 3 to 4 rate for diarrhea and vomiting was higher on axitinib than sorafenib as well as the overall rate. The grade 3 to 4 rate of fatigue was more than tripled on the axitinib arm compared to the sorafenib arm, and asthenia grade 3

to 4 events were more than doubled.

Hypertensive adverse events, both grades 1 through 4 and grades 3 to 4, were higher on axitinib. Additionally, there were two patients who experienced hypertensive crisis on the axitinib arm compared to zero on the sorafenib arm. Dysphonia was a frequent adverse event on the axitinib arm affecting nearly a third of the patients.

Finally, hypothyroidism was more than double on the axitinib arm compared with the sorafenib arm, keeping in mind that grade 2 hypothyroidism is defined as requiring thyroid hormone replacement.

Several adverse events had a higher incidence on the sorafenib arm compared to the axitinib arm. In particular, dermatologic adverse events generally were more frequent on the sorafenib arm. Grade 3, 4 palmar-plantar erythrodysaesthesia tripled on the sorafenib arm compared to the axitinib arm. And grade 3 to 4 rash also more than tripled on the sorafenib arm. The overall adverse event rate for pruritus,

alopecia and erythema also were higher on the sorafenib arm.

Finally, anemia was also more prevalent on the sorafenib arm.

To summarize, the two main findings for discussion with this NDA are as follows. First, the PFS results are driven by a subset of patients. And second, the PFS difference in this trial was two months, and there was no difference in overall survival compared to sorafenib.

The efficacy for results for PFS were driven by the subset of patients who were previously treated with a cytokine. Given the availability of numerous other agents with more attractive side effect profiles in the United States, this population of patients will be very small. Sunitinib was available at the time this trial was conducted in the United States. In fact, when you look at what patients in North America and Europe enrolled in this trial received for prior therapy, you can see that more than two-thirds of the patients in North America had received sunitinib

compared to approximately half in Europe and the trial population as a whole. In contrast, only 20 percent of patients in the U.S. had received cytokines as prior therapy compared to approximately a third in Europe in the population as a whole.

If you look at the PFS results in the subset of patients previously treated with a cytokine, a population that is unlikely to be prevalent in the U.S., the difference in median PFS between these arms is 5.6 months with a hazard ratio of 0.46. The Kaplan-Meier curve for this subpopulation is shown here.

In contrast, the difference in median PFS in patients previously treated with sunitinib, a population more reflective of the current U.S. population, is 1.4 months with a hazard ratio of 0.74. The large difference you saw in the cytokine subgroup is no longer there.

Shown here is the Kaplan-Meier curve for this sunitinib subpopulation. This is the population that is more relevant to the U.S., as

patients will have received sunitinib or another targeted therapy rather than a cytokine. Also note that the difference in medians is 1.4 months. At this point in treatment in the AXIS trial, the assessments were occurring every two months. Thus, the median difference is less than the interval between assessments and may not be reliable.

This trend is carried over to the OS analysis as well. Shown in this table for patients previously treated with cytokines, the hazard ratio is 0.74, where for patients previously treated with sunitinib, the hazard ratio is 1.007.

The same trend also holds for response rate. The overall objective response rate in this trial was 19.4 percent on the axitinib arm and 9.4 percent on the sorafenib arm. However, as you can see in this table, the number of patients with response on the axitinib arm who are in the cytokine subgroup is almost double that of the sunitinib subgroup despite the smaller number of patients overall in this cytokine subgroup. Thus, for PFS, OS, and response rate, efficacy is driven

in the axitinib arm by the subgroup previously treated with cytokines.

The second finding with this application is that there was a two-month difference in PFS and no difference in OS compared to sorafenib. The regulatory history for advanced RCC is that at the time of the sorafenib and sunitinib approvals, which were the first two drugs in the cascade of targeted therapies for RCC, there was little enthusiasm for the drugs available for treatment.

Sorafenib and sunitinib were given full approval based on demonstration of a PFS benefit, and subsequently approved agents received the same. However, there are numerous treatment options today, and we are not sure how to use even these agents in the first- and second-line settings. The only agent that has ever shown a survival advantage is temsirolimus, and this was demonstrated in a first-line setting versus interferon.

Axitinib did not show a survival advantage in the AXIS trial. No crossover was permitted. The sorafenib patients did not receive axitinib.

Subsequent therapies are summarized in this slide. Overall, a similar percentage of patients received subsequent therapy after discontinuing study treatment. We have no reason to believe that patients from the sorafenib arm would respond differently to these subsequent treatments than patients on the axitinib arm. Thus, this is not an explanation for why no OS benefit was seen.

In summary, axitinib was compared to an approved drug in a second-line setting. The magnitude of benefit in AXIS was two months for PFS for the overall population of patients who had received one prior therapy and 1.4 months for the prior sunitinib treatment population. Although the safety profile is not as daunting as for cytotoxic chemotherapy, axitinib is not without risks.

This application is being considered for regular approval. We have accepted PFS as evidence of clinical benefit for full approval in this disease setting in the past. We would like to remind the committee that unlike accelerated approval for which the drug must approve upon

existing therapy, for regular approval, the drug has to demonstrate safety and effectiveness.

The comparator therapy is an approved drug, though the magnitude of benefit for sorafenib after sunitinib has not been established. However, I will note that in the AXIS trial, sorafenib's median PFS is similar to that in the registration trial for sorafenib's approval.

We are asking the committee to consider the overall risk-benefit profile of axitinib in its recommendation.

Clarifying Questions from the Committee

DR. WILSON: Okay. Thank you.

We will now turn to questions from the committee to both the sponsor and the FDA, and let me open with the following question to the sponsor: We have heard that most patients in the U.S. will have had a prior TKI and that the efficacy in terms of progression-free survival is driven primarily by patients that have had prior cytokines.

In trying to assess the risk-benefit, one has to look at both efficacy or equivalency to

established therapy, plus the toxicity. My question to the sponsor is whether or not they have performed a subset analysis of toxicity, within the group that only received cytokines versus the group that had received prior TKIs, to determine whether or not the relative risk of the drug we are looking at is favorable among the subset of patients that have had prior TKIs, which will represent most patients in the U.S.

DR. ANDREWS: Glen Andrews, Pfizer. Yes, we have performed that analysis looking at axitinib's discontinuation rate relative to sorafenib in the prior sunitinib group, which I think was the intent of the question. We had a 10 percent discontinuation rate for axitinib in the prior sunitinib group compared to 16 percent in the sorafenib group, so the rate was slightly higher on sorafenib relative to axitinib.

In terms of grade 3 adverse events overall, it was 48 percent in both axitinib and sorafenib. In the treatment-related numbers, in the grade 3 all causality, it was 69 percent versus 66 percent,

and then in all adverse events, 97 percent essentially in both arms.

I would just like to maybe make a point around the treatment effect being driven by the sunitinib refractory group, and if I could show the forest plot that was presented in the main presentation just briefly.

I just want to draw your attention to the top line here, which is the overall effect, the yellow highlighted numbers here. The hazard ratio there was .67, and you can see the larger dot showing the larger sample size there. And if you work down to the sunitinib refractory group and you look at the hazard ratio there, it's .74; and I think entirely consistent with the overall population, and would be expected since the majority of the patients, 55 percent in this study, have received prior sunitinib.

Now, individual medians -- and I understand the need to look at individual medians as slightly different from time to time, but I think if you look at the hazard ratio which compares the overall

curves, then the data is here.

I just want to check if Brian, Dr. Rini, or Dr. Motzer would like to make any comments on the relative toxicity of prior sunitinib patients versus prior cytokine patients.

DR. RINI: Brian Rini from Cleveland Clinic. As Dr. Andrews mentioned in the numbers, the drug appears to be similarly tolerated in those subgroups, and I would say that would be our clinical experience having treated a lot of patients sort of from both subgroups, both on this trial and in the phase 2 trials.

DR. WILSON: Okay. Thank you.

I now would like to recognize Dr. Logan.

DR. LOGAN: I just would like a clarification first. The FDA put up a slide of survival for the prior sunitinib refractory subgroup. Was that the old survival data, or is that the updated survival data?

DR. MCKEE: We have not received the datasets from the updated, so that is from the interim analysis of overall survival.

DR. LOGAN: So the follow-up to that would be can the company provide the survival data for the sunitinib refractory subgroup?

DR. ANDREWS: Yes. We just recently carried out that analysis. That hazard ratio for the prior sunitinib group was .97. Just to reemphasize again, the FDA have not had a chance to analyze these data yet.

DR. LOGAN: And what are the medians?

DR. ANDREWS: The median is 15.2 months with axitinib versus 16.5.

If I may show slide E-305, what you see here is essentially overlap between the two arms, and I don't think the conclusions have changed from the original overall survival analysis for that sunitinib refractory subgroup.

DR. LOGAN: Okay. And then I have one other question, it's been alluded a couple times that axitinib may have a potentially favorable toxicity profile, but we're seeing some differences in the types of toxicities. And it's unclear whether there's an overall advantage, I guess, here.

Has there been any assessment of patient-reported outcomes to better assess what the impact is on patients?

DR. ANDREWS: Yes, there has. Functional kidney symptom index scores were analyzed, and I'll invite Dr. David Cella to just describe those in a bit more detail.

DR. CELLA: Thank you. Good morning. My name is David Cella. I'm professor and chair of the department of medical social sciences at Northwestern University's Feinberg School of Medicine. I'm a paid consultant to Pfizer. I have received travel expenses to attend this meeting, but I have no personal financial interests based upon the outcome of the meeting.

The patient-reported outcome tool used was the FACT Kidney Symptom Index, which is 15 questions. It includes one summary question from the patient's perspective as to the impact of side effects, that is, how bothered patients are by the accumulated set of side effects any given patient experiences.

In the early going, there was a numeric heightening of adverse impact on the sorafenib arm, but, overall, there were no differences over time between the sorafenib- and axitinib-containing arms. So on balance from the patient's perspective, the impact of toxicities were similar over time. And I'll add that this is from a dataset that is over 90 percent complete with regard to patients who are expected to provide those evaluations. So it's a very full dataset, suggesting that the patient perspective is quite comparable between axitinib and sorafenib.

DR. WILSON: Okay. Thank you.

Dr. Buzdar.

DR. BUZDAR: Yes, I have two questions. One is about the safety profile. According to the sponsor, it looks overall favorable. But looking at the rate of hypertension, it was like 40 percent versus 29 percent, and 40 percent being in the experimental arm. And I wanted to see, if they have information, what fraction of patients required therapeutic intervention to manage the

hypertension.

The second thing which I wanted to question is that much improvement in time to progression, that there is no hint of survival advantage. And when you look at one of their slides, 37, where it shows death during the treatment arm within 28 days from the last dose, like 10 percent was on the experimental arm, 7 percent in the sorafenib arm.

The question is whether maybe it is a liberal interpretation of the time to progression.

Those are the two comments.

DR. ANDREWS: So one question on hypertension and then a second question on overall survival, as I understood it. Briefly, if I may show from the main deck the overall incidence of hypertension, if I may show main deck slide 38, grade 3 is really an increase in dose, one additional medication, like CTC. You can see in the numbers there, 15 percent versus 11 percent limited grade 4 adverse events for either arm in this setting.

I think I would overall qualify the toxicity

as different. There are some differences between them that provide choices to the physician and the patient rather than necessarily saying one's much better than the other given the data we have.

I would maybe just like to ask -- I'll come to the survival in a minute, but I would just like to ask Dr. Rini if he'd like to just describe briefly hypertension and his view on that as an issue.

