FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE (ODAC)

Tuesday, September 19, 2017

8:29 a.m. to 12:04 p.m.

FDA White Oak Campus

White Oak Conference Center

Building 31, The Great Room

Silver Spring, Maryland

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:29 a.m.)

Call to Order

Introduction of Committee

DR. ULDRICK: Good morning. I would first like to remind everyone to please silence your cell phones, smartphones, and other devices if you've not already done so. I would also like to identify the FDA press contact, Angela Stark. If you are present, please stand.

My name is Thomas Uldrick, and I'm the acting chairperson of the Oncologic Drugs Advisory Committee, and I'll be chairing the meeting. I will now call the Oncologic Drugs Advisory Committee meeting to order. We will start by going around the table and introduce ourselves. We will start with the FDA to my far left and go around the table.

DR. PAZDUR: Richard Pazdur, Oncology Center of Excellence.

DR. BEAVER: Julia Beaver, Division of Oncology Products I.

DR. MAHER: Ellen Maher, FDA.

DR. AGRAWAL: Sundeep Agrawal, FDA.

DR. FERNANDES: Laura Fernandes, Office of Biostatistics, FDA.

DR. XU: James Xu, FDA

DR. HALABI: Susan Halabi, Duke University, ODAC panel.

DR. HOFFMAN: Philip Hoffman, University of Chicago.

DR. SHAW: Alice Shaw, Massachusetts General Hospital.

DR. CHEE: Cindy Chee, acting designated federal officer.

DR. ULDRICK: Thomas Uldrick, Center for Cancer Research, NCI.

DR. BURSTEIN: Harold Burstein, medical oncologist at Dana Farber Cancer Institute in Boston.

DR. NOWAKOWSKI: Greg Nowakowski, medical oncologist at Mayo Clinic Rochester.

MS. PREUSSE: Courtney Preusse, consumer rep and Fred Hutch.

DR. LUMLEY: Dan Lumley, patient rep, Kansas City, Missouri.

DR. PAGLIARO: Lance Pagliaro, medical oncologist, Mayo Clinic.

DR. BUKOWSKI: Ron Bukowski, medical oncologist emeritus at the Cleveland Clinic.

DR. REDMAN: Bruce Redman, medical oncologist, University of Michigan.

DR. SRINIVASAN: Ram Srinivasan, medical oncologist, Center for Cancer Research, National Cancer Institute.

DR. MORROW: P.K. Morrow, medical oncologist employed by Amgen.

DR. ULDRICK: For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson.

We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that 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.

Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Now I will pass it to Cindy Chee, who will read the Conflict of Interest Statement.

Conflict of Interest Statement

DR. CHEE: The Food and Drug Administration is convening today's meeting of the Oncologic Drugs Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the

exception of the industry representative, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

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

or when the interests of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

Today's agenda involves discussion of supplemental new drug application 0219-38/033 Sutent, sunitinib malate, oral capsules submitted by C.P. Pharmaceuticals International C.V., represented by Pfizer, authorized U.S. agent. The proposed indication for this product is for the adjuvant treatment of adult patients at high risk

of recurrent renal cell carcinoma following nephrectomy.

This is a particular matters meeting during which specific matters related to Pfizer's sNDA will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Ronald Bukowski and Dr. Susan Halabi. Dr. Bukowski's waiver involves a current study relating to a potentially competing firm and potentially competing products for which he receives between $0 and $5,000 per year.

In addition, his waiver covers his ownership of healthcare sector funds with the current aggregate value between $100,001 and $300,000. Dr. Halabi's waiver involves a study relating to the product at issue and potentially competing products. Dr. Halabi receives no compensation for her role as the study statistician.

These waivers allow these individuals to

participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drug/default.htm.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information division, 5630 Fishers Lane, Room 1035, Rockville, Maryland 20857, or requests may be sent via fax to 301-827-9267.

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

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

DR. ULDRICK: Thank you. We will now proceed with the FDA's introductory remarks from Dr. Julia Beaver.

FDA Opening Remarks - Julia Beaver

DR. BEAVER: Good morning, chairperson, members of the committee. My name is Julia Beaver. I'm the acting director of the Division of Oncology Products I. We are here to discuss the Sutent supplemental new drug application for the proposed indication of adjuvant treatment of adult patients at high risk of recurrent renal cell carcinoma

following nephrectomy. I will provide a few brief remarks to frame the points we hope to cover and discuss today.

There are no approved adjuvant therapies for renal cell carcinoma. The current standard of care for patients with early stage disease is partial or radical nephrectomy followed by surveillance. There is, however, an unmet medical need to develop therapies for patients as the recurrence risk is high, particularly for patients with T3/T4 lesions and node-positive disease.

The applicant has requested approval for Sutent based on the results of the S-TRAC trial, a multicenter, randomized, double-blind, placebo-controlled trial of one year of Sutent versus placebo in patients with high risk of renal cell carcinoma following nephrectomy.

The primary analysis demonstrated a statistically significant stratified hazard ratio of 0.76 observed with an estimated 8 percent absolute difference in disease-free survival at 5 years.

Overall survival was not mature, and the study was not powered to assess overall survival. And the probability of achieving a statistically significant result for OS is low.

In S-TRAC, patients experienced more toxicity compared to placebo, as reflected by the adverse event profile in patient-reported outcomes. The toxicity profile of Sutent is well-known in the metastatic setting and includes serious toxicities, some fatal in rare instances. The safety profile of Sutent in the adjuvant setting in S-TRAC did not identify any new toxicities compared to the metastatic setting.

We will also be discussing the ASSURE trial, a separate adjuvant trial of Sutent versus placebo in patients with renal cell carcinoma. ASSURE did not demonstrate a difference in disease-free or overall survival between arms, having enrolled a lower risk population, and a trial modification resulted in a lower starting dose of Sutent.

Given these differences and difficulties with cross-trial comparisons, we were not able to

make definitive conclusions about why S-TRAC showed a disease-free survival benefit while ASSURE did not. And therefore, some level of residual uncertainty regarding the discordant results remains.

As this would be the first adjuvant approval for renal cell carcinoma, any approval would be based on disease-free survival. It's important to place this endpoint into context. In other malignancies, improvements in disease-free or recurrence-free survival have been used as a measure of direct clinical benefit supported by evidence of an absence of detrimental effect on survival.

In some instances, the effect on DFS is associated with improvement in survival, but this has not been required by FDA. The majority of these examples come from breast cancer where generally at the time of occurrence, patients are biopsied and then treated with a therapy or combination of therapies, including systemic therapies, surgery, and radiation. There have also

been consensus groups, which have made recommendations about how DFS should be defined.

While the majority of patients on S-TRAC were not biopsied to confirm recurrence and were determined to have recurrence based on radiographic findings, the criteria used in S-TRAC were reasonable. Subsequent therapy after recurrence suggests a clinical relevance of recurrent disease.

On S-TRAC, the majority of patients received at least one or some combination of subsequent surgery, radiation, and systemic therapy after recurrence. The magnitude of benefit of DFS was substantial in S-TRAC and was similar to many of our prior adjuvant approvals in other malignancies.

Taking all of these points into consideration, we will ask the committee to vote if the risk-benefit profile of Sutent is acceptable for the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma following nephrectomy. Thank you.

DR. ULDRICK: 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's important to understand the context of an individual's presentation.

For this reason, the FDA encourages all participants, including the sponsor's nonemployee 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 on 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 the issue of financial relationships at the beginning of your presentation, it will not preclude you from speaking.

We will now proceed with the applicant's presentation.

Applicant Presentation - Sriram Krishnaswami

DR. KRISHNASWAMI: Thank you, Mr. Chairman, members of the committee, the FDA, ladies and gentlemen. I am Sriram Krishnaswami. I am the asset team leader for Sutent at Pfizer.

We would like to thank the FDA for the opportunity to present our data today from the Sutent treatment of renal adjuvant cancer for the S-TRAC trial, and we would like to express our sincere thanks to the physicians, patients, and their families for their participation in the study.

We propose Sutent as an adjuvant treatment option for adult patients with renal cell carcinoma who are at high risk of recurrence following nephrectomy. This is based on the intent-to-treat population in the S-TRAC study, and it represents about 15 percent of patients who undergo surgical resection for kidney cancer in the United States and who are at a high risk of recurrence.

The proposed dose is the same as that approved for advanced RCC, which is 50 milligrams

once daily given on a 4-weeks on/2-weeks off schedule for a treatment duration of approximately one year.

We appreciate Dr. Beaver's comments today and will be discussing the results of the S-TRAC study as well as data from the other adjuvant studies for the committee's consideration, but let me emphasize that we believe that as a well-designed and well-conducted randomized placebo-controlled study that met its primary endpoint, S-TRAC provides strong and ample evidence of the effectiveness of sunitinib in this setting.

As brief background, sunitinib is a small molecule tyrosine kinase inhibitor with an anti-angiogenic mechanism of action. It was first approved in the United States over a decade ago in 2006. The clinical trial experience consists of over 7,000 patients, and it is estimated that over 350,000 patients have been treated with sunitinib globally across the indications shown here, including gastrointestinal stromal tumor, advanced RCC, and pancreatic neuroendocrine tumors.

The wide use of sunitinib in first-line treatment today in metastatic RCC is supported by the high degree of efficacy in that setting. Shown here are the data from the pivotal phase 3 trial in metastatic RCC, where significant improvements in progression-free survival and overall survival was demonstrated with sunitinib.

These data and the fundamental relationship between activating mutations in VHL in RCC provided the theoretical basis for the S-TRAC study in a group of patients most likely to be harboring micrometastatic disease, which leads us to our presentation to you today.

We intend to make the case for the following: first, that there remains an unmet medical need for adjuvant treatment options for patients with RCC, particularly those at a high risk of recurrence; second, that sunitinib has demonstrated a statistically significant, clinically meaningful, and a durable disease-free survival benefit relative to placebo in this population; and third, that the safety profile of

sunitinib is predictable and the adverse events are manageable and reversible, thereby resulting in a favorable benefit-risk relationship for a selected group of patients at a high risk of recurrence following nephrectomy.

As you can see on this timeline chart, S-TRAC was initiated in 2007, a year after the approval for metastatic RCC. An external data monitoring committee was instituted to monitor the efficacy and the safety of patients in the study. Over the 10-year period, two interim analyses were conducted, and the final analysis of the primary endpoint, disease-free survival, occurred in 2016, 5 years after the last patient was randomized.

Let me point out that in this period, five other adjuvant RCC studies with tyrosine kinase inhibitors were initiated. More recently, three adjuvant trials with immune therapies have also been started. All of them have been designed to look at disease-free survival, which we feel reflects the opinion of the number of experts in the field that DFS is a clinically relevant

endpoint for patients and physicians in this setting.

Here now is the agenda for the rest of our presentation. Dr. Allan Pantuck from UCLA will first provide a perspective of current practice, the unmet need, and the opportunity that adjuvant treatment presents to improve the management of pre-metastatic RCC.

Dr. Daniel George from Duke University Medical Center will then provide a medical oncologist's view and discuss the clinical relevance of disease-free survival as an endpoint and the efficacy data from the S-TRAC study. Safety and quality-of-life data will be presented by Dr. Liza DeAnnuntis from Pfizer.

Finally, Dr. Robert Figlin from the Cedars-Sinai Medical Center will discuss the S-TRAC results in context with the other adjuvant trials, particularly ASSURE and PROTECT, and will provide a practicing clinician's perspective, focusing on what the benefits and the risks mean for patients and physicians.

We have additional experts today to address your questions, Dr. Gary Koch, professor of biostatistics from the University of North Carolina, and Dr. Jean Paty, an expert on quality-of-life from Quintiles.

I will now turn it over to Dr. Pantuck. Thank you.

Applicant Presentation - Allan Pantuck

DR. PANTUCK: Thank you. My name is Allan Pantuck. I'm a professor of urology at the UCLA Medical Center in Los Angeles. I'm a paid consultant to Pfizer, and I have no financial interest in the outcome of this meeting.

I'm here today to make the case on behalf of my patients for adjuvant treatment options to decrease or delay their risk of recurrence following surgical resection. In the next few minutes, I would like to discuss the unmet medical need in more detail.

I will start with a brief summary of the epidemiology of RCC. In the United States, the number of new cases of RCC is approximately 64,000

with 14,000 deaths annually, and there has been a steady increase in the incidence of both localized and advanced cases for several decades.

Currently, surgical resection followed by observation is the standard of care. After surgery, many patients will be cancer free and resume their normal lives, but a sizable subset will relapse after surgery. And once they become metastatic, their long-term prognosis is poor.

Metastatic RCC today remains a largely incurable disease. The 5-year survival rate from time of diagnosis of metastatic RCC is reported to be as low as 12 percent in the most recent SEER database. Therefore, it's important to identify the patients at greatest risk of relapse.

The prognosis of RCC strongly correlates with tumor TNM staging, which is based on tumor size and spread. This slide parses out the four stages of RCC. Stages 1 and 2 represent localized tumors limited to the kidney while stage 3 tumors are locally advanced and involve major veins or perinephric tissues. Finally, stage 4 tumors

involve adjacent organs and/or the lymph nodes.

These are the patients where surgery is unlikely to be curative and are at risk of harboring micrometastatic disease with the potential to develop clinically evident metastatic disease. This staging corresponds to the one in use at the time of the S-TRAC study.

The TNM staging alone is not sufficient to accurately predict the prognosis of RCC. This was the reason my colleagues and I at UCLA developed an integrated staging system in 2001 combining TNM staging with two additional tumor and patient variables, the Fuhrman grade, which is the most commonly applied nuclear grading for RCC, and patient performance status.

The UISS stratification was developed in the U.S. in 2001 and independently validated in the EU in 2004. We've categorized the risk profile into three subgroups: low risk, intermediate risk, and high risk.

These are the incidences and 5-year rates of recurrence for patients at low, intermediate, and

high risk. As you can see, patients with high-risk features in the bottom row represent about 15 percent of all RCC cases, and up to 60 percent of these will recur and develop metastatic disease within 5 years. Once they recur, their prognosis remains poor with 10-year survival rates in the 10 to 20 percent range in our institution.

This illustrates the poor outcomes of this group of patients and the high unmet need because they have no systemic treatment options to delay or prevent recurrence.

I will now conclude with a typical patient on whom I do surgery and who is very likely to relapse. This patient is in his mid-50s. He's active, has a busy family and social life. His abdominal CT scan reveals a large primary tumor is his right kidney with UISS criteria T3a, N0, M0, Fuhrman grade 3, and performance status 1.

This patient is representative of the 15 percent of non-metastatic RCC patients who are high risk of recurrence. Today, surgery is the only treatment option for this patient. With the

introduction of an adjuvant treatment, we have the opportunity to delay or prevent recurrence and shift the natural history of this disease.

I will now turn the lectern over to Dr. George to provide an oncologist's perspective and to discuss the S-TRAC efficacy data.

Applicant Presentation - Daniel George

DR. GEORGE: Thank you for the opportunity to speak today. My name is Dr. Daniel George, and I'm a professor of medicine and surgery at the Duke University Medical Center, and I'm a practicing medical oncologist. I'm a paid consultant to Pfizer, and I have no financial interest in the outcome of this meeting.

As an investigator in the S-TRAC trial and a member of the study steering committee, I would like to share the rationale behind the key design elements of S-TRAC and discuss the efficacy data supporting a clinically meaningful and durable benefit of the adjuvant sunitinib in patients following nephrectomy for high-risk T3/T4 kidney cancer. But before I do, let me follow up on the

patient that was reported by Dr. Pantuck and just say from my perspective, this is still one of our greatest unmet needs in kidney cancer.

As he carefully outlined for you, there's clearly a high-risk population of patients post-nephrectomy for whom the only option is to wait for their cancer to come back and to begin non-curative treatment.

Many of these patients are coming to physicians like me and asking the obvious question: "Doctor, what can I do to improve my chances of remaining disease free?" Sadly, despite all of our progress in metastatic disease, my only answer outside of a clinical trial is still nothing.

Now, let me start by outlining the rationale for sunitinib. Here's an outline of sunitinib's mechanism of action. First, on the left, sunitinib was selected for its high affinity for VEGF and PDGF receptors, but it also inhibits other tyrosine kinase receptors. The unique genetics of kidney cancer predispose its dependency on angiogenesis. Therefore, sunitinib was initially developed for

treatment of metastatic renal cell carcinoma.

On your right is a diagram that shows sunitinib inhibits angiogenesis in the tumor micro-environment, which is critical to tumor proliferation and spread. In addition, it's postulated that sunitinib inhibits tumor-associated macrophages and other immune modulatory cells. These mechanisms of action support the hypothesis that sunitinib could delay and possibly prevent this disease from recurring altogether.

In designing this adjuvant trial, we picked disease-free survival as our primary endpoint. The reason for this first and foremost was because being cancer free is the most important endpoint for our patients in the adjuvant setting.

Following nephrectomy, my patients anxiously await their scan results. When they come back with no evidence of disease, for that patient, for me, that's success and a meaningful real-time assessment of their disease status, as such, long-term disease-free survival is the primary goal of our patients.

In addition, disease-free survival occurs years earlier than overall survival, and disease recurrence drives subsequent intervention. This gives us an opportunity to evaluate the clinical benefits of treatment in this patient population many years sooner, and it allows us to more narrowly define our patient population to that T3/T4 disease, patients most at risk.

Finally, DFS is a consistent and accepted endpoint in many other adjuvant clinical trials involving solid tumors, including melanoma, colon, breast, and GI stromal cancers. And currently, all of our ongoing and completed adjuvant studies in renal cell carcinoma have incorporated DFS as the primary endpoint.

The patient population that we selected was unique to this study. It's based on the UISS criteria that Dr. Pantuck has just described to you. There are no other studies that have identified this particular population of patients prospectively in an intention-to-treat study.

The eligibility included patients with nodal

disease regardless of tumor stage and T4 disease. Although they make up the minority of the population, most of the patients in this study presented with T3 disease, that is, either symptomatic ECOG 1 or 2, resulting in a T3-high population or ECOG 0 prior to surgery, which would be a T3-low population.

Overall, this represents a high-risk population with a 50 percent or greater likelihood of disease recurrence in 5 years. This population is what we deemed to have the most urgent unmet need.

This is the study design for S-TRAC. Patients with clear cell carcinoma and T3 or greater disease and/or node-positive disease were included. The ECOG performance status prior to surgery was an enrollment criteria and ranged from 0 to 2. Lack of any residual disease following surgery was assessed by a blinded independent central review, and factors balanced at randomization included UISS risk score, ECOG performance status, and country of origin.

Patients were then randomized 1 to 1 to receive either sunitinib 50 milligrams daily on a 4/2 schedule for 9 cycles or placebo. Patients were followed for disease-free survival and overall survival status. DFS was the primary endpoint assessed by a blinded independent central review.

As noted earlier, there were two planned interim analyses and a final analysis at 5 years following the last patient enrolled. Secondary endpoints include overall survival, patient-reported outcomes, as well as safety.

The demographics and baseline patient characteristics by treatment arm are shown here. The bulk of our patients were younger than 65 and skewed roughly 70/30 male to female, which tracks with the natural history of this disease.

Looking at the baseline disease characteristics, all of the patients had clear cell carcinoma. The preoperative UISS risk scores are shown here, and the majority of our patients were T3 high.

Here is a summary of the dosing in S-TRAC.

The duration of treatment was roughly 1 year in both the sunitinib and the placebo arms. Dose reductions were common in this study; 46 percent of patients reduced from 50 milligrams to 37.5 milligrams.

Importantly, this study did not allow for dose reductions below 37.5 milligrams. So if a patient had ongoing intolerable adverse events on 37.5 milligrams, they would be discontinued from treatment at that point. However, dose interruptions independent of the scheduled 2-week break were allowed.

Fifty-six percent of patients completed 1 year of treatment with sunitinib versus 69 percent with placebo. The reasons for discontinuation with sunitinib were mostly adverse events. On the other hand, disease recurrence was the main reason for discontinuation with placebo.

Here are the results of the primary analysis for DFS. The Kaplan-Meier curve for DFS on the placebo arm is shown in orange, and in blue is the DFS for sunitinib. The relative risk reduction in

the incidence of disease recurrence was 24 percent, represented by a hazard ratio of 0.76 with a p-value of 0.03, which is a statistically significant difference between the two arms.

Looking at the curves over time, you can see they diverge rapidly within the first year of exposure. This suggests that there is a subgroup of patients that are rapidly progressing in the placebo arm who are delayed in their recurrence without sunitinib. We know that patients who metastasize within 1 year of diagnosis have an intermediate to poor prognosis in the metastatic setting from two independent multivariate models.

The curves then start to come together after one year, suggesting there is a subset of patients in whom sunitinib has delayed recurrence while on drug. However, the curves remain separate over time as more patients recur. This suggests that there's an ongoing clinical benefit beyond the treatment period of one year exposure to sunitinib.

Over time, the recurrence rate slows such that only about 10 percent of patients are

recurring between years 3 and 5. Interestingly, the curves remain apart with an absolute separation of about 8 percent all the way out to 5 years or more. Therefore, it is possible this persistent separation of the curves represents long-term prevention of relapse 5 years or more from enrollment, and consequently, a higher cure rate associated with adjuvant sunitinib.

Shown here are the results of the sensitivity analysis of DFS based on investigator assessment. The Kaplan-Meier curve for DFS on placebo arm is shown in orange, and in blue is the DFS for sunitinib. The relative risk reduction in the incidence of disease recurrence was 19 percent, represented by a hazard ratio of 0.81 with a pattern similar to that in the blinded independent review.

Having established that sunitinib delays recurrence in some patients and prevents recurrence in others, we next looked at what happens to patients who do relapse. Seventy-eight percent of these patients in the sunitinib arm and 76 percent

of these patients in the placebo arm received subsequent cancer-directed therapy. This histogram shows the time from relapse to the start of cancer-directed therapy with a median of approximately 3 months for each group.

This is a relatively short time to treatment intervention, and it's consistent with practice experience in the metastatic setting. Thereby, it justifies DFS as a clinical endpoint. Over the next few slides, I will cover additional sensitivity analyses to support the robustness of the primary DFS analysis.

The primary endpoint by blinded independent central review is shown at the top. The next two analyses used different rules relative to the date of the DFS event. The next three analyses use alternative event and censoring rules. The next analysis adjusts for any potential bias associated with a difference in assessment schedules. Lastly, the analysis of investigator DFS is presented. Regardless of how you alter these parameters, you are seeing a consistency of benefit, which speaks

to the strength of the data.

Numerous subgroup analyses were performed according to a number of predetermined baseline characteristics, including age, gender, performance status, UISS risk score, and Fuhrman grade. Overall, the majority of point estimates are shifted to the left in favor of sunitinib, and all of the confidence intervals overlap with the intention-to-treat analysis shown as a dotted line, suggesting there are no obvious outlier subgroups. These data are consistent with a broad treatment benefit in favor of sunitinib across the entire population.

This is the overall survival Kaplan-Meier curve, which at this point in time demonstrates no difference in overall survival between the sunitinib and placebo arms. The data are immature in terms of number of events for overall survival with a median follow-up of roughly 6 years from enrollment. The hazard ratio was 0.92 in favor of sunitinib, and there was no suggestion of a detrimental effect associated with up to 1 year of

exposure to sunitinib.

In conclusion, up to 1 year of sunitinib treatment demonstrated a statistically significant 24 percent improvement in disease-free survival assessed by blinded independent central review compared to placebo with a clinically significant absolute improvement in preventing disease recurrence by 8 percent at 5 years.

The primary disease-free survival result in favor of sunitinib was robust through the consistency of multiple sensitivity analyses, and there were no detrimental effects of sunitinib on overall survival observed for the population.

I will now turn over the podium to Dr. Liza DeAnnuntis to present the safety and quality-of-life data.

Applicant Presentation - Liza DeAnnuntis

DR. DeANNUNTIS: Good morning. I'm Liza DeAnnuntis, pharmacovigilance, Pfizer. Today I will be presenting the safety data from S-TRAC.

As you have heard, sunitinib has been on the market for many years. It received regulatory

approval more than 11 years ago. Since approval, it's estimated that more than 350,000 patients have received sunitinib globally. In addition, over 7,000 patients have been treated in clinical trials in the approved indications.

Sunitinib has a well-established safety profile, and the most common and well-known AEs include diarrhea, palmer-plantar erythrodysesthesia, also known as hand-foot syndrome or PPE, and hypertension. The risks are communicated via the product label.

In this presentation of the safety results from S-TRAC, you will see that the safety data are consistent with the known safety profile of sunitinib. The data presented include safety data from the entire study, including the active treatment and follow-up phase.

In the overall summary of AEs, as expected, sunitinib had more adverse events in most categories compared to placebo. Most patients in both arms experienced adverse events. The frequency of SAEs was 21.9 percent in the sunitinib

arm and 17.1 percent in the placebo arm. The frequency of grade 5 AEs was low, 1.6 percent in both arms. None of the grade 5 AEs were considered treatment related.

The frequency of the grade 3/4 AEs was higher in the sunitinib arm, mainly due to grade 3 events. Patients were managed by temporary discontinuation with or without dose reduction of sunitinib. Forty-six percent temporarily discontinued due to AEs, and 34 percent dose reduced due to AEs.

Some patients did not tolerate sunitinib treatment, resulting in 28 percent of patients discontinuing treatment at some point during the treatment course. However, 71 percent of patients were able to remain on treatment at 8 months, and 56 percent completed 12 months of treatment.

The most common AEs in the sunitinib arm are shown here. These events are all listed in the product label. When looking at the type of AEs reported in S-TRAC, they were consistent with the known safety profile of sunitinib. The most common

events are higher in the sunitinib arm compared to placebo, but you can see that for diarrhea, PPE, hypertension, fatigue and asthenia and nausea were also experienced in 10 percent or higher of patients in the placebo arm.