DR. RINI: Thank you, Brian Rini, Cleveland Clinic. So as noted, and as all of you know, hypertension is a class effect of these agents, and, in fact, we would expect more hypertension from a more biochemically potent drug. So I think it fits with the biochemical profile.

It's an early and predictable event, and so where this drug is coming in the course of kidney cancer is after years of this class of drugs. So we've become well versed in expecting hypertension and how to manage it. The protocol, as you can guess, a defined algorithm for dealing with hypertension. But our approach is sort of early

and aggressive management of hypertension throughout, and it really is quite easily managed for the vast majority of patients as evidenced that -- I think there's only one patient who discontinued treatment for hypertension.

DR. WILSON: Yes. FDA?

DR. MCKEE: This is just to address hypertension and also the subpopulations. This is from the sponsor's briefing document. I don't know if you have a slide on this. If you look at the prior sunitinib treatment groups, the incidence of hypertension is about 34 percent on the axitinib arm versus 18 percent on the sorafenib arm, where it's closer in the cytokine arm, 47 percent versus 42 percent. So it looks like there may be a differential effect in the subgroups there for hypertension. That's all grades.

DR. ANDREWS: Yes, I was referring to grade 3.

Can we call up -- can you remind me which table that is, just so we can show it to the rest of the committee, the table?

DR. WILSON: Does FDA know what slide that was?

DR. MCKEE: It's from your briefing document, Table 23.

DR. ANDREWS: May we show the sponsor's Table 23?

Finally, while it's coming up, one other point I'd make -- it's probably going to be hard for you to read.

[Laughter.]

DR. ANDREWS: But one other point I would make is the open nature of the study probably leads to different reporting of adverse events in this setting, and we can show you data on the blood pressure increases, which is a more objective measure and show some of that data as well.

So, yes, I would agree. I need to wear my reading glasses as well; 34 percent versus 18 percent for axitinib; 21 percent versus 11 percent. I guess, overall, 16 percent versus 9 percent difference in terms of the sunitinib refractory and the cytokine refractory in the overall grades.

Now, you asked a question about overall survival, and, specifically, you talked about the deaths in our main deck presentation.

If I could have that data briefly. Essentially, what we saw was a difference in deaths due to disease progression. I remind this was on treatment, or 28 days. And in terms of on treatment, axitinib patients were followed up for about a month and a half longer on average relative to the sorafenib arm. And all things being equal, these deaths were driven by disease progression, what you would expect in a RCC study, some deaths due to disease progression. And that 1.4 months, if you follow the Kaplan-Meier curves, would have led to about an additional 12 deaths, which is essentially the difference here, 26 on the axitinib arm versus 17 on the sorafenib arm.

DR. WILSON: Okay. Thank you.

Dr. Sekeres.

DR. SEKERES: Thank you, Dr. Wilson.

One of the challenges we have in deliberating about specifically an international

study is trying to determine whether the standard of practice ex-U.S. is the same as it is within the U.S., and that's why we're really in particular drilling down to the patients previously treated with sunitinib. I pulled up the NCCN guidelines, the Version 1.2012, and it says here, for first-line therapy, sunitinib is a Category 1.

Do cytokines have a category within the NCCN for first-line therapy?

DR. ANDREWS: Yes. I'd like to invite Dr. Bob Motzer to comment.

DR. MOTZER: The mainstay of treatment for many years was cytokines, and these have been largely replaced by the targeted drugs based on the phase 3 trials. High-dose interleukin 2 is a cytokine that was approved in 1992 for use in the United States and remains a viable option for patients with advanced renal cell carcinoma. It wasn't studied in a phase 3 trial, but it was approved largely because of durable remissions seen with the high-dose interleukin 2.

So for the most part, it is heterogeneous.

In the United States, it's heterogeneous. Some patients treated with sunitinib, some patients do get high-dose IL2, temsirolimus, bevacizumab plus interferon. It's clearly not just a sunitinib as the sole treatment in the United States. It's heterogeneous, and I think it's going to continue to change. Pazopanib used somewhat in first line as well.

DR. SEKERES: So for two-thirds of the patients on this study in the U.S., though, was the actual first-line treatment. So let me ask a more personal question of you or Dr. Rini. When is the last time you used cytokines as first-line therapy for your renal cell patients?

DR. MOTZER: Well, I think that in terms of high-dose interleukin 2, it's largely given at centers by people who give a lot of high-dose IL2. It's not used widespread, given in the community.

So I don't give interleukin 2 currently at Memorial Hospital. I did in the past, but I stopped because of the clinical trials that we were prioritizing. But when patients come to me in

terms of first-line therapy for RCC, if they're young patients, relatively young, or they lack comorbid conditions, then I talk to them about IL2. And if they're interested in that approach, they're referred to a center that gives high-dose IL2.

I'd also say that my practice is biased away from IL2 because I don't offer it at Memorial Hospital. If you were to talk to Jan Dutcher from New York or Michael Atkins, McDermott from Boston, or any number of other people in the United States, they would tell you that a lot higher proportion of people get cytokine therapy because those patients are generally referred to them.

DR. SEKERES: Okay. So it's a little complicated to think about a drug that's going to be used throughout the U.S. and the fact that there are only limited centers where cytokines are actually given, which would be the population, if we believe subgroup analyses, who really seem to benefit in terms of progression-free survival to this drug compared to sorafenib.

I don't think we give it at Cleveland

Clinic. Is that right, Brian?

DR. RINI: Brian Rini, Cleveland Clinic. So I would echo everything that Bob said. We commonly refer people for high-dose IL2. I refer several people a month. We don't give it, not because I don't think there's benefit, but just because we do other things. We can't do everything, and that's a very intense therapy. So I think there is a substantial percentage of patients who get cytokines, probably mostly high-dose IL2 in the U.S. Again, in the U.S. on this trial, it was 20 or 25 percent, and so for a modern trial, that's a reasonable percentage of patients who got cytokines. That's the actual data.

I would also say interestingly -- and that's why we analyzed the U.S. population, that despite the majority of the U.S. getting sunitinib, obviously again reflecting current treatment choices, there was still as much or more benefit to axitinib in that setting.

So, to me, that's the real test, is looking at the patients in the U.S. who actually got both

drugs in a randomized setting and seeing the benefit.

DR. SEKERES: So my second question is actually more for David Cella. There didn't appear to be a quality of life disadvantage to getting either drug. Was there a quality of life advantage to either drug?

DR. ANDREWS: Yes, can I invite David to come to the podium?

I would say about 20 -- just to the last point, about 20 percent of the patients in the U.S. received IL2 in our study. Those were the numbers for the U.S. population.

DR. SEKERES: Right. I guess I would counter that if you're talking about a major benefit in one out of five patients, we have to put that into our calculus as well.

DR. ANDREWS: Yes, I mentioned it because of the U.S. population overall and the effect there.

DR. CELLA: David Cella from Northwestern. Could I ask for slide SE-127?

This is the Figure 11 in your briefing

document. It has added a dotted line that represents where the U.S. general population would fall on this particular set of questions. These are the nine disease-related symptoms from the FACT Kidney Symptom Index that I mentioned earlier.

There was -- when you look at the treated patients, that is, the patients remaining on therapy, keeping in mind -- and this I think is the crux of the benefit question -- that there are 10 percent more over time in cycles across the first year to year and a half, patients on axitinib than on sorafenib. So axitinib keeps patients on therapy for a longer period of time overall to progression.

There is actually a fairly straight line of scores on this particular set of symptoms, if anything, a slight improvement in this group that stays on therapy over time. At the lower right of the plot is the average score of people at the end of treatment, indicating that when treatment ends, there is a lower symptom score, a worse symptom score.

So the message I think is it's good to be on therapy. Patients seem to have a fairly stable symptom reporting on therapy, and there were no differences between axitinib and sorafenib in that comparison. And their scores are about the same as the U.S. general population.

DR. SEKERES: So being treated by either drug appears to give you at least a comparable quality of life to the U.S. general population, but it doesn't appear to be an advantage to one drug versus the other?

DR. CELLA: That's right. In the patient-reported outcomes, they are comparable.

DR. SEKERES: Okay. Thank you.

DR. WILSON: Thank you.

Dr. Garnick.

DR. GARNICK: Thank you.

I have several clarifying points that I need in terms of the patient demographics. Some can be simple yes or no.

How were brain metastases patients handled, and were they prospectively looked for? And were

the thyroid function evaluations prospectively looked at or were they patient reported, is my first two.

DR. ANDREWS: I had brain metastases. I'm sorry. I missed the second.

DR. GARNICK: Were patients screened for brain metastases prior to entry into the study?

DR. ANDREWS: Yes, they were, and they were excluded.

DR. GARNICK: Okay. And do you have any experience in the thyroid function abnormalities?

DR. ANDREWS: Okay. That was the second question. Sorry.

DR. GARNICK: Yes.

DR. ANDREWS: So you're asking specifically about how many patients had thyroid abnormalities at baseline?

DR. GARNICK: No. My question is, was a case report from evaluation prospectively looked at or clinical symptomatology during the course of the study?

DR. ANDREWS: Symptomatology. We did

measure TSHs during the study, but at baseline, there was nothing really.

DR. GARNICK: So the 19 percent of patients with hypothyroidism were clinically picked up during the evaluations as opposed to prospectively evaluated?

DR. ANDREWS: I think it was prospectively evaluated. Sorry, let me correct myself for the record. We had TSH measurements during the study, and it was picked up by there, and then the majority were reported as adverse events as well.

DR. GARNICK: Okay. And the other question is, was there a central pathology review? You said that you just needed some clear cell components. Was there any attempt at looking at mixed tumors with papillary, and, if so, what percentage of the tumor had to contain clear cell components to be eligible for entry?

DR. ANDREWS: There was no central pathology review. There was the pathology lab at each center, and a diagnosis of the majority being clear cell.

DR. GARNICK: So any clear cell component allowed the patient to get in as opposed to a minority of the lesion being clear cell. Did you capture that information or not?

DR. ANDREWS: We captured the information that the majority were clear cell. There were -- we didn't capture the mix, no.

DR. GARNICK: And my last clarifying point is, to the extent possible, did you have any data or any way of looking at the response rate or the time to progressive disease on first-line therapy and whether there were any differences in the randomization between the axitinib and the sorafenib?

What was the biology of the patient population that went into each of the randomized arms, and were there any perceived differences? Because the biological behavior of this disease is so heterogeneous that we're looking -- I'm looking for potential differences in the subset of patients that ended up getting randomized.

DR. ANDREWS: Yes. I don't think this

answers your question, but I'm going to show this slide briefly. It's one of the analysis that we did that I think helps put some context around it.

We looked specifically whether response to prior sunitinib, whether you responded or not to prior sunitinib, drove any efficacy on axitinib or sorafenib. And specifically, there, if I can show E-63 -- this is the Kaplan-Meier curve for axitinib categorized by nonresponders versus responders. Essentially, the efficacy for axitinib, you can see the two curves overlapping to all intents and purposes.

We did another analysis that looked at less than three months or greater than three months, and we saw the similar results. The Kaplan-Meier curves intertwined.

DR. GARNICK: So there was no difference in either response rate or time to progressive disease with the first-line therapies?

DR. ANDREWS: No, not for sunitinib. And then what I'm showing you now isn't that answer, but, no, there wasn't for that, either.

DR. GARNICK: And for the cytokine-treated patients?

DR. ANDREWS: I don't know I've seen that data. Can I see if I can get it and come to that a bit later?

DR. GARNICK: Sure.

The last question I have is, I was struck by the incidence of venous thromboembolic phenomenon, where it's like five times more common in the axitinib arm compared to the sorafenib arm.