Of the most common AEs, few were grade 3 or 4 events, and importantly, there were no grade 4 events that were reported in more than 1.3 percent of patients. Of the most common AEs, these were primarily grade 1 and 2 events, and most events resolved.

The most common AEs occurring in at least 1 percent of patients are listed here. There were no SAEs that were reported in more than 2.6 percent of patients. Most SAEs in both arms were single occurrences. These SAEs are consistent with the known safety profile of sunitinib.

The summary of deaths is presented here. The number of deaths is numerically lower in the sunitinib arm than in the placebo arm. Overall, 66 patients have died in the sunitinib arm, and 74 in the placebo arm in this study. During the

treatment period, there were 2 deaths in the sunitinib arm; however, the deaths were not treatment related but due to disease progression.

The remaining deaths were in the follow-up period, 64 patients in the sunitinib arm and 74 in the placebo arm. The majority of deaths had been due to disease progression, and none have been considered treatment related.

A review of the deaths attributed to other causes did not identify any trends. They were primarily single events with no patterns in the type of events reported.

The data on AEs leading to permanent discontinuation is presented here. PPE was the most common AE leading to permanent discontinuation in the sunitinib arm. However, most events leading to permanent discontinuation were single occurrences, and no event resulting in permanent discontinuation was reported in greater than 4.2 percent of patients. Most adverse events leading to permanent discontinuation were reported as resolved.

Further details about the severity and reversibility of AEs leading to permanent discontinuation is provided here. As you can see, most AEs leading to permanent discontinuation were grade 2 and 3 events. Very few grade 4 events and 2 grade 5 events were reported. The two grade 5 events were considered unrelated to study treatment.

The bottom bar graph shows that most AEs leading to permanent discontinuation were resolved or resolving. Of those events recorded as ongoing, 8 patients had underlying illnesses and/or events considered disease related, which potentially may have contributed to the events.

While no contributing factors were noted for 3 patients, the AEs of PPE and increased thyroid function levels reported in these patients are known to be manageable.

In conclusion, sunitinib adverse events are well-known. The adverse events of sunitinib in the S-TRAC study were consistent with the known safety profile of sunitinib in the metastatic RCC setting.

No new safety signals were observed. No treatment-related deaths were reported. AEs were manageable via dosing interruption, dose reduction, and/or standard supportive treatment.

In summary, sunitinib adverse events were predictable and in most patients, manageable and reversible.

I will now discuss patient-reported outcomes. How patients who stayed on treatment were feeling and functioning were measured using a validated oncology-specific health-related quality-of-life measure, the QLQ-C30.

We had a very low rate of missing values with over 89 percent of available patients completing the instrument at each cycle. Here we see the global quality-of-life domain where patients tell us how they feel about their overall quality of life.

The patients are telling us that their overall quality of life while on treatment is around 68 to 75 percent where 100 equals excellent. As expected, the sunitinib patients' data separate

from placebo, but this does not reach the prespecified and established clinically meaningful change of 10 points as shown in the dotted pink horizontal line. Of note, despite the difference in the curves, both curves remain in the top one-third of the graph.

The QLQ included 15 functional and symptom subscales. A similar pattern was found in 13 of the 15 functional scales. The two exceptions were diarrhea and appetite loss.

Here you see the trend for appetite loss. Change from baseline for sunitinib approaches 10 points, the prespecified threshold. Note that the patients are telling us that appetite loss remains in a range between "not at all" and "a little."

For diarrhea, sunitinib patients' data separate from placebo early, and the gap continues to grow until cycle 6 with a change from baseline of 13 points for sunitinib. Patients are indicating they're experiencing a little diarrhea, and this result is consistent with the fact that

there was only 1 patient who permanently discontinued due to diarrhea on the sunitinib arm. Diarrhea and loss of appetite are known side effects of sunitinib and are known to be manageable and reversible.

In summary, patients at baseline started with few symptoms, a high level of functioning, and global health status consistent with being disease free. We did see worsening on two of the symptom scales, suggesting that the PRO measure was sensitive to the impact of treatment. However, there was no clinically meaningful impact on other symptoms on the functioning scales and the global quality of life. Thus, patients staying on sunitinib treatment for 9 cycles maintained a relatively high level of functioning in global health status.

Thank you. I'd like to turn the podium over to Dr. Figlin.

Applicant Presentation - Robert Figlin

DR. FIGLIN: I'm Robert Figlin, the Steven Spielberg Chair in Hematology Oncology at the

Samuel Oschin Comprehensive Cancer Center at Cedars-Sinai Medical Center in Los Angeles. I'm a paid consultant to Pfizer, and I have no financial interest in the outcome of this meeting.

I would like to discuss the clinical perspective in this setting and walk you through the evidence that the benefit-risk profile is favorable for patients at high risk of recurrence. It is important to recognize that we have spent several decades trying to identify risk factors that identify treatment algorithms for high-risk resected patients.

I have listed for you on this slide many of the early negative trials in the adjuvant treatment of RCC using agents such as radiation, hormones, and immunotherapy. There remains a large unmet medical need for the adjuvant treatment of patients at high risk for recurrence following curative resection.

Listed on this slide are the phase 3 clinical trials evaluating adjuvant-targeted therapies in kidney cancer. In the top portion of

the slide, you see those published studies. In the bottom portion of the slide, you see the studies that have completed enrollment but have yet to be reported. There are many differences among the trials, both with respect to the treatment arms, the patient population studied, and whether or not the doses chosen were modified specifically in some trials such as ASSURE and PROTECT.

The durations of treatment have also varied as have the radiologic review criteria. Some trials included both clear cell and non-clear cell histologies, and most of the trials had a heterogenous group of patients using various risk categories from intermediate to high.

S-TRAC studied a group of patients with the highest risk of recurrence compared to the other studies. One might ask the question as to why S-RAC succeeded. I think it has succeeded in large part because the study team and investigators set the stage for what is the right population of patients to study in the adjuvant setting. S-TRAC only evaluated patients that our community

considers to be at high risk of recurrence. These are patients with T3 and T4 tumors as well as those who were node-positive regardless of tumor stage.

The S-TRAC also included a specific population of kidney cancer patients, those with predominantly 50 percent or greater clear cell RCC, indicative of a population that is primarily driven by abnormalities in the VHL gene, a hallmark of angiogenesis-driven disease.

We also looked and understood that there was a higher dose and treatment exposure of sunitinib to maintain dose intensity, and as you can see from the slide and from the curves below, from the metastatic setting, the time to progression as well as the overall survival are significantly influenced when dose is maintained, as illustrated by higher median AUC when compared to a lower median AUC.

I believe strongly that starting at full doses, maintaining dose, and continuing that throughout the trial with minimum dose reductions is an important advantage when trying to obtain the

benefits in this treatment population.

I believe that dosing is critically important because all patients started at sunitinib at the full dose of 50 milligrams on a schedule of 4 and 2, and only 1 dose reduction to 37.5 milligrams was allowed. In contrast, in the ASSURE trial, one-third of patients received the starting dose of 37.5 milligrams on a similar schedule, and dose reductions were allowed down to 25 milligrams once daily on a 4 and 2 schedule.

As you can see in this table, these differences in starting dose and dose reduction levels resulted in a 29 percent higher average daily dose and a 42 percent higher cumulative dose in the S-TRAC study compared to the ASSURE study.

I would also note that the mean duration of treatment was one month longer in the S-TRAC study, and more patients in S-TRAC completed 9 cycles of treatment, which at least is in part driven by a higher rate of early discontinuation in the ASSURE study when compared to the S-TRAC study.

This slide looks further into the dose

differences. Here you can see the percentage of patients in ASSURE dosed at each cycle as well as the patients with greater than 75 percent relative dose intensity. When we contrast this with the S-TRAC data presented in figure 2 of the FDA briefing document, we see a difference in the number of patients treated and an even bigger difference in the dosing intensity. This speaks to the higher relative dose intensity observed in the S-TRAC trial when compared to ASSURE.

Another difference was in the types of patients enrolled. In S-TRAC, patients were predominantly more than 50 percent clear cell RCC at high risk of recurrence, locally advanced T3 or greater, N1 or N2. In contrast, in the ASSURE trial, 21 percent of the patients had a histology other than clear cell RCC, and a third of the patients had intermediate grade T1b and T2, which were not included in S-TRAC.

This can be visually noted in the risk group assignment slide you've seen before. The S-TRAC population is on the right in purple and contrasted

with the ASSURE trial in blue, which included patients in both T1b and T2 tumors as well as those that are included in the S-TRAC trial.

Let us look at these studies more closely. This slide lists a subset review of patients in the ASSURE study who did meet the S-TRAC eligibility criteria. In this retrospective analysis, only 30 percent of patients enrolled in ASSURE met the population and dosing criteria of the S-TRAC trial.

You can see the differences in the patient population with the majority of the ASSURE patients being T3 low, the majority in the S-TRAC trial being T3 high. Thus, the populations even when aligned between studies are considered to be substantially different.

Despite the imbalance in risk groups, there is evidence to suggest a treatment effect in the ASSURE trial patients who match the S-TRAC eligibility and dosing criteria. The top two rows are published results from the ASSURE trial in the intent-to-treat population and subset of patients who match the risk and histology criteria from

S-TRAC. The third row shows when the S-TRAC dosing criteria is applied to the ASSURE subgroup in row 2, the hazard ratio approaches the one seen in the S-TRAC intent-to-treat population.

Let me now contrast this with the other completed adjuvant study PROTECT. This study looked at pazopanib treatment for 12 months versus placebo in a randomized phase 3 study in patients with moderately high or high risk of developing recurrence following surgery. The starting pazopanib dose in this study was of the approved dose in the metastatic setting of 800 milligrams daily.

The protocol was later amended to reduce the dose from 800 milligrams to 600 milligrams because of a high discontinuation rate, and so the primary population was specified as patients enrolled only at the 600 milligram starting dose. About 74 percent received the 600-milligram dose in this study.

Here you can see in green that the PROTECT trial included many of the same populations of

patients as in S-TRAC with about 86 percent of the patients having RCC with T3 or higher or node-positive and clear cell histology.

This study demonstrated some interesting findings. On the left, you can see that the primary analysis did not show a statistically difference in DFS between pazopanib 600 milligrams daily and placebo. In contrast, the subset of patients that received full dose of 800 milligrams, almost 200 patients, showed a statistically significant improvement in DFS versus placebo.

As you can see on the right, the DFS curve for the 800-milligram dose separated early from placebo and remained separated throughout the trial. So overall, this result, shown with another TKI in a similar patient population as S-TRAC, confirms the importance of optimal dosing to achieving a treatment benefit in the adjuvant RCC treatment setting.

Now to bring the risks and the benefits of sunitinib in the adjuvant setting together, let me start with benefit. The primary endpoint, disease-

free survival by blinded and independent review, is again demonstrated in this slide for the S-TRAC trial. In my clinic, when I have the conversation with my patients around what the goals of therapy are, they tell me that they are willing to take systemic therapy to remain disease free for as long as possible. Disease-free survival is an important endpoint for patients.

What do the data show? There's a 24 percent reduction in relative risk of disease-free survival events. It starts early and is maintained over time. In absolute terms, we see an 8 percent benefit after 5 years. I believe this is clinically meaningful.

From a risk point of view, sunitinib has been an available RCC treatment for over 11 years and has a well-characterized and understood safety profile. The toxicities observed in S-TRAC were consistent with the known safety profile with no new safety signals observed.

Oncologists are familiar with the toxicities and the appropriate dose modification opportunities

of sunitinib, including modifying the dose or treatment schedule when patients do not tolerate the full dose or the 4 and 2 schedule. Consistent with my personal experience, the toxicities in S-TRAC resolve with discontinuation of sunitinib treatment with no evidence of long-term sequelae.

Overall, the AE data combined with the patient-reported outcomes show that sunitinib safety profile is acceptable to many patients in the adjuvant setting. The adverse event burden of sunitinib is clinically manageable with early identification and monitoring, allowing the ability to effectively apply dose modifications, dose interruptions, and/or standard medical care.

Even in those patients who are not able to tolerate sunitinib toxicities and require discontinuation, patients do not experience long-term consequences given the prompt resolution of adverse events post-treatment. Therefore, the benefit-risk profile is favorable, and I fully support that sunitinib should be a treatment option for patients at high risk of recurring kidney

cancer following surgical resection.

What do I believe this means for the patient with kidney cancer at high risk of recurrence? The conversation can be relatively straightforward. High-risk patients have a 5-year recurrence rate of about 60 percent. Metastatic RCC is associated with substantial morbidity, and survival after relapse remains unacceptably low. There are no other approved therapies for this indication.

Rather than take a watch and wait approach, many patients want to do everything they can to remain disease free. Doctors like me would much rather have a balanced discussion of the benefits and risks of sunitinib with our patients.

As a kidney cancer doctor, it is my opinion that if approved, adjuvant sunitinib will be a valuable option for those patients who are willing to accept the well-understood and manageable side effects for up to one year in exchange for a delay or prevention of tumor recurrence. Thank you, and this concludes our presentation.