Did you do anything to try to understand what the pathophysiology of that was in the patient populations treated?

DR. ANDREWS: Can I ask Dr. Sinil Kim to specifically come and talk about the VTs? We had 10 versus 2, and I think those are the numbers you're talking about. I would say the one grade 5 event occurred post-treatment when the patient was on everolimus, but it was in that 28-day period, so we reported it.

DR. KIM: Sinil Kim, Pfizer oncology. If I may show the slide that I showed previously, slide

45, I believe that this is what you are referring to.

There were a higher number of VTE numerically on axitinib versus sorafenib. And we don't -- and this is a common unknown adverse event seen with drugs of this class. But I'd like to also mention that on the other side of thrombotic event is the hemorrhage, and for axitinib, the hemorrhagic events, severe hemorrhagic events, seems to be numerically less compared to sorafenib.

DR. GARNICK: No, I understand that. I'm actually referring to 5.7.4 in the venous thromboembolic events on page 89 of your briefing document. Basically, you've got seven patients with pulmonary emboli; deep vein thrombosis, two patients; jugular venal thrombosis; retinal vein occlusion; retinal vein thrombosis; subclavian vein thrombosis; venous thrombosis; grade 3 -- they were grade 3 or grade 4.

My question is, did you look into was there any underlying predispositions in this patient population that could potentially identify them as

being at higher risk for developing VTE?

DR. KIM: I see.

DR. GARNICK: Had they had a previous history of VTE? Had they had a previous history of phlebitis? Have they been on anticoagulation therapy in the past? Some sort of clinical insight that a clinical person could identify saying this patient may be at higher risk?

DR. KIM: Yes, I understand. We looked at each one of these patients, and most of these patients came in as a narrative from the investigator, and we also discussed some of these patients with the investigator.

We tried to look for any predisposing factors, and the only thing that we could find is that these patients had cancer, which is a hypercoagulable condition. And we couldn't find anything definitive that we can identify ahead of time.

DR. GARNICK: Just to go back to the thyroid issue, so the 19 percent were patients that were either picked up by TSH testing or actual clinical

symptomatology of hyperthyroidism. I'm unclear of where that 19 percent number comes from.

DR. ANDREWS: It's a combination of both. I think the majority came from the TSH numbers, which we can show you as well. But I would say, again, all of it was grade 1 or grade 2, low grade, and most of it didn't come as symptoms, I don't believe, but by the TSH pickup and then reported as an adverse event.

DR. WILSON: Thank you, Dr. Garnick.

Dr. Vose.

DR. VOSE: It wasn't clear to me how quality of life was measured, and I'd like to know what kind of questions were asked and how they were administered, and what were the types of responses that you got.

DR. ANDREWS: Again, can I ask Dr. David Cella to come to the podium to answer that?

DR. CELLA: David Cella, Northwestern University. Could you bring up slide SE-26, please?

These symptoms that were asked about, or the

questions that were asked, were these 15 questions illustrated on the left. They range from fatigue to dyspnea, cough, pain, blood in the urine, fever, and then some more general questions about appetite, side effect, bother, and ability to work and enjoy life and sleep. So it's a range of the 15 most important things to kidney cancer patients who are receiving therapy for advanced disease. That's how the questionnaire was constructed. On the right is a subset of those questions that relate to what are predominantly disease-related symptoms, and we targeted in the questioning.

Earlier, if you could switch to slide SE-87 to look at, an example of one of these, because we had talked about the sort of bottom line to the patient with regard to the safety side. We do ask the patient in one of these 15 questions how bothered they are by side effects from their therapy. And I mentioned that there is a little bit of an increase in sorafenib both relative to axitinib in the beginning, but over time, they're really quite comparable with the lines really

superimposable and crossing over from time to time. And you can see the level of bother to the patient's perspective while they're on treatment is in the sort of little bit to somewhat range because it's being managed in the context of treatment and supportive care.

DR. VOSE: Was this a written questionnaire,and how was your response rate?

DR. CELLA: It is a written questionnaire. Patients complete it. It's on one page. There are five options for each question that are shown there on the left of that slide. The response rate for expected evaluations, which are expected all the way through, every four weeks, through the course from baseline through to end of treatment and then a 28-day follow-up, the response rate was over 90 percent, which in oncology trials is a very high bar, and I'm always happy when we achieve it. So it was over 90 percent across the period of time that patients were on treatment.

DR. WILSON: Okay. Thank you very much.

Dr. Fojo.

DR. FOJO: I needed a clarification, and I had a couple of comments and questions. In the patient demographics, you show 32 and 33.1 percent of patients that have MSKCC poor, and what the FDA showed us this morning is 1.1 and 1.1 percent.

Which is correct?

DR. ANDREWS: Yes. Our original submission used the first line 1999 criteria developed for treatment naïve patients, and that's the numbers reported by the FDA. We realized that the more appropriate criteria are for second line, and those are the criteria we used. One of the issues with those criteria is they both require a Karnofsky score, and we didn't collect that in our study. And we mapped ECOG to Karnofsky.

Another way of looking at this -- well, let me ask Dr. Motzer if you'd like to make any comments around the MSKCC.

DR. MOTZER: Can you show slide C-7, please?

So there was an original model that was created for MSKCC risk, and in that model, there was a mixed population of patients. And about

20 percent of patients had received prior therapy, the other treatment were treatment naïve.

There's a model -- it was refined, basically, and there was a model that was set up and reported in 2004 specifically in second-line treatment. And so we felt that that was really the most appropriate model for this patient population, and so we updated that from the original ASCO presentation to reflect the model that's most applicable in previously treated patients, and that's the one that's shown on the right.

So by that model, which was the similar model that we used with the RECORD-1 trial for RAD001, there are three different factors, and it applies more to previously treated patients.

DR. FOJO: So then the FDA numbers are maybe more accurate for this patient population is what you're saying?

DR. MOTZER: The numbers that we presented today with approximately 30, 30, 30 are the most appropriate numbers by what we felt was the most appropriate criteria.

DR. FOJO: So then as one looks at this -- actually, on a light note, if you will, I think Pfizer probably doesn't have to worry even if this drug isn't approved because Bayer is probably going to hire Pfizer to run their clinical trials because sorafenib did so well in this study.

But it actually did well, in my opinion, in the, quote, "cytokine refractory patients" and not so well in the sunitinib refractory patients. And when you look at that population, you have a PFS of 3.4 months, and if we look at the placebo data, such as it is, that's available in this population, the values that come for that are 1.9, 2.8 and 4.2 months for the placebo group, and this 3.4 is landing right in the middle of that.

You could say that well, maybe this is a little more advanced situation, which I don't think it is. I actually would say that, quite possibly, the patients that are enrolled in this were two years out from their original diagnosis and nephrectomy and more than a year out from their metastatic disease. So I think we're beginning to

select the patient population that probably has the biology you were just alluding to a little bit ago, and, in fact, it's probably a little more indolent. And actually, to get to 3.4 months, all you have to do is not have progressed at the first assessment, basically, and that gets you to 3 months right there.

So what I would argue is that in the sunitinib, quote, "refractory population," that you have used as a comparator a drug that is actually not active, and that sorafenib is really not active in this patient population, or at best marginally, marginally active.

But you did really well in the, quote, "cytokine refractory," which I think should be cytokine refractory, slash, intolerant since we know a lot of patients never complete that. And there, clearly, axitinib has outperformed sorafenib. And I would say there that, in fact, it was not only an active comparator but a very good active comparator.

So with regards to that, it was very good,

and I wondered -- the question had been asked how long was the sunitinib response. But I wondered if you know, especially for the patients who responded, which is 13.6 percent, what their prior sunitinib dose was because Dr. Motzer and some other folks from Pfizer reported not too long ago data that showed that with 25 and 37.5 really, there wasn't as much activity, in fact, almost no activity for sunitinib. So I wonder if these were really progressing on sunitinib or progressing on full dose sunitinib as far as their responses were concerned.

So do you know what the prior sunitinib dose was of the patients when they, quote, "progressed on sunitinib?"

DR. ANDREWS: Yeah, we didn't collect that data on the prior dose. We don't have that data. I just would make one comment. I mean, is sorafenib active in the sunitinib refractory group? This is a group where they have been progressing. It is determined progressed by CT or MRI scan. And in that setting where they've progressed on

sunitinib, 62 percent of the patients showed tumor shrinkage at some level in the waterfall plots, and the response rate was around 8 percent, 7.7 percent. And if you put that into context against the everolimus data that Dr. Motzer showed, where the response rate was zero percent, it provides some evidence of activity, I believe.

DR. FOJO: It does, assuming that they were on a good sunitinib dose when they progressed, which is why I was asking that. But I guess you don't have that data.

Then the other couple of points that I made, it seemed the titrating axitinib was important, and certainly, those that went up to 7 and those that went to up 10 had lower, before titration, AUCs. And then they got into the AUC of the 5 milligram BID patients who did not titrate, suggesting that, in fact, a fraction of the patients seemed to be metabolizing the drug more rapidly.

Is that the way you-all interpret it?

DR. ANDREWS: Yes, I'd like to invite Dr. Yazdi Pithavala, our clinical pharmacologist,

to talk more about that, pharmacokinetics.

DR. PITHAVALA: Yazdi Pithavala, clinical pharmacology, Pfizer. That is indeed our interpretation. Like most oral drugs, this drug has some inter-subject variability, and we expect that -- while we know for a fact that 5 milligrams BID is the appropriate dose for the majority of patients, we expect there is a subset of patients who are probably getting subtherapeutic exposures. And we want to allow those patients to catch up with the remaining subjects, and that was the hypothesis behind the implemented dose titration. And, indeed, after collecting PK data across our pooled phase 2 studies, we found that the subjects who eventually went up to the 7 and 10 milligram BID dose had lower exposures to begin with. And, therefore, dose titration allows those patients to catch up. It's acknowledging that one size doesn't fit all and in an effort to get optimized exposures.

DR. FOJO: But then one would have to note that sorafenib titration was not allowed, and one

would wonder what if you did allow sorafenib titrations since sorafenib would, like axitinib, be expected to have a fraction of patients who had AUCs that weren't as robust. And that's also something that one sees commonly in these patients.

Then I had two other things. You actually showed slide 127. Could we see that again?

Am I allowed to ask for a slide?

DR. ANDREWS: Can we show Slide, I believe, E-127?

DR. FOJO: Yes, the one looking at symptomatology in the patients.

DR. ANDREWS: Yes, can we see slide SE-127?

DR. FOJO: Right, this one.

So based on this, I believe that the submitted material said that -- and you were alluding to it a second ago, said that, well, axitinib allowed patients to stay on treatment longer, and they were feeling well with it. And so, consequently, it's better in terms of symptomatology. But one really has to ask because all of these patients then crossed over to other

agents that in RCC have been proven to be effective to varying degrees, and, clearly, it helped them survive just as long because the overall survival is coming in at the same.

So one assumes that when they switched over to another agent, they probably had comparable benefits. So I'm not quite sure that -- it's a little bit of a chicken and an egg, that you stay on longer on this drug, and so you must do better, but you were also able to transition over to other drugs and probably do as well.

The other thing is here, the drop looks dramatic -- the drop -- I mean the Y axis starts on 25, not at zero. So it's not that dramatic a drop off therapy, but we're assuming that these are then going onto other treatments. I don't know what your thought was on that as to whether that would be a fair way to characterize the benefit.

DR. LOGAN: Can I just make one other comment on that slide? This is patients on -- if I understand, it's patients that are on treatment actively. And so you're not in a situation of

informative censoring where you're losing people that come off treatment or progress. So the patient populations may no longer be comparable at this point. So you got to be very cautious in interpreting this kind of figure.