DR. ULDRICK: Thank you. We will now

proceed with presentations from the FDA starting with Dr. James Xu, clinical reviewer.

FDA Presentation – James Xu

DR. XU: Thank you, Mr. Chairman and committee members. My name is James Xu. I am one of the clinical reviewers for FDA. I am also a practicing medical oncologist and hematologist.

I will be presenting the clinical portion of the FDA's presentation for the review of this supplemental application. Following that, Dr. Laura Fernandes from the FDA biometrics team will discuss the efficacy analysis, and then Dr. Sundeep Agrawal will be discussing the safety review and summarize the reviews from FDA's findings.

This is a supplemental application from C.P. Pharmaceuticals International and Pfizer for the use of Sutent as an adjuvant treatment for renal cell carcinoma. Here is the FDA's review team for this supplemental application. This is the outline of our presentation. We will focus on the three topics arising out of the review of this

supplemental application.

The first is whether DFS improvement has been demonstrated in the S-TRAC study. This will be discussed in the context of trial design and study results. The second is the interpretation of the results from the S-TRAC in light of results from ASSURE, which is another adjuvant trial in which Sutent is compared to placebo in renal cell carcinoma.

We will also be describing the safety profile of Sutent in the adjuvant setting. And the last topic will be the use of disease-free survival as an endpoint in adjuvant treatments of renal cell carcinoma.

This is the proposed indication for Sutent. Sutent is a kinase inhibitor indicated for adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy.

Sutent was first approved in January 2006 for treatment of advanced renal carcinoma. The primary mechanism is VEGF inhibition, but Sutent is also known to act on other tyrosine kinase

receptors. Sutent does appear to have a dose-response effect when studied in these trials of metastatic renal cell carcinoma.

In this slide, we will discussing the prognosis for patients with renal cell carcinoma after nephrectomy. The current treatment approach for localized resectable renal cell carcinoma involves nephrectomy alone to surgically remove the cancer. However, the prognosis of post-nephrectomy patients depends on risk features of their diseases.

The UISS model was developed to predict the prognosis of these patients. As outlined here, the 5 years of freedom from local or distant failures among node-negative patients is 64 percent in the intermediate group and 37 percent in the high-risk group. Patients with node-positive disease appear to do even worse. Therefore, there's a need for adjuvant therapies to improve the outcome of these high-risk patients.

A number of VEGF receptor inhibitors has also been studied in the adjuvant setting for renal

cell carcinoma. As mentioned before, ASSURE was a three-arm trial in which patients with renal cell after nephrectomy were randomized to Sutent, sorafenib, and placebo. Both Sutent and sorafenib failed to demonstrate improvements in DFS or OS in the adjuvant setting.

Another VEGF inhibitor, pazopanib, at a dose of 600 milligrams also failed to demonstrate improvements in DFS in the adjuvant setting. Currently, there are several other ongoing adjuvant trials in renal cell carcinoma as outlined in this slide.

Let us proceeds to topic number 1. Here is the study design of S-TRAC. It enrolled patients with clear cell renal cell carcinoma. Patients with higher risk features were enrolled. This included the patients with pathological T3 or T4 and N0, M0 of any tumor grade in the performance status. Patients with node-positive disease were also enrolled, and for those patients with node-positive disease, any tumor size grade and performance status was allowed for this trial.

Microscopic disease at the surgical margins was allowed. Patients who had no evidence of disease by IRC review in a post-operative setting is a requirement for enrollment of this trial.

The stratification factors for randomization were performance status, country, and UISS risk group. The control was a placebo. The primary endpoint is DFS based on central review.

The disease characteristics and risk categories for the enrolled patients are outlined here. Notice that most patients were high risk based on the UISS model and that the vast majority of patients had clear cell renal cell carcinoma in the S-TRAC study.

The definition of IRC determined recurrence was detailed and in general, reasonable. There is no consensus definition in renal cell carcinoma regarding the DFS by our central review. Importantly, the IRC could override the criteria within the definition to determine recurrence, but biopsy was not required to confirm a recurrence in this study.

With this, I'm going to turn the podium over to Dr. Laura Fernandes, who will be discussing the efficacy analysis of the supplemental application. Thank you.

FDA Presentation - Laura Fernandes

DR. FERNANDES: Thank you, Dr. Xu.

My name is Laura Fernandes, and I'm the statistical reviewer for this application. I will be presenting the analysis and evaluations conducted during our review of this application.

According to the prespecified statistical analysis plan for S-TRAC, the primary endpoint was disease-free survival per central review. Overall survival was a secondary endpoint, and disease-free survival per investigator and patient-reported outcomes were supportive endpoints.

The original planned sample size for the study was 228 patients with 127 DFS events, which was finally changed to 615 patients with 258 DFS events to provide an 84 percent power to detect a hazard ratio of 0.69.

The timing of the final DFS analysis was

changed from being event driven to occur at 5 years after randomization of the last patient to account for the low frequency of events. Accounting for the two interim analyses, the final alpha allocated for testing the hypothesis is 0.476.

The results of the primary efficacy endpoint, disease-free survival per central review are shown here. There were a total of 257 events in this analysis, 37 percent on Sutent, and 47 percent on placebo, resulting in a statistically significant hazard ratio of 0.76 stratified by UISS risk category. The median DFS time is 6.8 years for Sutent and 5.6 years for placebo.

In the DFS analysis per investigator, there were a total of 290 DFS events resulting in a hazard ratio of 0.81 with a 95 percent confidence interval spanning from 0.64 to 1.02. Disease-free survival per the investigator was expected to be similar to that of the central review since investigators were asked to submit their scans for central review prior to making any treatment decisions.

Several sensitivity analyses were done both by the applicant and the agency, some of which were presented earlier by the applicant. The agency conducted an additional sensitivity analysis as indicated in the third row.

To maintain consistency, the agency reclassified all patients who progressed based on radiological progression to the first scan date. Patients requiring a biopsy for confirmation of recurrence were said to have recurrence on the biopsy date.

A larger number of second primary malignancies were identified. Non-invasive second primary malignancies and other non-melanoma skin cancers were excluded. The stratified hazard ratio for this analysis was 0.76 in this modified data set. All of the sensitivity analyses are found to be consistent with the applicant's primary analysis.

An analysis of overall survival was performed based on the available survival data as of January 2017. There were a total of 141 deaths,

22 percent on sunitinib and 24 percent on placebo. The hazard ratio is 0.92.

According to the statistical analysis plan, the applicant will perform the final overall survival analysis 3 years after the primary disease-free survival analysis. Assuming the current trend in the survival data, the probability of observing a statistically significant result in overall survival is very low.

As mentioned earlier by Dr. Xu and the applicant, ASSURE was another randomized clinical trial that evaluated Sutent in the adjuvant setting of renal cell carcinoma. Data from this trial was submitted to the agency for review. In the next few slides, we examine the patient population and results of ASSURE.

ASSURE was a three-arm clinical trial with equal randomization to placebo, Sutent, or sorafenib. Patients could have T1b to T4 node-negative disease or node-positive disease. Patients with clear or non-clear cell histology were included in the trial. Patients were

stratified by risk group, performance status, clear cell histology, and type of nephrectomy.

Initially, patients were randomized to Sutent 50 milligrams, but due to tolerability issues, a protocol amendment reduced the starting dose to 37 and a half milligrams. Of the 647 patients who received Sutent, 453 patients were randomized to 50 milligrams, and 194 patients to 37 and a half milligrams. A total of 647 patients were randomized to receive placebo.

The on-treatment tumor scanning frequency differed from that of S-TRAC. ASSURE trial had a heterogenous mix of patients with some overlap with the S-TRAC patient population. These differences will be presented in a later slide.

Disease-free survival per investigator was the primary endpoint in the ASSURE trial. There were 571 events in total on the Sutent and placebo arms, resulting in an estimated hazard ratio of 1.02 with respect to placebo. The median disease-free survival was 5.8 years on Sutent and 6.6 years on placebo.

With 297 deaths on the Sutent and placebo arms, the hazard ratio for overall survival was 1.17. The median overall survival was not reached, and the 5-year survival probabilities were 78 percent on Sutent and 80 percent on placebo.

The results of this trial did not favor Sutent. Key differences between the S-TRAC and ASSURE trials will be examined in the next slide.

Some differences between S-TRAC and ASSURE are summarized here. In ASSURE, about 92 percent of the patients were enrolled in the United States while S-TRAC was an international study and enrolled only about 8 percent of the patients in the United States.

S-TRAC enrolled patients with T3 and T4 disease while ASSURE included patients with T1b to T4 disease. Both trials enrolled patients with regional lymph node involvement. S-TRAC was limited to patients with clear cell tumor histology.

With regard to dosage, all patients on S-TRAC began at 50 milligrams while patients on

ASSURE began either at 50 milligrams or 37 and a half milligrams, depending on the timing of enrollment. ASSURE was amended to initiate dosing at 37 and a half milligrams after a large number of patients discontinued due to an adverse event or patient withdrawal.

The primary endpoint in S-TRAC was disease-free survival per central review while ASSURE used disease-free survival per investigator. The definition of the second primaries differed slightly in the two studies. Both ASSURE and S-TRAC enrolled patients with UISS intermediate- and high-risk categories.

The agency conducted an exploratory analysis of DFS in patients on ASSURE who were similar to the S-TRAC patient population in order to understand the differences in the results of the two studies. The selected subgroup was limited to patients with T3 or T4 disease or regional node involvement, clear cell histology, and who received 50 milligrams of Sutent or placebo as their initial dose. Patients with metastatic disease at study

entry were not included in this analysis.

A total of 460 patients satisfying these criteria were identified in the ASSURE trial for an exploratory analysis to check if the subgroup would help explain the differences and results observed in S-TRAC. The agency's numbers differ from those presented by the applicant since the agency included all patients who began at 50 milligrams of Sutent irrespective of their dose reductions.

Even in this selected subgroup, it should be noted that the distribution of the patients among the UISS risk strata differs between S-TRAC and the ASSURE subgroup of 460 patients. S-TRAC has a higher proportion of patients in the high-risk category while ASSURE has a higher proportion in the intermediate-risk category. This difference in distributions is one of the limiting factors of this subgroup analysis.

The results of the disease-free survival analysis stratified by the risk category in this subgroup of patients from ASSURE are shown here along with the S-TRAC DFS results. The stratified

hazard ratio for disease-free survival in this subgroup of patients is 0.98 with a 95 percent confidence interval spanning 0.75 to 1.28.

We note that there are limitations to this type of exploratory analysis, and note that this is not a randomized comparison and does not account for imbalances that may exist in other covariates.

After extensive review of the data, our efficacy conclusions are that S-TRAC demonstrated a statistically significant difference in disease-free survival. This difference in disease-free survival was supported by a series of sensitivity analyses and careful review of the data.

Another study in the adjuvant setting of renal cell carcinoma, ASSURE, failed to show improvement in disease-free survival. No difference in overall survival has been observed in both S-TRAC and ASSURE.

There were differences between S-TRAC and ASSURE trials, including study population and trial conduct. The exploratory analyses of the ASSURE subgroup could not explain the observed difference

in the results between the two studies. However, there are limitations to this type of exploratory subgroup analyses.

Dr. Agrawal will now continue with the presentation.

FDA Presentation - Sundeep Agrawal

DR. AGRAWAL: Hello. My name is Sundeep Agrawal. I'm a medical oncologist in the Division of Oncology Products I. I will be discussing the safety aspects of Sutent in the adjuvant setting based on the results of the S-TRAC study. I will also discuss disease-free survival as an endpoint in adjuvant therapy.

The safety profile of Sutent is well-characterized as it has already been in use for the treatment of metastatic renal cell carcinoma. The adverse event profile of Sutent in S-TRAC was consistent with that seen in the metastatic setting.

In the S-TRAC study, 3 patients died while on treatment or within 30 days of the last dose of Sutent, though none of these deaths were related to

study treatment. No patients died within this time period on the placebo arm.

In the placebo arm, permanent discontinuations, dose reductions, and dose interruptions were less common than on the Sutent treatment arm. Fifteen percent of patients in the placebo arm experienced a grade 3 or 4 adverse event compared with 60 percent experiencing a grade 3 or 4 event on the Sutent arm.

Patient-reported outcomes were assessed using the EORTC QLQ-C30 questionnaire and the EQ-5D-3L health status questionnaire. The QLQ-C30 questionnaire is a standardized instrument for measuring health status consisting of 30 items and 5 domains: physical, role, emotional, cognitive, and social function domains. Each domain is measured on a 4-point scale with 4 being the worst health status.

The EQ-5D-3L is a two-part instrument that captures five descriptors of current health status as well as a general health status as measured by a visual analog scale.

These questionnaires were completed on day 1 and approximately every 6 weeks until the end of study treatment. The completion rate of all questions on both arms while on treatment was greater than 89 percent. Patient-reported outcome data was collected during therapy and at the end-of-treatment visit, approximately one month after discontinuation of study drug.

We selected certain items from the EORTC QLQ-C30 questionnaire based on the adverse event profile of Sutent for an in-depth look. These items were nausea, weakness, limitations experienced in work or daily activities, appetite loss, and diarrhea.

As would be expected when compared to placebo, patient-related outcome analyses demonstrated that Sutent had an unfavorable impact on patients' assessment of their own general quality of life, their overall functioning based on the functional domain of their questionnaire, and their own symptoms.

Patients were more adversely impacted by

Sutent compared to placebo in terms of percentage of patients reporting a decrement through the treatment cycles and at the end-of-treatment visit. In addition, symptoms and limitations were generally reported as more severe on the Sutent arm. Further information on the FDA review of the PRO assessment is available as backup slides.

Our safety review noted that adverse events occurred less frequently in the adjuvant setting compared to the metastatic setting with the exception of palmar-plantar erythrodysesthesia or PPE. No new safety signals were identified with the use of Sutent in the adjuvant setting, but limited data is available on long-term toxicities, including the reversibility of thyroid disease associated with adjuvant Sutent.

I will now discuss the clinical relevance of the disease-free survival endpoint in the adjuvant setting. An improvement in disease-free survival or DFS represents delaying symptoms of recurrent disease and delaying the need for toxic treatment of recurrent disease. There have been no previous

approvals of adjuvant therapy in renal cell carcinoma, so to evaluate disease-free survival as an endpoint in this setting, it may be of value to examine the basis of adjuvant approvals in other malignancies.

Breast cancer, colon cancer, gastrointestinal stromal tumors, and melanoma are all diseases where adjuvant approvals have occurred based on disease-free survival or recurrence-free survival. In these diseases, disease-free survival prolongation represented clinical benefit with the magnitude of benefit outweighing the toxicity of the treatment supported by no detriment in survival.

Some of these diseases have standardized DFS criteria while others do not. Absolute improvements in 3- to 5-year disease-free survival have ranged from approximately 2 percent to 11 percent with hazard ratios ranging from 0.4 to 0.87.

To evaluate the clinical relevance of disease-free survival, examining the need for

subsequent therapy following recurrence may also be helpful. In S-TRAC, 78 percent of patients in the Sutent arm and 76 percent of patients in the placebo arm who recurred received subsequent treatment. This was systemic therapy in approximately 40 percent of patients.

After reviewing the safety and efficacy of adjuvant Sutent, we conclude that S-TRAC demonstrated a statistically significant and substantial difference in disease-free survival in this patient population with an unmet medical need. Differences in the patient population and the Sutent dose prevent a definitive conclusion regarding differences in the results of S-TRAC and ASSURE, and therefore, uncertainty regarding the discordant results remains.

The adverse events associated with the use of Sutent are substantial, but may be acceptable in a high-risk population, and the magnitude of benefit seen in disease-free survival is similar to other adjuvant approvals.

In our question for the committee, we will

ask the committee to vote if the benefit-risk profile of Sutent is acceptable for the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma following nephrectomy. Thank you.

Clarifying Questions to Presenters

DR. ULDRICK: Thank you. We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak. If you can, please direct questions to specific presenters. Please raise your hand, and you will be called on by the chair.

Dr. Nowakowski?

DR. NOWAKOWSKI: Thank you. I have two questions. Maybe I will start from the sponsor.

Dr. Figlin nicely presented the differences between the ASSURE and S-TRAC study and postulated that there are significant differences in the risk of the patients, which were enrolled in both studies.

This was demonstrated on slide MA-67, and we can see that a number of patients from a lower-risk

disease by UISS risk stratification had been enrolled in the ASSURE study. However, UISS risk stratification is just a surrogate marker for DFS. If you look at the ASSURE trial as presented by the agency on slide 19, the DFS was actually very similar to what we had seen in the S-TRAC study. It was 5.8 and 6.6 years -- in the placebo arms.

How would you explain that there is very little difference in DFS in those two studies if indeed their population were at the higher risk?

DR. KRISHNASWAMI: Thank you for the question. I'd like to ask Dr. Figlin to comment on this. I'll just note these are the cross-study comparisons. But within these limitations, I'll invite Dr. Figlin to further add.

DR. FIGLIN: Bob Figlin, Cedars-Sinai. Thank you for the question.

I think that we're left with two different studies with different populations. S-TRAC had a higher proportion of what we call T3 high as compared to T3 low in the ASSURE study. We believe that -- and I believe that -- the hazard ratios

continue to fall as a result of going from T3 high all the way to T4, whereas the further advanced the disease is, the more effective the adjuvant therapy is. And except for the subgroup analysis in ASSURE and a cross-study comparison, we're left with that discordance, unfortunately.

DR. ULDRICK: Dr. Burstein?

DR. BURSTEIN: Harold Burstein, Dana Farber. I raised a very similar issue in my own mind as Greg had, so can I just ask for a little more explication of that? Because when I read the petitioner's request, much of this does center on the idea that this is a higher risk patient population, and yet the 5-year disease-free survival outcomes are all but superimposable in the ASSURE and S-TRAC populations.

I'm really struggling to understand how this classification of a higher risk based on the criteria, or is it just that -- I take your point that there are two different studies and it's a cross-study comparison, but I'm not seeing the higher risk signal, I guess. So I'm trying to

understand if I'm just missing it in the ASSURE study or something like that.

DR. KRISHNASWAMI: To further discuss the UISS classification and the relevance of this, I'd like to ask if Dr. Pantuck could shed some insight into this.

DR. PANTUCK: Allan Pantuck, UCLA. Can you pull up MA-22?

This slide shows the UISS classification for the S-TRAC study, and this includes patients with nodal disease, patients with T4 disease. These fall into the high-risk category. T3 disease with either impaired ECOG performance status or high grade falls strictly into the high-risk category.

The T3 patients with low grade and good performance status by the UISS criteria fall into an intermediate-risk category, although risk is really continuous. It's not really -- patients don't all fall uniformly into these three categories.

So patients with low grade T3 are still at higher risk than patients with T2 disease, for

example. This is a population that is the high end of intermediate-risk as well as high-risk patients.

DR. KRISHNASWAMI: I think one more point to add is really that within the study when we compare the DFS data, there's the difference that we see. We'll argue that that would be a more reliable comparison within study differences in the DFS in this context.

DR. ULDRICK: Dr. Redman?

DR. REDMAN: Thank you. Nice presentation. This is to industry. I've heard several times mentioned that this is to delay or prevent recurrence. I'm interested in kidney cancer specific events, not the other events that define disease-free survival.

My reading, and you can correct me if I'm wrong, that there are 101 events in Sutent and 129 events in the placebo arm with kidney cancer events defining disease-free survival. And I was wondering if that number was significant, if you looked at that, and do you have the median time to kidney cancer event only, not the other events in

disease-free survival, and is that statistically significant?

DR. KRISHNASWAMI: I'd like to ask Michelle Casey to answer the question, please.

DR. CASEY: Michelle Casey, Pfizer. If we can have EF-16, please. So we have looked at time to recurrence, which is specifically related to kidney cancer recurrence, and this does include deaths due to disease. We can see that the hazard ratio is 0.87, which is consistent with what we see in the primary analysis.

DR. KRISHNASWAMI: 0.77.

DR. CASEY: Oh, sorry. Excuse me. 0.77.

DR. ULDRICK: Courtney Preusse?

MS. PREUSSE: Hi. Courtney Preusse, consumer rep and Fred Hutch. My knowledge of renal cell carcinoma is limited. However, would it be safe to assume that there are molecular events or molecular responses happening at subtype level of renal cell carcinoma where this drug is more effective in the more aggressive cancer -- in more aggressive subtypes of renal cell cancer, and are

there any analyses of RCC subtypes?

DR. KRISHNASWAMI: I'd like to ask if Dr. Figlin as well as Dr. George could speak to this point because there are a couple of different aspects that you raised.

DR. FIGLIN: Bob Figlin, Cedars-Sinai. Thank you for the question. We continue to evolve our understanding of kidney cancer biology. Although the majority of mutations arise from the von Hippel-Lindau gene, we've identified other genes, pBRM2, SETD2, and others in the clear cell histologic subtype. We've yet to been able to pharmacologically attack those subtypes.

As published in the New England Journal just a very few years ago, we understand that if you biopsy different parts of the kidney cancer tumor, you see very different molecular heterogeneity. So it's a complex biology whose majority is driven by VHL, but accomplishes other genetic abnormalities, which we've been yet unable to target.

DR. GEORGE: Dan George, Duke. I'll just add that in the S-TRAC trial, we embedded in there

some prospective exploratory analyses to look at the tumor tissue and to correlate this with outcome. Although these are exploratory, we did see that PD-L1 positive status was a poor prognostic indicator in the placebo group, but in the sunitinib-treated group, we saw a similar outcome, suggesting there could be in that more aggressive phenotype some interaction with the anti-angiogenic or immune modulatory mechanisms. But again, that is exploratory.

DR. ULDRICK: Dr. Redman, a follow-up?

DR. REDMAN: Again, the numbers are small here, but from my reading, especially on page 40 of the syllabus that was presented, that the kidney cancer deaths that occurred in the Sutent arm and the placebo arm were identical, 47 and 50. I realize those numbers are small, but was there a difference in the median time to kidney cancer death on trial? And again, I know the numbers are small.

DR. KRISHNASWAMI: We do not have that information to share the median time.

DR. ULDRICK: Dr. Bukowski?

DR. BUKOWSKI: Yes. Can you clarify two things for me? One, the dosing of Sutent in the trial, you allow dose reduction to 37.5, but not to 25. And what was the rationale for not including the 25 as a dose level to which they could reduce the therapy?

DR. KRISHNASWAMI: I'd like to ask Dr. George to speak to it as he was a member of the planning committee during the design of the trial.

DR. GEORGE: Dan George, Duke. Thanks for the question because I think this was one of the many assumptions that both we made as part of the S-TRAC trial as well as others made as part of the ASSURE trial regarding the subsequent on-treatment management of patients on these studies.

I think one of the premises we had early on was that we wanted to maintain as close to the maximum tolerated dose as possible by limiting the dose reductions. It really does influence practice in the management of those patients because physicians know they need to keep them on that dose

or they're going to have to take them off.

I think it's maybe one of the explanations for why we see a different management pattern in ASSURE and that ability to lower down to a dose that at the time really was unstudied in terms of its efficacy. And allowing physicians to do that may to some extent have created a bias within the outcomes of this study.

So it was one of the assumptions we made upfront. Right or wrong, I think it does have an impact on how patients were dosed through the study.

DR. BUKOWSKI: I have one other clarifying question. The histologic criteria for both studies were somewhat different. Your study required 50 percent clear cell elements. Was that determined by pathology review or just review of the pathology reports? And number two, were any tumors with sarcomatoid elements in these patients allowed in the study?

DR. KRISHNASWAMI: I'd like to ask Dr. George to answer the question, please.

DR. GEORGE: Dan George, Duke. We did not do a central pathology review to look at those subtypes, so I can't answer that question. But sarcomatoid elements were allowed on that study. And for those of you who aren't renal cell carcinoma experts, that is associated with a more aggressive phenotype of kidney cancer, so it would speak a little bit towards that aggressive subtype.

DR. ULDRICK: Dr. Hoffman?

DR. HOFFMAN: Philip Hoffman, University of Chicago. Can someone from the company clarify, it seems odd that the disease-free survival by central review would show a more statistical difference at lower hazard ratio than investigator assessment. I'm not sure what accounts for that, if that's meaningful in some way.

DR. KRISHNASWAMI: Thank you. I'd like to ask if Michelle Casey could further describe the analyses of the BACR and the investigator, discuss the discordance, in fact, the high concordance in the analyses, and as well as the sensitivity analyses to support the results.

DR. CASEY: Michelle Casey, Pfizer. So we did look at the difference between investigator and independent review, and if we could bring up EF-13.

While the overall discordance rate that we saw between the two was low, especially compared to what we see in the published literature in the metastatic setting, we were seeing differences in early and late discordance, which was an indication that the investigators were calling relapse earlier, more frequent on the placebo -- sorry.

The investigators were calling events earlier more often on the sunitinib arm compared to the independent review, and they were actually calling events later more often on the placebo arm compared to the independent review, which actually indicated that there was somewhat of a bias in favor of placebo in the investigator assessment, which may explain some of the differences.

However, if we could go back to the sensitivity analysis slide, I would just like to reiterate that although the investigator analysis was not statistically significant, it was in favor

of the -- MA-35, please -- it was in favor of sunitinib and consistent with the other sensitivity analyses that were shown.

DR. ULDRICK: Actually, Dr. Chen first.

DR. SHAW: It's Alice Shaw.

DR. ULDRICK: Sorry.

DR. SHAW: This is a question for Dr. George just to follow up on your slide MA-36 about the subgroup analysis, and you had commented that the DFS benefit was seen across subgroups. However, looking through these, there are a number of subgroups where clearly the 95 percent confidence interval crosses 1.

I was just wondering if you could comment on a few of these subsets, the younger patients, women, and particularly, ECOG 1 and above patients.

DR. KRISHNASWAMI: Thank you. I'd like to ask Dr. George.