DR. ANDREWS: Yes, acknowledged, and we didn't -- that's why we wouldn't present it in our main presentation.

Just to the comment, the drop, I believe, is three points which is considered to be clinically meaningful and validated, and Dr. Cella could talk about that.

I interpret this curve to say while a patient's cancer is being controlled, as you've said, there's benefit for both arms. When they come off treatment, when it's not controlled, that benefit drops. That's the way I would interpret this.

DR. FOJO: And then the last comment at the risk of sounding to be on a pulpit here, it's remarkable. So sorafenib was first dosed in 2003 in the randomized trial. We're eight years into

the VEGF in kidney cancer. And there isn't even a single marker, and this trial has no markers at all, anything to predict efficacy. And when you look at the data for both sunitinib and sorafenib, 30 to 40 percent of the patients are off within three months.

Clearly, a large percentage of the patients are deriving absolutely no benefit from these drugs, and we haven't a clue as to how we might predict that. And it's a shame that hasn't gone on further. Thank you.

DR. ANDREWS: I'd like to ask Dr. Brian Rini just to comment briefly on that.

DR. RINI: Thank you. Brian Rini, Cleveland Clinic. Before I get to the biomarker question which I think is critical, I wanted to address two of Dr. Fojo's earlier comments, one on previous sunitinib dosing and one on sorafenib dose titration.

So, unfortunately, we don't have data on the previous sunitinib dose. I agree it'd be interesting to look at. I guess I would say, my

experience, patients who do the best on sunitinib the longest term actually are probably the ones who end up 37.5. I think most people end up 37.5 over time, whereas if you progress after two cycles, you may have gotten 50 for two cycles and progressed.

So I'm not sure that looking at dose would actually show you. It might actually be the opposite. It might be people who tolerate it and are on it for a long time who actually end up at a lower dose. I don't know what Bob's experience is, but that would be mine. So it'd be interesting to look at, but I'm not sure in which direction it would fall.

In terms of sorafenib dose escalation, as you're aware, there was data presented at ASCO this year by Martin Gore, a multicenter trial, looking at sorafenib dose escalation because there had been prior single center phase 2 studies that seemed to be promising. What was shown in a multicenter prospective experience is that sorafenib dose escalation is neither tolerated nor efficacious and is not routine in clinical practice, and that's why

it wasn't allowed in this study.

Then lastly, in terms of biomarkers, I couldn't agree more, and many of us are dedicating a lot of our academic lives to finding biomarkers in kidney cancer because right now, we have an empiric list of therapies. And that's why trials like this to sort of define therapy in a specific circumstance are critical.

As you may know, one of the interests of mine has been blood pressure. As a biomarker, some of the first data was with axitinib in a pooled analysis of phase 2 studies.

If we could just pull up slide SE-362.

This is published data not from the prospective phase 3 but from prior phase 2 experience looking at a landmark of patients who do or not develop elevations of diastolic pressure on treatment, showing an advantage to patients who do develop hypertension. Now, obviously, this requires you to be on therapy to know, so it doesn't allow you to avoid therapy in patients.

What we're looking for obviously is some

genotype that correlates with this phenotype that we could test before treatment. So this is a clue. It's a signal. I think it's a strong signal for this drug and promising, but there's a lot of work to be done.

DR. WILSON: Okay. Let's move on. I believe Dr. Sekeres has a very brief comment that's relevant to what we've been discussing.

DR. SEKERES: Yes, just about your recent comment about the patient-reported outcomes.

We can't say that patients' quality of life drops when they're off drug because it wasn't measured. It's just as likely that their quality of life may improve because they don't have side effects of the drug. So bottom line, patient-reported outcomes, there's no advantage to either drug above the other.

DR. WILSON: Okay. Thank you.

Dr. Curt.

DR. CURT: Thank you, Dr. Wilson.

Question for the FDA. In the agency's presentation, we saw that the PFS was being driven

by a patient subset which would be likely underrepresented in the U.S. population. But in the sponsor's presentation, if you look at the actual data from the U.S. patients, the hazard ratio is, if anything, a little better than the general study population. And I'm wondering if you could help me square those two facts.

DR. ANDREWS: Yes. My interpretation would be that the confidence intervals are wide around the hazard ratio, and I don't know the numbers have changed too much. I showed you the overall, and I showed you the sunitinib refractory.

If I may show again slide 28 -- I mean Deck 28; again, if you draw down on the hazard ratios, which I think are a better estimate of the overall treatment effect, the hazard ratio for the overall was .67. I think in the U.S. population, it was .61, you quoted. I don't know it's changed that much. It's reassuring, to me, though, that the effect is maintained in the U.S. with lower numbers of cytokine refractory patients.

DR. CURT: The data is the data overall.

DR. WILSON: Okay. Thank you.

Dr. Freedman.

DR. FREEDMAN: Thank you, Dr. Wilson.

I'd like to get some clarification from the FDA, first of all. Apparently in May 2007, the FDA recommended overall survival as the primary endpoint, and then it seems that the SPA was denied in January of '08. But then in April, there was a change in position, and I think -- I was just wanted to know what was the thinking when you made the change.

DR. MCKEE: The initial SPA submission included an interim analysis of PFS, which we generally don't give SPA agreements for. And one of the major changes in the two SPAs that were submitted to the agency is that the one which was accepted and agreed to by the FDA did not have an interim analysis of PFS, and that was one of the primary differences.

DR. FREEDMAN: I see. I had some other questions for the sponsor.

With regard to the PRO, we see that the

graphs show that there isn't a real difference there. On the other hand, I was interested, whether any of the individual symptom items in the instrument showed a deterioration? For example, we see that fatigue was increased in the population that received the test drug. That's the one question.

The other question that I have is the number of patients who were indeterminate, or not assessed for their primary endpoint, seem to be double in the control group.

Can the sponsor explain that? There's a figure of 6.1 percent versus 11.6 percent for the sorafenib.

DR. ANDREWS: First, coming to the fatigue, there was one question on fatigue in the individual --

DR. FREEDMAN: As part of the PRO, I think it's understood that the PRO -- the QRL is made up of multiple points, and knowing what those individual symptoms are is probably quite important to patients. For example, if fatigue is

significantly affected during the course of the treatment, one patient may -- certain patients may want to know that specifically.

DR. ANDREWS: I understand, and if I may show SE-91, these are the results from that one question, subset again and with acknowledging the other comments that have been made around this.

What you can see there is the axitinib in blue, the sorafenib in yellow, a little bit to very much. The majority of the fatigue in both arms was around a little bit prior to entry, went up a bit on study, but it didn't appear from these data that fatigue was that bothersome. And I'd also mention that overall fatigue discontinuations in Dr. Kim's presentation were approximately the same between the two arms.

DR. FREEDMAN: Were any symptoms -- did any symptoms deteriorate as part of the instrument?

DR. ANDREWS: No.

DR. PAZDUR: Could I just make a point because there's been several comments regarding PROs here? I'd like to remind the committee that

this was a unblinded trial here, and, hence, any evaluation of patient-reported outcomes have to be placed in that perspective. And I think if there were huge differences, big effects here, then we could probably just have a discussion here of perhaps any therapeutic influence here. But given the fact that this was a unblinded trial, one has to put the whole issue of patient-reported outcomes in that perspective.

Likewise, claims that there are no differences between arms, remember, sloppiness, et cetera, obscures differences. And, hence, to try to make any therapeutic claim of a benefit of a drug based on no differences between two arms is relatively tenuous here. So I just want to put this in perspective.

DR. FREEDMAN: And I had another question there.

DR. ANDREWS: Okay. Yes, sorry. You had one more question. Apologies. I didn't answer the question about the numbers not assessed?

DR. FREEDMAN: Yes.

DR. ANDREWS: Yes, the majority of those were early discontinuations on the sorafenib arm relative to axitinib. So there were more discontinuations early prior to the six-week planned scan visit for the sorafenib arm.

DR. FREEDMAN: Do we know the reasons for the early discontinuation?

DR. ANDREWS: It was really the same kind of reasons as was shown in the overall population.

If I may just show slide E-33, this summarizes the data you're talking about.

Here then are the differences, and what I hinted is two versus seven discontinuations, axitinib and sorafenib. The others were relatively similar except for refuse continued treatment. And these were all before six weeks. That was the majority of the driver. We did do a number of sensitivity analyses looking at treating discontinuations differently.

Particularly if I may show slide E-34. The numbers did change where we moved the missing on study scan right to the end of the study and

treated them right at the end as opposed to when they dropped out. But, in essence, the benefit was still maintained for axitinib over sorafenib.

If I may also briefly show slide E-26, just to put this in context, we did a number of sensitivity analyses across a number of different assumptions, and really, the fact it was maintained throughout all these hazard ratios to the left of 1, showing benefit in favor of axitinib over sorafenib.

DR. FREEDMAN: One more question.

So a number of patients on both arms were treated beyond the progress of disease endpoint. Do you know why that was permitted to happen, and, also, what was the average duration on each arm for that treatment? Obviously, that could affect your results related to the duration of treatment for either arm, the interpretation of those results.

DR. ANDREWS: If I may show E-211. These then, I believe, are the data you're talking about. We've split it out by various different subgroups. There's always the top line, then sunitinib

refractory, cytokine refractory. And you can read the numbers here. And we permitted -- well, let me stay with that point.

Essentially, there was slightly more patients continuing on treatment on sorafenib arm versus axitinib, which may have muted the effect on overall survival. It's hard to determine that to be definitive. Why was this permitted? Essentially, the primary endpoint was progression per IRC. We didn't want the -- and we didn't share that assessment with the investigators. We didn't want patients discontinuing per investigator and then not having that assessment confirmed by IRC, and losing them to the primary efficacy analysis. I believe this is common in a number of clinical trials and happens in practice.

DR. FREEDMAN: But you do have more than 10 percent of patients that are continuing treatment beyond 56 days?

DR. ANDREWS: Yes.

DR. FREEDMAN: That's quite a large amount.

DR. ANDREWS: Yes, and if I may, just

briefly to show the subsequent treatment as well, there were a number of other subsequent treatments. A lot of those were effective and received in both arms, E-243.

Combined with continuing on the active therapy, a number of patients went on to subsequent therapy, 54 percent in the axitinib arm overall, 57 percent in the sorafenib arm. And you can read then numbers there. I would identify one difference. More of the axitinib patients went on to sorafenib. Less of the sorafenib patients continued sorafenib here, and then there was slightly more temsirolimus, bevacizumab, and pazopanib with the sorafenib arm.

DR. WILSON: Okay. Let's go ahead and move on.

Ms. Meyer.

MS. MEYER: I was just curious of what were the age requirements for this. Were there any exclusions on age?

DR. ANDREWS: Yes, can I ask Dr. Jamal Tarazi just to briefly describe the study? He's

the study commission.

DR. TARAZI: Jamal Tarazi, Pfizer oncology. This study inclusion allowed all patients above 18 years old globally to be enrolled in the study, except for Japan. Their regulatory system allows over 20. There is no limit for age.

MS. MEYER: I also wanted to ask you, there was something about the difference when you started, you increased -- there was a dropout rate that you -- there was a patient dropout rate for something about the population you had to increase with the original protocol.

DR. ANDREWS: Okay. I understand.

MS. MEYER: Could you explain that? I'm sorry.

DR. ANDREWS: I understand. So the original study was powered on a different hazard ratio of .714, and it required 402 events. It's an event-driven study. That drives the power of the statistical properties. As we went through the study, we realized that there would be some patients lost because of discontinuations early

that don't contribute to that -- sorry, 409 events; let me correct myself; 409 events. And so we increased the size of the study to make sure we had 409 events to complete the analysis.