DR. GEORGE: Dan George, Duke. Thanks for the question. In the interest of time, I didn't have an opportunity to go through this in detail, but let me just say when we look at a subgroup

analysis, particularly in a study of this size, we recognize that many of these are going to be underpowered.

What we're primarily looking for are the outlier groups, groups in particular where the confidence intervals are not crossing the point estimate for the primary analysis. What you can see here is across the board in each one of these, including ones that have shifted more to the median, more to the edge, all the confidence intervals are crossing that point estimate shown in that dotted line.

That's really telling us that there are no outlier groups in this. They're going to be, just by random chance, some movement of these along those confidence intervals, so some of them shifted a little bit more towards the 1.0. Others shifted further out.

We try not to overestimate the significance of those, but it does give us some sense overall that there is a response and benefit associated with all of these when taken in total.

Does that answer your question?

DR. SHAW: It often speaks to the robustness of the data when we see that there's no overlap over there across the 1 line, and there's quite a few of those. That's why I was just --

DR. GEORGE: Yes, with regard to the 1 line, we kind of look at that as that speaks a little bit more towards the size of the study. So whenever we have small numbers like this, you're going to have some of this. We try not to over-interpret that in these small settings. Thank you.

DR. ULDRICK: Dr. Burstein?

DR. BURSTEIN: I wanted to follow up with a question of investigator report to FDA. You also looked independently at the investigator-reported outcomes versus independent radiologic review. Since in the real world, it's the treating physician or investigator who will be telling the patient whether or not the cancer has recurred, I wonder if we can say a little more. The argument that there was perhaps bias may be the explanation, knowing the toxicity of the Sutent in the setting,

but did you uncover anything else in the review you guys did that speaks to why the difference is narrow on investigator-reported outcome versus not?

DR. MAHER: We really spent quite a bit of time looking at the investigator review and the IRC review, and particularly one of the points that was brought up earlier, the issue of the medians in the placebo arm being so different between the IRC and investigator. And we believe that has to do with excessive censoring.

DR. BURSTEIN: (Inaudible - off mic)?

DR. MAHER: You really have to talk with the statisticians about that one, and maybe Laura could.

DR. FERNANDES: The median time by the investigator is 5.8 years on placebo, and it's 4.8 years as per the central review. The applicant said in their justification that the investigator favored sunitinib, but when you look at the median times, we don't see this favor for sunitinib. It seems like it favors placebo because the median time is lower in investigator as compared to the

central review.

There could be several differences. We looked into those, and one of the possible explanations is the difference where the patients do not match is where the investigator calls the match earlier as an event as compared to the central review, which accounts for that difference.

DR. BURSTEIN: If I understand what you're saying, your analysis of investigator review in S-TRAC actually found that the investigators predicted a worse outcome for the placebo, arguing against the argument of the biases put forward by the company in this analysis; is that correct?

DR. FERNANDES: Yes. And it's the same analysis proposed by the applicant.

DR. BURSTEIN: That is the same analysis.

DR. FERNANDES: It's the same. We both report the same.

DR. SRIDHARA: Dr. Raje Sridhara, FDA, Division of Biometrics V. So what's happening in the independent review is what we call as informed censoring. So the investigator has already

declared that there is an event, but when the independent reviewer is looking at this, they are saying, no, there is no event. So it's being censored, whereas probably at a later time point, there is recurrence there.

With that, you will have the shift of time, and because of the difference in number of censoring, if more events were being called in Sutent which were not agreed upon by independent review, then it favors the Sutent arm in that case.

DR. BURSTEIN: Just to extend the discussion, so in the ASSURE trial, which was a NCI-supported study, obviously, there was not an independent radiologic review, so that was all based on investigator-reported information. Of course, that's what would be communicated to the patient in real time, I suppose, in day-to-day operations.

DR. SRIDHARA: Even if you look at S-TRAC investigator reported, the hazard ratio is 0.81, and it is much closer to ASSURE in that sense than the independent review.

KRISHNASWAMI: Would it be appropriate to add a comment to this point? I would like to ask if Michelle Casey could add a comment on this, please.

DR. CASEY: Michelle Casey, Pfizer. Could we have that slide, the previous one with the overlays? Sorry, I don't what -- EF-2, please.

When we evaluated the discordance, we also plotted the two curves on top of each other. And I think it's important to reference -- I understand the FDA's point about the medians, but the medians is a single point on the curve, and you really have to take the totality of the curve into consideration as that's where the comparison is.

This might be a little hard to see, but the two bottom curves are the placebo curves. You can see they're pretty well on top of each other except at the end where there is a lot of censoring because patients were followed for 5 years. So that's to be expected.

What we're seeing is the investigator-assessed sunitinib curve, which is the dotted blue

line, is actually below that of the independent review. When we looked at discordance in terms of cases where an investigator called an event and there was no further follow-up, the number of those discordance cases was actually relatively low.

This is where we're showing that there's a potential bias in favor of placebo. So it's the differential discordance where the investigators are actually calling events later on the placebo arm is what we were seeing in the context of our data.

DR. ULDRICK: Thank you. Dr. Pagliaro?

DR. PAGLIARO: Yes. My question is about the burden of therapy and benefit-risk ratio. If we understand that there's no overall survival benefit, and it seems that most of the speakers have accepted that, then it's important to look at the burden of therapy, whether it's in terms of the type of therapy and whether an adjuvant treatment is something more benign than the definitive treatment later that might be avoided or the duration of therapy.

My question is, regarding the burden of therapy, it appears that in the adjuvant setting, you're actually having a greater duration of exposure to sunitinib both in half of the patients who are being treated unnecessarily -- these are the half who don't recur in the placebo group. And even among those patients who have disease, when they're being treated in the setting of measurable disease, you can identify responders and non-responders, and thereby the average exposure would be less.

We have somewhat of a paradox that the adjuvant group is getting a greater exposure to sunitinib, and the first-line treatment that they might be avoiding later on is actually sunitinib or a drug very much like that. This all presumes that there's no overall survival advantage.

My question for industry is, can you comment on the apparent increase of burden of therapy in the adjuvant group and how is that justified in light of the data?

DR. KRISHNASWAMI: Thank you for the

question. I'd like to ask if Dr. Figlin could share his thoughts further on this topic.

DR. FIGLIN: Bob Figlin, Cedars-Sinai. Thank you for the question. That is, in fact, the major dilemma for kidney cancer patients. And I can tell you that from my own practice and my own experience, patients very much want to remain disease free.

The disease-free status for a cancer patient is associated with the concept of survivorship. Obviously, they don't know if they're going to recur or not, and when confronted with the opportunity for extended disease-free survival balanced by a manageable, reproducible toxicity profile in the hands of people who have used this drug for over a decade, I think that patients individually will make that choice. There will be patients whose comorbidities would not justify such an approach, and there are patients without comorbidities who are certain ages where remaining disease-free would be an attractive opportunity.

Clearly, your comments are correct. The

benefits of being disease free have a cost, and that's the cost of therapy. But I would just translate that further to the management of people that have metastatic disease where they are facing the end of their life. They're being told, they know that they have a terminal disease, and the difference between manageable toxicity and a disease-free state and a similar toxicity toward the end of one's life and trying to extend it are really very different and require in my practice the comprehensive discussion with the individual.

DR. ULDRICK: Dr. Srinivasan?

DR. SRINIVASAN: Thank you. I'm going to follow up on Dr. Pagliaro's question to try and highlight one other issue.

Dr. Figlin, I think you appropriately mentioned that many patients would want to go on therapy despite toxicities if there is a real benefit, and a perception of real benefit in this setting could be delaying disease recurrence.

On the other hand, we also see a lot of patients with metastatic kidney cancer with slowly

progressive disease who opt not to get therapy because they fear toxicity.

Do you think the calculus of these patients might change if they knew that, yes, your disease may recur longer, but I can't tell you that this is actually going to impact on your survival? I do think that's a relevant question to consider when we are talking about treatment burden.

DR. KRISHNASWAMI: I'd like to ask Dr. Figlin to speak to this. I'd like to also ask Dr. George to speak to some of the data that's available in terms of the active surveillance information.

DR. FIGLIN: Bob Figlin, Cedars-Sinai. You have very nicely summarized the dilemma for doctors and their patients. When I think about this, I look at it as an option, not a mandate. I think that the conversation is really a conversation around what are the goals of therapy at a time when you're at risk for recurrence versus what might happen if and when you do recur.

As you know, in the last decade, we've

approved a large number of drugs for kidney cancer, and it's a constantly moving goalpost. But I think you've summarized very nicely that it is a dilemma. And I think not all patients will choose A or B, but my own personal view in my own practice would be that I'd like to offer them the opportunity for A or B.

DR. ULDRICK: Dr. Burstein? I apologize. Go ahead.

DR. GEORGE: Dan George, Duke. I just wanted to add another point on this because you raised a second question, and that was about the population of patients with metastatic disease that elect to do active surveillance.

There actually isn't a lot of prospective data, but there is a prospective study that's been done, a multicenter, multinational study looking at patients with low-burden disease who then elected to go on to active surveillance.

What we learned from that study is that for those selected patients, about 14 months to the time of systemic therapy, but the median overall

survival for that population was 44 months. This is still a lethal disease even in those relatively indolent patients.

If I could also have slide EF-62 up because this question of overall survival has been raised around DFS. I just want to make two points here. One, first off to clarify, it's not that there is no overall survival benefit. It's that the data is too immature at this point. And if we're going to see a population separate in terms of overall survival, it's likely to be late, not early.

So in terms of the overall survival curve, I wouldn't say there is no association between DFS and overall survival. I would just say in this study, it's too early to tell. But one thing we can do is look at DFS events that do occur early and is there any association with overall survival?

This was an analysis that was done, and I'll point out one thing to you here. That is, for those patients that have disease recurrence that occurs within 2 years and then whether or not they have overall survival beyond 5 years, if you look

at the bottom left corner here, you can see 318 patients who have disease-free survival greater than 2 years and overall survival of greater than 5 years. That's a very strong association.

Conversely, if you have disease-free recurrence within 2 years, your overall survival at 5 years is much less. In fact, that odds ratio is 15, meaning there's a 15 times greater chance that you're alive at 5 years if your disease hasn't recurred by 2 years. And if you have recurred within 2 years, a 15 times greater chance you're going to be dead in 5 years.

That's an incredibly powerful association for just one study. We'll need to see a meta-analysis and further studies, but to me, this is really an important association to recognize that DFS is a clinically significant endpoint.

DR. ULDRICK: Actually, I have a question to follow up on the burden of disease question. I was wondering when you looked at the patient-reported outcomes, whether there were differences between those who discontinued and those who didn't.

DR. KRISHNASWAMI: It is the case that we did observe a larger reduction in patients who did discontinue compared to those who remained on treatment. And what we see, what we've shown in the main presentation, is a reflection of the overall quality-of-life data in the study. So it is in a way reflective of the sensitivity of the measure in that patients who did discontinue had a larger reduction.

DR. ULDRICK: I guess conversely, the patients who stayed on tended to be towards no to little --

DR. KRISHNASWAMI: That's correct.

DR. ULDRICK: -- that's what you presented for the median for the whole group?

DR. KRISHNASWAMI: That's correct.

DR. ULDRICK: In thinking about this question, it'd be interesting to see if you've done any analyses looking at how those patients did. Did you do any subgroup analyses or no?

DR. KRISHNASWAMI: Divided by. So I would like to ask Dr. Jean Paty to talk about this,

please.

DR. PATY: Hi. Thank you for the question. Jean Paty with Quintiles IMS. I'm a paid consultant, and I have no financial interest in the outcome of this meeting.

We did do some analyses where we looked at completers versus discontinuers, and I just put up one -- can I have EP-78, please? If we just look at diarrhea, which is a common effect of Sutent and so it helps us understand some of the differences, you'll see here, these are the completers, and you see a difference in diarrhea as expected between Sutent and placebo.

If we can look at EP-79 for the discontinuers, you'll see that there is indeed a larger difference. And this is consistent with some other analyses we've done where, not surprisingly, those that discontinued reported that they had more symptomatology.

Again, one of the things to consider -- and remember, these are the patients' own words. If you look on the right-hand side, these are the

actual responses they gave. Even in this context, they're reporting, at least in the C30, that this was at the level of a little on average.

DR. ULDRICK: Dr. Burstein?

DR. BURSTEIN: I had a couple questions, one technical one. In the New England Journal of Medicine transcript, there's reference to a cohort from China that was accrued for registrational purposes potentially of Chinese authorities, but was not included in the New England Journal analysis. I'm wondering if those data are included in the sponsor presentations here.

DR. KRISHNASWAMI: No, the China cohort is still ongoing at this time.

DR. BURSTEIN: Okay. Secondly, I want to talk about dosing. Dosing is a complicated thing. It reflects patient motivation, performance status, socioeconomic status, comorbid illnesses, and things like that. So as I understand the argument contrasting ASSURE and S-TRAC, that part of the argument is that you were better able to maintain dose, and therefore saw more of a positive signal.

And I'm wondering if you've done correlations with things like performance status, socioeconomic status, comorbid conditions.

The second related question is, in the cohort of patients, which are about a third to a half who had either dose reductions in S-TRAC, I wondered if the outcomes differed for those patients in terms of disease-free survival.

DR. KRISHNASWAMI: There were two questions with respect to summarization of dose information by risk factors, and the second one was DFS outcomes in those who dose reduced versus those who did not.

We do have analysis supporting the second question. What we have not looked at is the dose summarization by different factors. So I would like to ask Michelle Casey if she can present the information on the patients who dose reduced.

DR. CASEY: Michelle Casey, Pfizer. Could I have EF-22, please? We looked at this in a variety of ways. This is within the sunitinib arm, so more of a correlation.

We looked at sunitinib completers, which included patients who relapsed on treatment versus those who discontinued. We also looked at sunitinib patients who had dose modifications versus those who did not, and dose modification included interruptions as well as reductions. Thirdly, we looked at patients who had dose reductions versus those who did not.

What we're seeing is that the patients who had to have dose modifications still had some benefit, so they didn't really perform any worse than patients who were able to maintain and complete the dose.

DR. ULDRICK: Dr. Redman?

DR. MAHER: Can we just add a little bit about the dose intensity, please? Could we put backup slide number 44?

This is on the FDA backup slides number 44. Actually, we have a bit on 45. There was also some information in the briefing book where we looked at dose intensity on S-TRAC, specifically looking at patients who got greater than 75 or less than

75 percent dose intensity.

We actually saw that patients who had a lower dose intensity, we were very surprised by this because we expected that to be a good reason that S-TRAC had shown an effect, that for those who had a dose intensity less than 75 percent, the hazard ratio was 0.55 in this certainly exploratory post hoc analysis.

The dosing data on ASSURE was not well collected, so we weren't really able to look at dose intensity on ASSURE and really restricted our analyses of this to S-TRAC.

DR. BURSTEIN: Burstein, Dana Farber. If I can put into words -- both FDA and Pfizer comment then -- with the limitations of dosing, neither study showed that reduced dosing compromised outcome; that is to say there was a benefit even if you had reduced dose in S-TRAC, in both analyses.

DR. MAHER: Yes, that's correct.

DR. BURSTEIN: So there isn't an argument or there aren't data at this point that losing dose intensity compromised efficacy based on S-TRAC at

this point?

DR. MAHER: Right, although we did make the point in our presentation that there is in metastatic disease a dose-response effect with Sutent.

DR. ULDRICK: Dr. Redman?

DR. REDMAN: I have a question, but first a comment -- and I know Dr. George knows this -- that 2-year disease-free survival predicting for overall survival is a biology effect, not a treatment effect, just to clarify that.

The question I had is -- I forgot who presented it, but the median time to first treatment for recurrence was 3.1 months versus 2.5 months. I'm assuming that's from time of recurrence.

Do we have data that says, from the start of study, the median time for the two groups to start treatment for recurrence?

DR. KRISHNASWAMI: In terms of specific numbers, we do not have the exact numbers, but I think what we can say is it is

approximately -- when we add the median times, DFS times, plus the time from relapse to intervention, it's approximately 7 years.

DR. REDMAN: You really can't add that to your DFS because your DFS includes others that don't have recurrence or disease, specific disease, study-specific disease.

DR. KRISHNASWAMI: That's correct.

DR. ULDRICK: Dr. Srinivasan?

DR. FERNANDES: The FDA has a slide on time to first intervention of post-adjuvant therapy. It's slide number 50, backup slide number 50.

In this analysis, we looked at the time to first intervention, which includes any intervention, systemic therapy, surgery, radiation, any form of intervention. There were 125, or 41 percent, on Sutent and 45 percent on placebo. This provided a hazard ratio of 0.88, and the median time in years is 7.42 years on Sutent and 7.23 on placebo.

DR. ULDRICK: Thank you, Dr. Fernandes.

Dr. Srinivasan?

DR. SRINIVASAN: I want to go back to overall survival assessment. I think it was very appropriately pointed out by Dr. George that overall survival, they do not mature. However, I think the FDA's assessment, if I recall correctly, is that maturity is unlikely to show a benefit based on the statistical parameters you're observing now.

I want to try and focus on a different aspect of overall survival. Because these data are immature, can we also say that it is difficult at this point to conclude that there won't be a detriment in overall survival as the data mature? This is data -- I'm not sure whom to address it to. I think either the sponsors or the FDA.

DR. FERNANDES: We have not actually looked into what's the exact value of what it's going to be towards the end, overall survival. But based on our estimate, it does seem to be low.

DR. SRINIVASAN: But is it possible to say now that there is unlikely to be detriment in terms of overall survival based on the survival data that

we have at this point?

DR. FERNANDES: As mentioned earlier, to answer that question, we need two different things. We need to know if the study was powered for overall survival, so we need to know what was the hazard ratio that we were targeting in the study. This study was not powered for OS, so we don't know what was the final hazard ratio that we are looking out for.

We need that to put in the equation to calculate what it is that we are finally going to see, if we're going to hit that target. Since the study was not really powered to detect a particular hazard ratio, we do not have that answer.

DR. KRISHNASWAMI: If I could add a further comment on that, I'd like to ask if Dr. Koch could speak to some of the available data that we have and what evidence we have around this topic.

DR. KOCH: I want to look at the core slide for overall survival.

Gary Koch, biostatistics department, University of North Carolina. My only financial

relationship with the sponsor is I'm the principal investigator for a cooperative statistical methodology agreement between the sponsor and my university.

The information on overall survival is indeed limited, but potentially, there is some usefulness in the upper confidence limit, which is 1.28, so that could be interpreted as hazard ratios that would be worse than 1.28 could be ruled out as a disadvantage in terms of overall survival. In some areas, sometimes 1.3 has been identified as a useful threshold to rule out a detrimental effect for outcomes like this.

The data are still immature. As the sponsor has indicated, there's going to be the accrued needed number of events in about 2 to 3 years. So it's often hard to interpret data that are not mature, but oftentimes for these kinds of outcomes, one does look to the upper confidence limit as a way to identify whether there's some suggestion of harm or not.

DR. ULDRICK: Thank you. Courtney Preusse?

MS. PREUSSE: Courtney Preusse, consumer rep, Fred Hutch. In a study like this with limited clinical benefit, if that would be safe to say, and limited patient population, it seems to me that it would be imperative really to look at the demographic data as it speaks to patient characteristics and patient preference. But what I've heard so far is that no data was collected on socioeconomics or biobehavioral outcomes or other demographics other than age, gender, and age.

If you do have that data, please share; otherwise, please confirm. Thanks.

DR. KRISHNASWAMI: We can confirm that we do not have socioeconomic information on these patients.

DR. ULDRICK: Dr. Hoffman?

DR. HOFFMAN: Philip Hoffman, University of Chicago. It's been noted early on that the magnitude of the benefit in disease-free survival is along the lines of what has also been seen in some of the adjuvant studies in breast cancer and colon and perhaps melanoma.

I guess my concern, though, as a clinician is what the burden of symptoms is during that time. For example, in breast cancer, while chemotherapy can be very difficult, it tends to be much shorter than a year. Endocrine therapy, which goes on for a number of years, many years sometimes, tends to be consistent with continuing to work and carry on reasonable normal activity.

I don't know whether that was -- that data may not have been collected, but I see that three-fourths of the patients here were under age 65 and presumably in working ages. By contrast, melanoma, a year of interferon would be a great burden.

So I just don't know whether -- while we do have some information that you've presented about quality of life, I'm just wondering, extending it a little bit more, what is the burden for that difference.

DR. KRISHNASWAMI: I'd like to ask if Dr. George could add some comments on this topic.

DR. GEORGE: Dan George, Duke. Thank you for the question. I think it's a really relevant

one, and let me just say I think a lot of this data and a lot of this safety profile can be judged on an individual basis in terms of the eye of the beholder.

Some people might think a 24 percent reduction in the risk of recurrence is not great, but for many patients, that's tremendous. And an 8 percent absolute improvement in 5-year disease-free survival is meaningful to others. So I think for all of this, it's going to come down to how individual physicians and patients interpret this data.

With regards to safety and tolerability around sunitinib, one of the good things we have is an 11-year experience of using this agent. We know this drug well in the field of kidney cancer, and this is one of the front line treatments that patients will be facing on an indefinite basis, if not this drug, then other sequentially over years if their disease recurs.

For this high-risk patient population, that's a real reality they have to face. So

looking at this in the adjuvant setting is an option for them.

This was an intention-to-treat analysis. Not everybody made a whole year on treatment. Not everybody maintained a full dose. But as you could tell from our quality-of-life measures on our patient-reported outcome tools, patients recovered in their profiles. We have two-weeks breaks built in to this regimen, and during that time, you can see the quality of life get near to the placebo group, although not quite touching.

My own personal experience managing these patients is that many of our younger patients, who are going to be attracted to adjuvant therapy, are exactly the kind of people able to maintain work and maintain function on this.

For those that can't, that's where we dose reduce, and it's interesting to suggest that the data doesn't suggest they do any worse. In fact, that may be a group that is still benefitting as much or more.

For many of our patients looking at

12 months or less of therapy managed over time, this is a reasonable strategy to consider. And that's what we're looking for, not a mandate to treat all patients, but an option for those who need it and want it most.

DR. ULDRICK: Thank you to the committee members for clarifying questions and the presenters for your answers. We will now take a 15-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any members of the audience. We will resume at 11:00 a.m.

(Whereupon, at 10:47 a.m., a recess was taken.)

Open Public Hearing

DR. ULDRICK: Welcome back. We will now start the OPH session.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA

believes it's important to understand the context of an individual's presentation.

For this reason, the FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have such financial relationships. If you choose not to address this issue of financial relationship at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances

and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. Thank you for your cooperation.

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

MR. LAWING: Good morning. My name is Michael Lawing, and I'm not representing any particular organization. I have no financial interest in this matter. I'm not receiving any support from anyone in this.

Panel members, I'd like to thank you for your attention this morning. You've got a very, very difficult question that they've asked you to consider, and in reading that, it says, "Is the benefit-risk profile of Sutent acceptable for the

adjuvant treatment of patients at high risk of recurrent renal cell carcinoma following nephrectomy?" But what it really boils down to is will you give the patients an opportunity to have treatment if they're at high risk of developing metastatic disease or will you continue to deny them that option?

You see, we're trying to work in an era of informed consent between the medical community and the patients. I'm a 20-year survivor of renal cell carcinoma. I will celebrate that anniversary in November of this year.

When I was diagnosed, my doctor gave me 5 years to live, not because I had metastatic disease but because my tumor had completely enveloped my right kidney. And it was so huge, he told me that "You're probably going to have metastatic disease within 5 years, and there's nothing else I can do for you except for surgery."

Now, he didn't know about a treatment option that Dr. George and a lot of other doctors were using at the time called interlukin-2, but that

drug only had about a 10 to 15 percent response rate overall, a very brutal form of treatment.

Had I had the opportunity to take Sutent right after my surgery in 1997, even knowing the safety profile and all the data that you've presented this morning, I would readily have taken it because somehow a patient that's diagnosed with cancer wants to live disease free even there are accompanying side effects with their treatments and with their medications.

Now, a lot of the comments that I'm going to make, I know it's abbreviated, I've only got five minutes left, but a lot of the comments in more detail are in your notes that I've previously submitted.

Mark Twain said something that I would misquote every once in a while, but he says, "First you get your statistics, and then you can distort them any way you want to."

So you folks can look at all the data that's been presented this morning. You can look at the retrospective analysis and everything else, and you

can read into all those statistics anything you want to. You can look at the number of adverse events that the people have had, and you can infer from that this is a really terrible drug to take.

Well, it was one of the two treatment options that I had left in 2007, in January, when I had metastatic disease not only in a lymph node in my abdomen that we'd been battling for already six years, but it had spread to a lymph node in my neck. And the biopsy said, "Consistent with renal cell carcinoma."

My doctor and I sat down, and we had a lengthy conversation. He went over the laundry list of possible side effects. Sutent had been approved about a year, and a lot of the conventional thinking among the oncologists at that time was that maybe Sutent will work for 18 months, and then it's going to wash out and you're not going to get any more results out of it; and possibly that your metastatic disease will take off with a vengeance once you stop treatment. That was the thinking back in 2006-2007 about this drug.

We've got about 11 approved treatments for kidney cancer right now. All of them have side effects. None of them are a piece of cake. But the person that has metastatic disease for the most part realizes that once they start a regimen of treatment, their disease is, as Dr. George and a few others have indicated this morning, ultimately terminal.

I had a nurse practitioner write that on my insurance submission for disability way back in the early 2000s. "This condition is ultimately terminal." Well, I'm glad I'm still here.

But I was able to take 39 rounds of Sutent on the 4-week on/2-week off dosing schedule and endured the side effects and had a very reasonable quality of life. I could do just about anything I wanted to.