Again, the power didn't change because it's driven by the 409 events, which is what we hear. We did do a retrospective analysis just looking at the results if we'd just recruited the original sample size, and the results were very similar again there.

DR. WILSON: Okay. Thank you.

Dr. Vose.

DR. VOSE: Thank you.

I just wanted to get back to the cytokine refractory issue and kind of in the U.S., the patients are going to be eligible based upon that, since those are the patients that seem to benefit the most. So we are a center that does high-dose IL2 for this indication, and we've seen a huge drop-off in patients receiving it or being referred for this indication.

So my question was to the sponsor, over the

time of the study, from the beginning to the end, did you see a change in the percentage of patients that were entered on the study because they were cytokine refractory as compared to the other indications for being entered on the study?

DR. ANDREWS: Yes, I don't believe we've had that data or have that analysis to show you over the study. We did do one analysis -- again, I think Dr. Rini mentioned this -- looking at the U.S. population excluding the cytokines that were used and looking at the results just in the U.S. population for those that didn't receive a cytokine. Again, the hazard ratio was around about .6 in that analysis, in fact, .556.

So I don't believe the cytokines had any effect on the U.S. population, acknowledging this is a subgroup of a subgroup and the issues with that.

DR. WILSON: Okay. I'm going to take one more question, Dr. Kelly, and then we're going to take a 15-minute break. And then we will come back and resume questions to the sponsor and FDA because

we have a little extra time.

So, Dr. Kelly.

DR. KELLY: Thank you, Dr. Wilson.

I have one comment and three questions. The first comment is to answer Dr. Sekeres and Dr. Vose's question, in the U.S., around 60,000 patients a year have renal cell carcinoma; 25 (thousand) to 35,000 have advanced renal cell carcinoma. And current research actually shows that only around 2,000 patients actually get high-dose IL2 currently. How much get interferon is questionable, but it's actually a small number.

The question to the sponsor, eligibility, you had an amendment come through that actually said that you could actually use combination upfront. How many patients actually got combination therapy upfront?

DR. ANDREWS: Yes, the primary group was the bev-interferon.

DR. KELLY: Right.

DR. ANDREWS: And some of those patients actually entered on bev-Torisel. There were 60

patients in total -- 59 patients in total with bev-containing regimes. Of about 21 of those, 35 of those were bev-interferon, 15 of those were bev-Torisel, and another nine were bevacizumab and another regime.

DR. KELLY: Can you break those down in percentages for us? You know, overall, how many actually got combination upfront versus single agent?

DR. ANDREWS: Well, the 60 patients which was the total combination --

DR. KELLY: Sixty on both arms?

DR. ANDREWS: Yes, it's equally balanced. I can show you slide C-17, if it helps. These are the numbers. I didn't have the percentages here, but, as you can see, bev-interferon was 17; 18, bev-Torisel; temsirolimus was 7, 8; and bevacizumab another 5 and 4.

DR. KELLY: Okay. Thank you.

Another question is, going back to the first-line treatments, do you have the median duration which patients are on the first-line

treatments? That's another way -- I've been asking -- what everybody else is doing, but I'm trying to get to the answer here.

DR. ANDREWS: I understand, and I'm not -- can we answer that as soon as we come back after the break?

DR. KELLY: Yes. Then one last question is, using a lot of these TKIs, a lot of us know that they have some profound effects, biological effects. And one thing that we're noticing, as you discontinue the drug, you get flare effects. So it's very intriguing looking at the deaths during 28 days after discontinuation of the drug.

So the question will arise, you have a very potent TKI here. When you discontinue the drug, do you have a flare of disease leading to increased deaths; any data to show that it's not true?

DR. ANDREWS: I think if I take you to the cytokine refractory population, acknowledging there's comments around how much is used, the overall survival there, the hazard ratio was .81 in favor of axitinib over sorafenib, and we didn't see

any indication there.

Bob? Dr. Motzer?

DR. MOTZER: Robert Motzer from New York. There has been some data, preclinical data, to suggest that RCC tumors exposed to VEGF-targeted agents accelerate when the drug is withdrawn, but there isn't any clinical data for that. There's no clinical data to say when you stop sunitinib, there is a more rapid growth of tumor or tumor explosion or anything like that. There's no clinical data to support that.

I can tell you in my own practice, taking care of kidney cancer patients since the mid-1980s, I've seen lots of patients progress with RCC with all different therapies, and I personally haven't noticed any kind of a difference with accelerated growth when these targeted drugs are stopped.

DR. KELLY: The question was, did you see any data in this population that tells me that's not true?

DR. ANDREWS: Again, short of the cytokine data, it's very hard to show one way or the other

in this study.

DR. KELLY: Thank you.

DR. WILSON: Okay. So we will now take a 15-minute break. We will reconvene at 10:30. I would like to remind the members of the panel that there should be no discussion of the issue at hand during the break amongst yourselves or any members of the audience. Thank you.

(Whereupon, a recess was taken.)

DR. WILSON: Okay. May I have everybody take their seats so we can go ahead and get started?

So I do want to note that there are no speakers for the open public hearing this morning, and so that's why we have a little bit of extra time to continue with the questions to the sponsor and FDA.

So I'd like to recognize Dr. Armstrong.

DR. ARMSTRONG: Thank you, Dr. Wilson. I wanted to address something that several other questioners had addressed, which is the apparent contradiction in the good outcome in the U.S.

patients but the fact that there was fewer cytokine pretreated patients in the U.S. population, and yet the benefits seemed to be greater in cytokine.

One of the questions I had, it seems like most of the cytokine treatment in the U.S. is high-dose IL2. Is it different cytokine treatment outside the U.S., and could that be a potential explanation as to why the difference of why the U.S. population, even with a low percentage of cytokine pretreatment, does well, but overall cytokine pretreatment patients do better?

DR. ANDREWS: Glen Andrews, Pfizer again. In the rest of the world, it's primarily interferon. And we did look to see whether the response was different to axitinib to IL2 or interferon. Now, the numbers are, again, small, but we didn't see a difference overall in response.

Let me see if Dr. Motzer would just want to make any comments on the interferon and the interleukin 2.

DR. MOTZER: Robert Motzer, New York. Nothing really to add to Glen's statement. In the

U.S., cytokine use now is primarily high-dose IL2 or interferon in combination with bevacizumab. I suppose there are some others that are using interferon first line. Outside the United States, it's predominantly interferon, and interferon or interferon plus vinblastine have regulatory approval in many countries in Europe for standard use.

DR. ARMSTRONG: Thank you. I had one other question. Was the assessment of the outcome based on cytokine pretreatment or not a preplanned subgroup analysis?

DR. ANDREWS: So you're referring to the primary endpoint of progression-free survival?

DR. ARMSTRONG: Right, the difference between the cytokine group.

DR. ANDREWS: We stratified in the randomization for that. We stated we would look at it. We didn't look at it. We didn't power any of those subgroups to actually go down into those subgroups and detect statistical differences. We were trying to run a real-world trial, so we didn't

fix the numbers, either, in any of those subgroups. As you can see for the temsirolimus and bevacizumab-interferon, they're much lower. So this reflected the real-world population.

Back to your question, we planned to look at it, but we didn't power it to detect a statistically significant difference in any of those subgroups.

DR. ARMSTRONG: Let me just ask the agency, because you were the one who actually presented the data of the breakdown on the PFS. Although it was clearly less in the non-cytokine and pretreated patients, it was still statistically significant, correct?

[Dr. Chattopadhyay nods yes.]

DR. ARMSTRONG: Thank you.

DR. ANDREWS: And if I may, again, over an active comparator, sorafenib.

DR. WILSON: Okay. Thank you.

Dr. Diehl.

DR. DIEHL: So one of the things I struggled with as I was going through the application is

where exactly this drug would fit in the armamentarium against renal cell carcinoma. So what I would like to do is direct a hypothetical question to Dr. Motzer or Dr. Rini.

The question is this. If you were referred a patient who had renal cell carcinoma, failed sunitinib, and the patient did not want a protocol of chemotherapy, and axitinib was available, and the patient sat on your exam table and said, "Doc, you know more about this disease than I do and you know something about me now. What exactly do you recommend?" I'd like to know what your answer would be to that question.

DR. ANDREWS: Yes, let me ask both Dr. Rini -- I think it's an important question -- both Dr. Rini and then Dr. Motzer to maybe make some comments around that point.

DR. RINI: Brian Rini, Cleveland Clinic. So just to clarify the question is a metastatic kidney cancer patient who's sunitinib refractory, who then comes for an opinion about treatment?

DR. DIEHL: Correct.

DR. RINI: Thank you. So if available, I would absolutely recommend axitinib. I mean, I've been working with the drug, again, for many years, probably treated over 50 patients. I think it's the most potent kidney cancer drug out there. Hasn't been compared to every drug, so I realize that's my opinion, not supported by randomized data yet. But there's no question that I would be absolutely comfortable treating a patient with this drug in that setting.

DR. MOTZER: Robert Motzer, New York. I think that if you go strictly by the evidence-based guidelines, sunitinib is the first line. Axitinib has a trial dedicated specifically in second line. Everolimus, the trial was in a TKI refractory population. So I think, specifically by evidence-based guidelines, that would be the paradigm.

Now, that being said, I think there is controversy in terms of which one to use second and which one to use third. I mean, I think that the treatment options for subsequent therapy should be axitinib, following approval, or everolimus. The

order, not so clear on. It may depend on the individual patient.

So I think that most patients with renal cancer get a series of these different drugs, often three or four. My own feeling from this trial is sorafenib should be out. Sorafenib should be replaced by axitinib. Axitinib's more effective. I don't see any downside in terms of the toxicity profile.

So with the choice, it's going to be which one do you give second, which one do you give third. Everolimus followed by axitinib, or is it going to be axitinib followed by everolimus? I think it's going to be an individual decision. And oftentimes, we make that decision based on the patient's comorbid conditions.

For example, one of the most troublesome side effects with everolimus is worsening diabetes. So that in a patient with diabetes already, I would tend to hold off as long as possible on the everolimus. On the other hand, my own feeling is if a patient had difficulty with TKI symptoms or

uncontrolled blood pressure, I might offer that patient everolimus and hold axitinib for third line.

But in the current paradigm, all these patients get sorafenib. They either get sorafenib second line, or they get sorafenib third line. And so my feeling from this data is that sorafenib should be out of the picture and replaced by axitinib.

DR. WILSON: Okay. Thank you.

Dr. Buzdar.

DR. BUZDAR: Yes, I have one question about the proposed indication for this NDA, which is essentially that it is indicated for treatment of patients with advanced renal cell carcinoma, and all the data which we are looking at it over here this morning is patient population which has been previously treated, and, essentially, the drug is being compared as a second-line therapy. So if the label, if it is approved as it is being proposed, there is no data which we can say that it has efficacy which will be similar to currently

available drugs in that type of setting.

DR. PAZDUR: Let me address that. Generally, we do not talk about the indication as such. Giving an indication to a drug, we generally assign that indication to the population that was studied. As you can see from the question that we're asking the committee, a risk-benefit in a second-line setting, I believe the question is worded.

As Amy mentioned during her presentations, when sunitinib and sorafenib came out, when they were the first drugs approved really for this disease, we gave them broad indications, and I'd like to explain the reason behind that. Those broad indications were based on the fact that we did not want patients to go through relatively ineffective therapies to reach an effective therapy for this disease, i.e., we didn't want them to be treated with Megace or interferon or low-dose IL2 when these drugs probably represented a major advance in the therapy.

So that's why we gave these drugs initially

large indications. I think now that we have six or seven already approved, or six drugs approved in this, it's time to look back and really get a little more specific in these indications.

So as far as the indication, that is something we will discuss with the sponsor. I understand where they're coming from. I think the agency's point of view is probably to label this as the population studied as a second-line type of therapy rather than a broad indication. I think I've given you the reason why the other drugs have gotten those indications. That was then; this is now. It's a different world.

DR. WILSON: Okay. Thank you.

Dr. Garnick.

DR. GARNICK: I just want to clarify something that to me is a critical component of the operation of the protocol. So patients that were refractory to either cytokine or sunitinib, they obviously had some sort of study examination, physical examination already, a graphic examination, that deemed them as having progressive

disease, thus making them eligible. So the patient then gets baseline evaluation, so some probably additional scans were done at that time.

Was there any comparison between the baseline scan to make them eligible compared to their scan or determination that enabled them to be considered too refractory to first-line therapy? And if so, were those compared, and were there any differences looked at in terms of the end of their first-line program till the time that they became eligible for your study?

I'm trying to get at the issue of heterogeneity of patient populations and trying to get some surety that they were balanced through the two arms of the randomization.

DR. ANDREWS: Let me be clear. We didn't have the prior scans from the previous first-line treatment. We had the baseline scans, and every patient had documented disease at baseline at that time. So we couldn't make that comparison to the prior scans.

I was asked in an earlier question about the

prior treatment duration of sunitinib, and the data I was remembering, we don't have. It was prior duration of treatment from -- sorry -- duration of time from prior metastatic diagnosis, and that was the same in both arms and supports to some extent that there weren't any differences there.

DR. GARNICK: So I assume that the independent review committee did not confirm the true refractoriness of the patient on first-line therapy?

DR. ANDREWS: That's correct.

DR. GARNICK: Okay. So we really don't know if there was comparability in terms of rate of progressive disease at the time that they entered the study?

DR. ANDREWS: Yes, I think, again, we did -- so the scans were confirmed by either CT or MRI or bone scan by the principal investigator at each site. There was a limited number of patients, about 1 percent in each arm, 2 percent in each arm, that had their scans diagnosed by other reasons. When we excluded those patients, and it was about

the same in each arm, we got the same over estimate of hazard ratio again, and this estimate around .67.

In this case if I could show Slide E-37. This then excluded those patients that didn't have documentation. Per investigator, it was refractory by CT or MRI. And you can see again the hazard ratio here of .68, on the right-hand side, the original one of .67, really no difference in the medians. So I don't believe this contributed to any of the results.

DR. GARNICK: And my last point is on your briefing document, you make reference to a small Japanese study in which a refraction study seemed to reverse after axitinib was discontinued. Do you have any clinical data from the phase 3 study if that occurred?

DR. ANDREWS: Yes, the majority of the TSH issues were easily treated with hormone replacement therapy. Again, the majority was grade 1, some of it was grade 2, which indicates treatment, and most of it reversed by the next cycle.

DR. WILSON: Okay. Thank you.

Dr. Kelly.

DR. KELLY: Yes, just want to follow up on Dr. Diehl's questions and the comments by Dr. Motzer and Dr. Rini. We have to remember what the goals of care are for these patients. They're metastatic renal cell carcinomas, noncurable, so most of this is palliative therapy.

The question I have is when you use axitinib is, do you get a quicker response when you do it? It's a more potent drug, but just because using a more potent drug doesn't mean it's a better drug. And the question is, is why would you use it over sorafenib if you don't have a survival benefit? Is there a benefit that you can actually tell us that a more potent drug in this situation would be more beneficial, and have we seen that in the phase 3 trial? Remember what our goals of care are for that patient.

DR. ANDREWS: Yes, let me ask both Dr. Rini and Dr. Motzer to respond. I would say, again, the hazard ratio in the cytokine refractory, except in

that, shows the potency both for PFS, hazard ratio of .046, and a benefit in overall survival, hazard ratio of .81, not statistically significant but similar to other of the studies here.

DR. RINI: Brian Rini, Cleveland Clinic. So I agree with you, the goals of care are really controlling patients' disease because this is a palliative setting by and large. And so I think there is evidence that you are controlling disease for a longer period of time compared to a biochemically weaker agent, i.e., sorafenib.

The first part of your question I thought was in terms of speed of response. There's an increase in objective response rate. Does that happen quicker on this drug? I don't know if we have data to support that it does or doesn't.

I can tell you my clinical experience with this and with sunitinib is that it does occur quicker. If it's going to occur, you generally can see it. You can see clinical responses in a matter of days to weeks. Now, obviously, we don't do radiographs until six weeks on this study and in

clinical practice often 10 or 12 weeks.

DR. WILSON: Okay. Thank you.

Dr. Sekeres.

DR. SEKERES: Thank you, Dr. Wilson.

I wanted to follow up a little bit on the path that Dr. Garnick was taking. In your table in your submission, and that's Table 11, the median time since diagnosis for patients on each arm was approximately 100 days. It raises the question of truly how refractory patients were to previous therapies.

So is 100 days, approximately three months, enough to determine that somebody is refractory or intolerant of a therapy? What I'm kind of driving at, again, is whether this is truly a population of patients who were refractory to a previous therapy or whether they were inadequately exposed to a previous therapy. And, really, we're talking about more some truly first-line patients who were mixed into this group versus second-line patients who were here.

So do you have information on relapsed

versus refractory and duration of treatment to previous therapies, including cytokine regimens and sunitinib?

DR. ANDREWS: Yes, I'm just looking at the table, and I believe it's weeks, not days.

DR. SEKERES: I'm sorry.

DR. ANDREWS: And while I was trying to find the table, I missed the second question.

DR. SEKERES: So do you have data on whether patients were truly relapsed or refractory to previous therapy and duration of treatment with previous therapy for both sunitinib-containing regimens and cytokines?

DR. ANDREWS: Well, we have documentation in the case report form by the principal investigator that they were indeed refractory, either by CT, MRI, bone scan? I showed you those data just a moment ago which supported however they were confirmed by CT or MRI or weren't, the hazard ratio was still the same.

It's also just worth returning because I think a number of people have asked me this

question again, just to look at, if I may show slide E-65. Just in terms of response to prior sunitinib, whether it was less than three months, the duration of time that they were on sunitinib, or greater than three months, three months we picked. And it's a bit arbitrary, but I could show you the same for six in terms of early refractory patients. The efficacy, the Kaplan-Meier curves were identical. Here, the dotted line is less than three months and the solid line, greater than three months for prior therapy.

So although I can't show you the data that shows you the balance, what I can show you is it doesn't appear to drive the axitinib effect.

DR. SEKERES: Okay. Just to follow up again on the proposed scenario that Dr. Diehl gave of a patient walking into your clinic, so, Dr. Motzer, if you were chairing the NCCN panel, what category would you give this trial?

DR. ANDREWS: Can I ask Dr. Motzer?

DR. MOTZER: I think this would -- you want to pull up slide 65? I think based on the phase 3

nature and the data itself, I think it's a high level, Category 1, randomized trial showing benefit in this particular setting.

DR. SEKERES: So that it doesn't have a survival advantage like the everolimus data, would -- I'm sorry -- like other data, the temsirolimus data, wouldn't influence that?

DR. MOTZER: No. I mean, a survival benefit has been elusive in studies for RCC. The only two that have shown a survival benefit was one in Europe with interferon and the temsirolimus, which was in a kind of special patient population. All the rest have been in PFS, and for the most part, PFS is kind of the benchmark we use in the RCC academic community for a benefit.

Although the studies by themselves haven't shown benefit in OS within the study, we have all seen a remarkable improvement in overall survival, overall, for our patients with RCC in the era of targeted therapy.

DR. SEKERES: Thank you.

DR. WILSON: Dr. Pazdur.

DR. PAZDUR: Let me bring this into some regulatory reality here for everybody, okay? In fact, let me come to Pfizer's help here, and I'm surprised you guys didn't bring this better out in your presentation.

What we're talking about is regular approval here, okay? Regular approval carries with it the obligation that one demonstrates safety and efficacy. There is no requirement that one demonstrates comparative safety and efficacy. Obviously, if you had a drug that was remarkably worse in safety profile or a efficacy parameter, then we would have to address this. This is not the case here.

But I really want to underscore the issue that we do not have a comparative efficacy standard here. It is the demonstration of safety and efficacy and has the sponsor done that. Remember, in other therapeutic areas that deal with non-life threatening diseases -- and I'll come back to oncology because it is a special situation because we're dealing with life-threatening diseases here.

But in non-life-threatening diseases, the agency frequently approves multiple, multiple renditions of drugs, me-too type of drugs -- and I'm not calling this a me-too drug; I want to make that quite clear. But they do approve multiple drugs on the basis of placebo-controlled trials. They're able to do placebo-controlled trials because even if you have other comparators approved, or other non-comparators, they're able to do placebo-controlled trials because they're dealing with a non-life-threatening disease.

Here when we're dealing with a life-threatening disease, we have to really take a look at an active comparator here. And we've gotten around that in oncology frequently by doing add-on trials. This was not the case here, okay? We sometimes do placebo-controlled trials, and we've had actually sponsors come to us after five of these drugs were approved and wanted to do a placebo-controlled trial, and we said no way. We really think that this is a situation where you need to either do an add-on trial or an active

comparison.

But when one is doing an active control trial such as this, particularly with a recently approved drug, one has to understand the issue, both in a regulatory perspective and also the magnitude of difference that we're looking here at. When we're seeing that there is a delta of approximately two months here in median survival, one needs to add that onto the control effect of the drug that you're comparing it to.

So that's why we're harping about it, and I think the sponsor needs to really answer this question to everybody's satisfaction; well, what is the control effect, or at least an estimation of that control effect in this setting, in this second-line setting. So we're adding it on. So it's not just two months. It's two months plus the effect size of sorafenib in this situation. Again, we don't have a comparative efficacy requirement here. It's just the demonstration of safety and efficacy.

Given that, if somebody could do a non-

inferiority trial, if we had a good idea of what the control effect of these trials is, they could get the drug approved simply by doing a non-inferiority trial to any of these agents here. They don't have to beat the agent. They would have to do a non-inferiority trial.

That is particularly problematic here in this situation or in the treatment of renal cell cancer because we've rapidly approved multiple drugs on the basis of one trial. It's very hard to determine accurately control effects for consistency or constancy on the basis of only one trial. So the doing and the execution of trials based on non-inferiority is very difficult.

My own personal opinion is that the sponsor is to be commended to actually trying to put this drug in some type of order here to what would be a second-line therapy, and actually going against an active control. Let me remind you that many of the sponsors that do active control trials, they generally don't put their drug up against a recently approved drug. They're looking at ancient

drugs like DTIC or other drugs that have marginal activity here.

So here again, we're really comparing it to a drug that has been recently approved here. And I think the reason why we brought this drug to ODAC was really to have a discussion about the problems here with developing a drug where you have multiple approved drugs in a relatively tight sequence here. Since 2005 or so, we have six therapies that are approved here.

So here again, the point I want to get across, there is no comparative efficacy issue here. It is does this drug have safety and efficacy. If we were talking about accelerated approval, yes, you have to be better than available therapy because we're approving that drug on the basis of a surrogate endpoint. Here, we have already stated that from our past approvals from a regulatory perspective, PFS of a sufficient magnitude would be of clinical benefit.

So the real issue here is what is the control effect of sorafenib here. And, here again,

I realize we do not have randomized trials. This is not a perfect world, but what do people feel comfortable with, with regards to the effect of sorafenib, because that's what you have to add this delta on to.

So am I making myself clear? I don't know if we brought these points out really well in our presentation, but, here again, people have constantly emphasized this is an active control, this is an active control. But one has to understand what the implications of that active control is, that you have a delta here but you add the control effect to that -- you have to add that delta to the control effect, and also the issue of we don't have a comparative. You don't have to beat this drug necessarily. They did.

DR. WILSON: So, Rick, I want to thank you for those comments. It is something that I think we will talk a little bit more about.

Let me just ask a couple of questions of the sponsor, and then we're going to move on to the voting question, and we'll have a discussion. And

I think Dr. Pazdur's comments I will put my own spin on.

We noted here in the randomized study that in the treatment arm, discontinuation due to AEs was 9 percent of all cases whereas in the control arm, it was 13 percent. One of the things about this drug is that I don't know if it's fair to say it is less toxic or more toxic. It simply has a different constellation of side effects, and different people are going to get different side effects. And putting efficacy aside, I think it is worthwhile and important to have active agents that may have a different side effect profile because one patient may not be able to tolerate one versus another.

So my question is -- I know the 9 and 13 percent is what was found in a relatively rigorously controlled clinical trial. My question, though, is to the two clinicians, in actual practice, can you give us some idea about how often you have to take patients off a specific TKI so that we have a better idea of what the reality is

of the need for drugs with a different constellation of side effects.

DR. ANDREWS: Can I ask Dr. Motzer to answer?

DR. MOTZER: In clinical practice, generally, we start out with the full dose of the drug, for example, 50 milligrams of sunitinib if that's what you're using. And we dose modify for toxicities. A lot of the toxicities, for example, hypertension, is managed by additional anti-hypertensives. And so we generally try to manage the toxicity as best as possible without dropping the dose.

When we have to, we drop the dose, and for the most part, the proportion of people who actually stop treatment, the drug, specifically for toxicity is small. I think it's relatively representative for here and in the sunitinib studies. I think it's probably between 10, 15 percent that actually have drug stopped for toxicity, and most instances, it's progression.

DR. WILSON: Okay. So that's a very good

point. Then can you please comment on the following. Dropping dose below a therapeutic or effective level, even though we may not know where it is, and its attendant side effects may be, in reality, equivalent to stopping the drug altogether, therefore, is it of use to have drugs -- if you have a drug that you know is potent with a different side effect profile, would you, with that drug in hand, be more inclined not to drop the dosing of your current drug so low to avoid the side effects but going over to another class? Because, again, it's all about whether do you stop it or do it so therapeutically, which you don't know; the consequence for the patients, the same?

DR. MOTZER: I think that's a very good question. I don't think we really know the answer to that. In my own practice, what I normally do is follow the guidelines for the trial that established efficacy and use those guidelines in terms of dose reducing, but very good question in terms of should we go with a lower dose or just

simply switch to a different TKI that has a different toxicity profile.

I think that it gets back to the point of individualized medicine. These drugs all have different toxicity profiles. One drug may be better for one person, and one drug may be better for another. And that's why I think it's very important to have them available if they meet the guidelines for approval so that we doctors can have that choice in terms of making individual decisions for our patients. I think that's critical.

DR. WILSON: So I think the fact that this drug has a different toxicity profile would suggest that it may have a niche, and that it is useful to have a drug like this available. I think one of the questions that Dr. Fojo was trying to get at -- and I think that a lot of people here have been trying to dissect whether or not axitinib is better than sorafenib -- but one of the issues that Dr. Fojo brought up was in terms of the dosing. I believe you're the one who commented on the fact that they were allowed to increase the axitinib

dose but not on the sorafenib dose. I think it's telling, though, that if you do look at the dose of modifications, at least those in which the drugs were reduced, actually, the 52.1 percent of the patients on the sorafenib arm had their dose reduced, whereas only 30.6 percent on the axitinib arm, suggesting to me that the effects were not driven by an under-dosing of the sorafenib arm.

Yes, Dr. Fojo?

DR. FOJO: The material that was handed out has the PFS, in 40 and 30 percent of the patients, they're censored because you said that it was close to the termination. So you showed us today the update on the overall survival.

Do you have the update on the PFS that hopefully will have less censoring and how that breaks down for all patients and for, quote, "cytokine refractory and sunitinib refractory?"

DR. ANDREWS: Yes, we haven't had an opportunity to perform the additional PFS on this updated survival. We did in response to a query from a European regulator update the data. I would

emphasize the final for the protocol was at 409 events. But we did update. We had about approximately 70 additional events.

If I may show slide E-8, this is the overall numbers, and there was a cutoff date of June, 2010. And you can see relatively there's less censoring, and the curves have been extended out. The hazard ratio again is still .67, and the difference is around two months still.

If I may, you asked about the subgroups, and, again, I don't think in the subgroups the numbers had changed. If I may, just to go back to an earlier point and put in context slide E-2, this then was the earlier discussion around relative to sorafenib.

The left-hand slide is the target study on which sorafenib got approval, and you can see the difference in curves between placebo and sorafenib with a hazard ratio of .44. The right-hand side then is the additional benefit that axitinib brings over and above sorafenib, which again showed benefit over placebo in this setting.

Questions to the Committee and Discussion

DR. WILSON: Okay. Thank you.

Let me then conclude the questions to the sponsor, and I would now like to move on to the questions to the committee, and we will be having a discussion. If a compelling question comes up during that discussion where you would like to ask a question of the sponsor, certainly, I am open to that.

So, Dr. Pazdur, would you prefer the FDA to read the -- well, give the overall and the question to the committee?

DR. MCKEE: So this is just to summarize once again the results from the single randomized study with axitinib versus sorafenib. There was a median PFS Of 6.7 months for axitinib versus 4.7 months for sorafenib, with a hazard ratio of 0.67. In the previously treated cytokine subgroup, the median PFS difference was 5.6 months, and the previously treated sunitinib group, the median difference was 1.4 months. There was no difference between arms in overall survival, and the safety

profile is similar to other VEGFR TKIs.

So the voting question is, is the benefit-risk evaluation favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy, and vote yes, no, or abstain.

DR. WILSON: Okay. So let me start out by giving kind of my summary and perspective on this. I think that Dr. Pazdur summarized it very well, but I think it's important to recognize that for regular approval, the criteria for that is that the drug is effective and that has a favorable risk-benefit ratio.

I think we've heard extensive data regarding the toxicity. I think it's fair to say that the toxicity is probably, overall -- if you balance both drugs, it's probably at a similar level, but the toxicities are different. And, therefore, different patients will have different toxicities. And I think that if you have two drugs that are equivalently effective, having drugs with different toxicity profiles can be very useful for the

individual.

I also am struck by a number of the toxicities associated with the axitinib seems to be possibly class driven, hypertension and also a number of vascular events that we know is associated with inhibition of VEGF. And so one might anticipate that class-driven effects are going to be seen more prominently in a drug that may have a greater effectiveness, but we don't know that. But I do think it's fair to say that the toxicities are different but probably overall equivalent.

One of the things I think that is quite striking about this application is that it is the first drug in RCC that has been compared against an approved agent. As you can see -- and another approved TKI. All the other TKIs were not set up against other TKIs. And the regulatory requirement is that this drug -- if we assume the other TKI that's been approved is effective, which has been established by virtue of the fact it is an approved agent, all the sponsors really need to do is show

that it is equivalent to the other TKI, and that would be a non-inferiority study.

In fact, this trial showed improvement in the hazard ratios even among those patients that had had prior TKI therapy. I'm not saying it was a large amount, but if you're going to see an improvement in hazard ratios, I think one can certainly say that it is no worse, or it is equivalent, or it would be found to be not inferior to the other drugs that are approved out there.

So I believe that actually they have come up to a higher hurdle, which is that they have shown that it is marginally but nonetheless has a better hazard ratio using progression-free survival.

Now, we can argue whether or not two to three months is worthwhile, but that is the endpoint, and that is a legitimate endpoint. And that is the endpoint for which all the other TKIs were approved. Now, what we know is that, if anything, it's slightly longer. And I think all they need to do is show that it is equivalent to it.

So I think we've spent a lot of time trying to dissect out whether or not this drug is really going to offer a meaningful benefit over other TKIs. I don't -- that is not the regulatory hurdle that this drug has to show. And I think by making drugs like this available, one really doesn't know whether or not if you have a more effective TKI. With postmarketing studies done by cooperative groups, et cetera, maybe this would turn out to be the front-line TKI. You won't know that until those kinds of trials are done.

So, certainly, it is my take that the toxicity profile is different. There's benefit there, and I think we have evidence that it is not inferior to currently approved TKIs. And so that's just my summary, and I just want to open it up to the committee to have their questions, discussion, et cetera.

Dr. Fojo, you look like you have something running around in your head.

DR. FOJO: No. I mean, I generally agree with most of what you said. In getting back to

what Dr. Pazdur was saying, I mean, I think he's saying added above and what sorafenib did. I think in the refractory sunitinib patients, sorafenib did basically nothing. So I think that the drug in that setting has two months, and that's about what it would have been had it been compared against an inactive or placebo. So, again, we can discuss how important two months are. But I think that that's all it had.

In the more favorable setting of the cytokine refractory, obviously, it outperformed sorafenib quite well. And I think sorafenib did, as I pointed out, better than it has in the past, which is reflecting that we're getting a lot of experience with these agents and administer them better and for a longer time.

I thought it was interesting that, like for example, the PPE rate grade 3 for sorafenib was 16 percent, which is two and a half to three times what it was in the original trial. It just shows you we're willing to push with these drugs a little bit longer. And when you look at it here, and

you're alluding to the fact that it could come to the upfront setting -- obviously, when you look at the numbers, you say 12.1 months PFS for this, 8.8 for sunitinib, 7.4 for pazopanib, it seems better, but I think months are getting better with age. And if you were to run the sunitinib trial again, it would be higher than 8.8 because we know how to manage that drug better, and we would do better with it.

So in the end, there will be the studies that will compare this to other drugs, but, to me, the activity is most impressive in the cytokine refractory. And in the sunitinib refractory, it is what it is, not a whole lot.

DR. WILSON: So, again, it doesn't -- what we really are looking here is it worse than what's already out there. So I don't think we need to argue about whether two months is meaningful. I think what we can say is that it's not -- at least two months is in the positive direction.

DR. FOJO: Yes, so I think it's an active agent. It's toxic, but it's, as has been alluded

to, toxic in a different way. And Dr. Rini said hopefully, someday we'll have some markers. Maybe we'll have some markers as to who develops hypertension, who develops PPE, who develops what toxicity, and then those things will be better and more informed. Currently, it's just a clinical acumen, a clinical body language that one basically makes these decisions on. But it certainly is an active agent, comparably, or better than what it is out there. And it is different toxicity but not worse.

DR. WILSON: Dr. Curt.

DR. CURT: Yes, thank you, Dr. Wilson.

Just to comment, we heard in the sponsor's presentation from Dr. Motzer who chairs the NCCN kidney cancer guidelines committee, and his opinion that if approved, this would be a Category 1, highest evidence drug both in the post-cytokine and post-TKI settings. And if it's approved, it would be the only Category 1 drug in both of those treatment settings. And I think it's something important in the voting members' consideration on

how to address the question to the ODAC. Thank you.

DR. WILSON: Thank you.

Dr. Kelly.

DR. KELLY: Yes, the drug does definitely have activity, and it looks like it does have clinical benefit. The one thing I would caution is this is showing efficacy. We don't know in comparison to other drugs, so really knowing where it's going to fit in the armamentarium, we have to be very careful until we do the appropriate trials.

One thing I would ask the FDA is that you keep on here, is we're in the era of targeted therapy, but you go and keep on, say, advanced renal cell carcinoma. And this was only studied in the clear cell setting. I mean, should we start looking at these drugs in the cell types now because I think that's one of the first steps; we have to start looking at targeted therapies.

DR. PAZDUR: I think that would be a good suggestion, and we will take a look at that. Here again, generally, we give the indication of the

patient population in the entry criteria that was studied, but, here again, I think advice to sponsors should be to really take a look at this early on in the development of their drugs, basically.

DR. KELLY: Yes, and I guess to the sponsor, the question is, do you have any data on non-clear cell cell types that you can help us with this?

DR. ANDREWS: Glen Andrews, Pfizer. I think we have about four patients or five patients, really too few -- the definitively non-clear cell, it's really too few to make a conclusion on.

DR. KELLY: Thank you.

DR. WILSON: I did want to just follow up. I hope I wasn't misinterpreted in terms of saying where this drug -- if it was approved, where it might end up. The point that I'm making is you don't know where it's going to end up until it's studied, and it's not going to be studied if it's not out there to be studied. So the only thing is that I think if you have drugs that are a little bit different but the same class, I think until you

study it, you just don't know where it's going to be.

Yes, Dr. Garnick?

DR. GARNICK: I would just like to make a comment to both FDA and to the sponsor. It would seem to me that in the drug development, when you have any sort of signal toxicity, whether it be hypothyroidism or VTEs, that the sponsor really should have an obligation to try to better understand the etiology of that, with or without biomarkers, because there are other clinical parameters that can be looked at more extensively.

From the FDA, from an ODAC perspective, it would be very helpful if PFS is going to be used as the primary endpoint, that we sort of understand what the starting point is of patients entering trials, and information is easily obtained prospectively before the study's begun.

DR. WILSON: I think this trial -- I mean, this presentation has been a very -- is very useful because we have not that long ago discussed how two months in improvement in progression-free

survival -- and I'm talking about the Avastin in breast cancer -- was not a clinically meaningful endpoint. And I just think that it's very important to put these within their contexts. And that is why I think that it's impossible to just say this -- to give a number across all different settings. And I think that it's a little bit, you'll know clinical benefit or you'll know the regulatory hurdles or thresholds when you see the actual indication and the actual trials. And I think that two months with the Avastin in that setting was a very different situation than two months here, because here, we're really determining, number one, is it any more unsafe than current TKIs? I think we all agree that it's different but not more unsafe.

So, really, we're only looking -- we only need to show that it is -- that it has activity and it has equivalent, perhaps somewhat better activity. One can argue whether two months progression-free survival is meaningful. I would say, in general, it's probably not. In fact, I

would say it's not. But I think that is nonetheless a legitimate endpoint to show that it is equivalent to a drug that is already shown that it is active.

Dr. Sekeres.

DR. SEKERES: You know what, I would add to that. There's a difference in the bevacizumab considerations that we had for breast cancer versus this. In that setting, it was approved based on accelerated approval; and, therefore, had to show the effect size was as great and, ideally, that it was showing overall survival advantage in a, quote, unquote, "confirmatory study," whether or not that's confirmatory.

In this setting, this is full approval, and I think the FDA has clearly defined the bar for efficacy that they're expecting. And it was a bar that was agreed upon years ago between the FDA and the sponsor. So given that that's the bar, there's not much that I can recommend as a member of an advisory panel to that. And I would say the toxicities are different, but the degree of

toxicity is equivalent to other drugs that are out there within the same class.

DR. WILSON: Yes, Dr. Logan.

DR. LOGAN: I guess I would maybe just kind of point out some of the numbers. These are -- the point that Dr. Pazdur was making about we need to take this in context with the control effect of the sorafenib, these cross-study comparisons are difficult. But if you'll go back to the everolimus study, the median progression-free survival for the placebo was 1.8 months, and for the axitinib study, it was -- the sorafenib control was 3.4 months. So that's not a very active agent in this second-line setting. And, granted, these are different populations. The everolimus is probably a third line, actually, primarily third-line setting, so you would expect that that would be even longer in that group.

So the benefit that we're seeing here is very modest. It's about 1.4 months in a median progression-free survival in this sunitinib pretreated group. Even if you add that on to the

potential benefit of the sorafenib control, it's still unlikely to be that much more. The difference there was 1.8 to 3.4 if you take a placebo from a different study versus the sorafenib control here. So it's still not a very large benefit, so I would just acknowledge that.

Now, I also acknowledge that toxicities are similar overall, although the profiles are different, but I think the overall benefit should be considered to be moderate, I guess.

DR. WILSON: Dr. Fojo.

DR. FOJO: I mean, in terms of if you look at the overall survival and it's the same, then you can say adding this into the mix of what we currently have is not going to change the overall survival of patients with kidney cancer. We've got plenty of drugs out there already to manage them, and that gets them out to a comparable place as having or not having axitinib. So in that sense, it's not adding a whole lot.

But, again, I think we come back to it's a different toxicity profile, and it might provide

alternatives to the physicians treating them. But at the end of the day, we already have the answer with what we have. This doesn't add anything to the overall survival.

DR. WILSON: Right, but, of course, that's not the question we're being asked.

DR. FREEDMAN: I think with the clarification that Dr. Pazdur provided, we can certainly say that the drug is safe and effective, not in relation to the magnitude of difference for the prior TKIs. But the toxicity profiles I think you can see are clearly different. I think it's interesting that there was no enhanced liver toxicity, which has been a major issue for these drugs.

I think it's going to be important, however, for the sponsor to try to sort out what is the importance of having a restricted targeting effect here. Is it going to contribute to efficacy, or is it contributing to a different toxicity profile? And I think that would be useful area for further exploration.

DR. WILSON: Okay. Do we have any other further compelling -- Dr. Zones.

DR. ZONES: I'm not going to say this is compelling, but I have two questions. One is I'm interested in why the FDA gave in on overall survival. And the second is what is the benefit of -- I can see the benefit of two months' additional life, but it doesn't contribute to overall survival. And I find the quality of life data really odd because towards the end of the -- towards the 20-month period, the people reported having a slightly higher quality of life than the average U.S. population, and yet they had advanced kidney cancer, and they were on these toxic drugs. So I find that confusing.

DR. WILSON: Yes. Do you want to respond?

DR. PAZDUR: I'd be happy to answer that. Amy already addressed the issue. When we were having the discussions regarding PFS, the reason why we suggested overall survival was an interest that the company had in coming with an interim analysis. And we have had very strong

conversations with other sponsors about problems looking at interim analysis of PFS and the variabilities and the changing that could occur from that interim analysis to final analysis. So the implication was if we were going ahead with an interim analysis, please look at overall survival for an interim analysis.

Here again, we have to be consistent with other sponsors, and we have a track record here that has ranged of six drugs that have been approved and six companies given advice with a PFS endpoint, so we can't hold one sponsor up to a higher standard than another sponsor; that's for sure.

Please remember also, to say that we have to demonstrate an overall survival advantage from the last approved drug for any other new drug to be approved is a very high bar here and really is a comparative efficacy standard, which we do not have the legal authority to impose.

DR. WILSON: Okay. Well, with that, let's go ahead and vote. I want to have you turn your

attention to your mic. Make sure that your name is on the mic. And you press either the yes button, the no button, or the abstain button. And let me just say that a yes means that the risk evaluation is favorable for axitinib treatment in patients with advanced RCC after failure of a first-line systemic therapy. No is it's not, and abstain is obvious.

So with that, let's go ahead and vote. And then after we vote, the votes will come up on the screen, and then I'm going to have each of you go around the room and explain or give us a very short statement about why you voted as you did. And so let's vote. Thank you.

[Vote taken.]

DR. WILSON: Okay. I'd like to read into the record the voting results: yes, 13; no, zero; abstain, zero.

So with that, let me go ahead and start on the right side of the room with the first voting member, and if you could please state -- well, we know how you-all voted. Just if you could briefly

say why you voted how you did. Thank you.

DR. ARMSTRONG: Thank you. I think this is, as pointed out --

DR. WILSON: Would you please state your name into the record?

DR. ARMSTRONG: Oh, sorry. Deb Armstrong. This is probably the most robust randomized trial in that the comparator arm is an active and approved agent that's really contemporary treatment, not sort of more historic treatments. I think the data in the U.S. population is compelling, and I do agree, having certainly used sorafenib before, that the toxicities, while they may be manageable in both of them, that having something with a different toxicity profile for those patients who don't tolerate sorafenib is actually certainly a plus.

DR. BUZDAR: Aman Buzdar, I voted yes based on that when you look at it against the standard approved therapy in every subset in the forest plot, there was no subset in which there was any detrimental effect. And the safety profile was

somewhat different, but it was still, I think, within the range of the other five compounds, which are already on the market. So I voted yes.

DR. FOJO: Tito Fojo, I voted yes. I think I expressed why. So I think it's an active agent. I think it's a different toxicity profile but acceptable. So hopefully it'll be tested in the operant setting. It seems that would be a next best step.

DR. DIEHL: Lou Diehl, simply put, it met the regulatory criteria.

DR. LOGAN: Brent Logan, I voted yes as well. I think overall, it probably has a modest effect, and I think there are -- in this particular kind of study design, there are some difficulties in ascertaining the control effect of the sorafenib, which you kind of add the effect to. But the toxicities seem to be manageable and seem to be comparable but not worse than, although slightly different than what's out there already. And so with all those considerations, I thought that the efficacy and benefit ratio was acceptable.

DR. VOSE: Julie Vose. I voted yes. I believe that it's a well-designed trial. It met the regulatory guidelines and does offer an alternative for patients with different toxicity profile.

DR. ZONES: I'm Jane Zones, and I voted yes because it has a slight benefit over the risk, and it offers more options for patients in this subgroup.

DR. WILSON: Wyndham Wilson, I voted yes. I felt that it met the regulatory bar and offers an important or useful alternative.

DR. SEKERES: I'm Mikkael Sekeres. I voted yes, but I did so reluctantly. I think axitinib moves the ball forward for renal cell cancer. It didn't score a touchdown. I'm not even sure it got a first down, but it moved it forward a few yards. It gives an alternative to patients who can't tolerate other tyrosine kinase inhibitors for renal cell cancer. And my hope is that in the future, drugs that are up for approval for renal cell carcinoma will have an overall survival guideline.

DR. FREEDMAN: Ralph Freedman, I voted yes. The drug is safe and effective. And I think that it has an adverse event profile which will be useful both to physicians and to patients.

DR. KELLY: William Kelly, I voted yes for the reasons stated mostly before me, but it has a good safety profile. It has shown efficacy. I think that we just have to be cautioned to make sure we have the appropriate comparable trials that we know how to use this drug appropriately in this population.

DR. GARNICK: I'm Marc Garnick. I voted yes, also very reluctantly. I don't think the toxicity profile has been fully elaborated, and I would urge the sponsor in postmarketing evaluations to more fully understand both the hypothyroidism, which can affect other systems in patients with cancer as well as the VTE. I don't think those have been adequately studied, and I would really urge some postmarketing evaluations with or without biomarkers.

MS. MEYER: Mary Meyer, and I voted yes. I

think that they've proven that this drug is safe, and kidney cancer patients need more alternatives. And I just wanted to throw in there that two, three months does make a difference. Thank you.

Adjournment

DR. WILSON: Okay. So with that, let me conclude the morning session, and we will meet -- we will reconvene at 12:30. Thank you.

(Whereupon, at 11:33 a.m., the morning session was adjourned.)