I've wound up talking to literally hundreds of patients in my time of survivorship since Sutent has been approved, and many of us have been able to deal with those side effects. It's in conjunction with your oncologists and with your medical team

that you address the side effects. You learn which foods to eat and which foods to avoid, but you can endure most of it. You saw that several people had to come off the treatment because of inability to control that. Well, that's normal.

But ladies and gentlemen of the committee, I would urge you to approve this medication because, as you've been told this morning, when the patient sits in front of the oncologist and says, "Okay. Doc, what can I take to prevent a recurrent of disease," they have to say, "Right now, until you get metastatic disease, we can't do anything for you. I'm sorry." And they have to walk out of the office and just go home and wait.

Thank you for your time. Thank you for your favorable consideration of Sutent.

DR. ULDRICK: Thank you. Will speaker number 2 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MS. BATTLE: My name is Dena Battle. I'd like to thank the panel for giving me the

opportunity to tell me story. I received no compensation to be here today.

In the spring of 2009, I rushed out of work to meet my husband at the ER for what we thought was appendicitis, but instead, our lives were turned upside down in an instant when the doctor told us that it wasn't his appendix. It was a massive tumor on his right kidney invading the renal fat.

There was no time to stop and think, ask for a second opinion, to consider our options. Chris was scheduled for an nephrectomy two days later. After surgery, we asked the doctor what we should be worried about, whether we should see an oncologist. He told us it wasn't necessary, that Chris was cured.

After weeks of insisting, the surgeon finally sent us our pathology report which showed that Chris' tumor was an 11-centimeter high grade clear cell renal cell carcinoma. When we asked about chemotherapy, radiation, anything to prevent the cancer from coming back, we were told, "You

don't need it," but that wasn't the truth. It wasn't that Chris didn't need adjuvant therapy. It was that adjuvant therapy didn't exist for him.

Chris' disease recurred to his lungs nine months after his surgery. Four and a half years later after seeking care at 4 different comprehensive cancer centers, participating in 3 clinical trials, enduring 9 different treatments, Chris died at the age of 45.

Looking back to the spring of 2009, if you had given us the option of anything that could have potentially prevented recurrence for my husband, we would have taken it. The nine months of watching and waiting were helpless and agonizing as if we were watching a ticking bomb with no hope of defusing it.

After his diagnosis of metastatic disease, we maintained hope. We sought out treatments that might offer a complete response. We lived from scan to scan, desperate to see his tumor shrink. When those options failed, we hoped for a stable disease. We hoped maybe he would have live to see

our youngest daughter turn 4. And then in the final days when he weighed 115 pounds and was completely dependent on oxygen, I just hoped for his pain to end.

Having endured years of watching cancer slowly ravage my husband's body, I can honestly say that if we had access to therapy that could have even delayed onset of metastatic disease, it would have been worth it regardless of toxicity. The side effects he endured while on treatment paled in comparison to the devastation that was caused by his cancer.

Approval of this drug today can't change the ending to our story, but it might change the course for others. This isn't for all patients, but it will work for some. They deserve that choice, and they deserve that chance.

Thank you for listening. I'm grateful for your time and consideration.

DR. ULDRICK: Thank you. Will speaker number 3 step to the podium and introduce yourself? Please state your name and any organization you are

representing for the record.

MR. PHILLIPS: My name is Robert Phillips. I represent no company, and I received no financial compensation for this visit.

At 57 years old in April of 2016, I was diagnosed with renal cell carcinoma in the right kidney. Subsequently, I had surgery and had the kidney removed in June of that same year. My follow-up visit revealed that the cancer was stage 3 with no treatment option. That was unacceptable to me and my family, and upon much research, we found the trial that Duke University and Dr. George were participating in.

Subsequently, I made the trip to Duke, met with Dr. George, and we started me on the 50-milligram, 4/2 Sutent treatment for one year, and I'm happy to say that as of two weeks ago, I've completed that treatment.

Through my treatment, I did not miss one day of work. I'm an extremely active individual, a lot of outdoor activities. I went on all my trips. I did anything I wanted to do the entire time I was

on the Sutent, and very thankfully, I'm through that now.

My other doctors are amazed at how well I've done through this treatment and also very interested in this trial. Regardless of the outcome for myself, I would definitely do this again. As a patient in this trial, I feel very, very strongly this medication needs to be a viable treatment option for kidney cancer in the future. Thank you for your time.

Questions to the Committee and Discussion

DR. ULDRICK: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments.

We will now proceed with the question to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may

not participate except at the specific request of the panel. I will now read the question.

The question to the committee, is "S-TRAC randomized patients at high risk of recurrent renal cell carcinoma following nephrectomy to 1 year of Sutent or placebo?

"Sutent was administered as 50 milligrams orally 4 weeks on and 2 weeks off and could be reduced to 37.5 milligrams. Patients were followed for disease-free survival with scans every 12 weeks for 3 years and then every 6 months for the duration of follow-up. Scans were reviewed by the investigator and by an independent radiology review committee. Patients were also followed for overall survival.

"The results of the primary analysis disease-free survival as determined by the independent radiology review committee are shown below. The median disease-free in the Sutent arm was 6.8 years, and in the placebo arm was 5.6 years for a hazard ratio of 0.76. This was significant at p 0.03.

"The safety profile of Sutent in the adjuvant setting is generally similar to that in patients with metastatic renal cell carcinoma. Adverse events during the treatment period resulted in permanent discontinuation in 28 percent of patients on Sutent and 5 on placebo.

"Dose interruptions or delays were required in 46 percent, and dose reductions in 35 percent of patients on Sutent. Grade 3/4 adverse events occurred in 60 percent and 15 percent on the Sutent and placebo arms, respectively.

"There have been 21 percent and 24 percent deaths on the Sutent and placebo arms respectively. As of January 2017, the estimated hazard ratio for overall survival is 0.92 with a 95 percent confidence interval that crosses 1. A final analysis is expected in 2019.

"The question before the committee is, is the benefit-risk profile of Sutent acceptable for the adjuvant treatment of patients at high risk of recurrent renal cell carcinoma following nephrectomy?"

We'll open it up to discussion. Before we start, are there any questions or comments concerning the wording of the question?

(No response.)

DR. ULDRICK: If not, then we'll open it up to discussion. Please raise your hand, and we'll call on you. Dr. Nowakowski?

DR. KOWAKOWSKI: Greg Nowakowski, Mayo Clinic. This is not maybe a discussion comment but just a point of clarification. So FDA showed the analysis, which looked at the time to first therapy on the trial. Is my interpretation correct that there was no difference in the impact of time to first therapy on this trial based on the placebo versus sunitinib arm?

DR. FERNANDES: Yes, there appears to be no difference between the placebo and the Sutent arm.

DR. NOWAKOWSKI: Thank you.

DR. ULDRICK: Any other questions?

(No response.)

DR. ULDRICK: Let me summarize what we discussed earlier and see if there are any

additional considerations when we think about the risk-benefit profile of Sutent for the adjuvant treatment of patients at high risk for renal cell carcinoma.

S-TRAC was a well-conducted study that showed that in patients with high risk for disease, disease-free survival was superior with Sutent. The questions that were discussed during the clarification portion of the session focused largely on differences in the outcomes of this study versus the ASSURE study and discussed differences in patient selection and dosing, specifically maintaining the dosing at 50 or 37.5 milligrams.

We discussed disease-free survival as an endpoint and pointed out that there's a low likelihood of an overall survival detriment, although the data of overall survival is not complete.

We also discussed briefly differences between investigators and central reviewers in ascertainment of disease-free survival endpoints,

suggesting that censoring may have favored or had a bias towards the placebo arm.

Lastly, in discussing the burden of treatment, an important concept in adjuvant therapy, we noted that there were no new AE signals and that there was some patient-reported outcome to support the findings in applicant's application for this indication.

Are there any discussion points, things that people would like to bring up related to the benefit-risk profile that were not discussed in this morning's session?

DR. XU: This is James Xu. I just have one more point to add based on what Dr. Fernandes said. We do see a favorable trend in terms of time to systemic therapy in the Sutent arm.

DR. BURSTEIN: The other thing I've struggle with here is the issue of reproducibility in the multiple trials. As a breast cancer specialist, we spent a long time sorting that out. It needed an overview analysis, and it took time for data to come forward to clarify the role of things like

chemotherapy and endocrine therapy and stuff. But here, the two studies you alluded to seemingly showed discordant outcomes, and I've listened this morning to try and understand why. I'm still struggling a bit to understand why.

There's a third trial, the PROTECT study, with a drug that is largely similar to sunitinib in its mechanism of action, and I believe indication in metastatic cancer has shown a very similar outcome. That too is a negative trial in the adjuvant setting, the PROTECT trial.

What I've not heard and I'm interested in some of the expertise from my GU colleagues and others, is there a way to tease out who's really likely to benefit from this such that in an encounter with a patient, you could say this patient but not this one, this one, this one, or the other ones really would be the ones to make that risk-benefit worthwhile? I wonder if my colleagues can help me understand that.

DR. BUKOWSKI: I can try to address some of that issue. I don't treat patients currently, but

I did exclusively treat patients with kidney cancer in the past. There appears to be no way at the present to discriminate between who will benefit and who will not benefit in any way based on molecular classifications, what have you.

Now, that's a very active area of research, but we just don't have that at the present time. So we generally treat all patients who are eligible for that kind of therapy.

I think it's important to think about the two trials that are reported as negative. Both of those studies were altered during their conduct to reduce the dose of the primary therapy, both the pazopanib trial and the ASSURE trial. That didn't occur with the S-TRAC trial.

Now, that's one difference. That may not be the difference. It may not be that dose is important, but everything we know about treating metastatic disease, the starting dose of these agents is important and trying to maintain a dose is important.

I wish we had a way of identifying the

patients who would benefit. I don't think we do.

DR. ULDRICK: If I could comment on the same issue, when I looked at the study, I do think that there were a couple of clinical parameters that were used, the T3/T4, and the clear cell histology, that I think are helpful for clinicians picking who would benefit. It does not reach the degree of precision medicine you are alluding to, but I think those are still important points.

Dr. Srinivasan?

DR. SRINIVASAN: I have a comment to add. I do believe and I think this is based on the experience of most people who have treated kidney cancer in this room, that patients with non-clear cell forms of kidney cancer tend not to do quite as well with single agent VEGF receptor-targeted tyrosine kinase inhibitors.

It is important in this slide to note that the ASSURE trial did include around 20 percent of patients who didn't have clear cell histology, while S-TRAC included exclusively patients with clear cell, at least that was the intent.

It's very hard for me, however, to glean from the way the histologic eligibility criteria was described, which is greater than 50 percent clear cell histology, without central pathology review, how many of the patients on this trial were truly clear cell.

When I see a pathology report from most centers, I don't see a percentage of clear cell component indicated. Usually, I see a report that says it's clear cell or something else, and sometimes, there's a descriptor.

If there are components other than clear cell, there's often a description of what those components are. So sometimes I'll see a pathology report that says clear cell with papillary features or clear cell with sarcomatoid differentiation. But I seldom see reports that say we have a tumor here that has 50 percent or more clear cell kidney cancer.

So I have a slightly difficult time determining how robust the selection based on clear cell histology is here, but assuming that it is, I

think that may account for at least some of the differences that we see.

DR. ULDRICK: Can I actually follow up on that? Dr. Srinivasan, or others on the panel, if the diagnosis is clear cell carcinoma on the pathology report, how often is there a mixed histology component?

DR. SRINIVASAN: It really depends on who's reading the pathology. I think if you have an experienced GU pathologist, you may see a higher incidence of mixed pathology. I treat a lot of patients with papillary kidney cancer, and I see a fair number of those patients having a clear cell component to their papillary kidney cancer. It may be a small part, but again, it depends on how much tissue you have. If you systematically look at every slice from all tissue material available, you may find more mixed histologies. If not, you may find less.

My perception, though, is in general, if you have had the pathology reviewed by somebody who is very experienced in the field, the proportion of

patients with mixed histology is not going to be that high, but it's still not going to be negligible. I would guess something like 10 to 20 percent, but it's a number I'm making up at this point.

DR. ULDRICK: Thank you. Dr. Pagliaro?

DR. PAGLIARO: I also want to follow up on Dr. Burstein's question. As a medical oncologist who treats renal cell carcinoma and the issue here of two clinical trials, thinking of ASSURE and S-TRAC with different results, I think the subgroup analysis of the patients with clear cell who meet S-TRAC criteria, who started at 50-milligram dose, that subgroup in the ASSURE trial is critically important. It's really the only comparison that, in my view, is relevant because non-clear cell, as has been said, it's a whole different ballgame.

We had a hazard ratio of 0.76 on the S-TRAC trial and a hazard ratio was higher on the ASSURE trial for that subgroup; that's a difference. And we had a 5-year disease-free survival rate of 59 percent in the Sutent arm on the S-TRAC trial.

It was 50 percent on the ASSURE trial. That's a difference.

I for one am not able to explain that away. We've heard about differences in performance status and tumor grade. Again, from my perspective as someone who treats renal cell carcinoma, those are not major drivers of outcome. And in fact, if you look at the placebo group, again focusing on the subgroup that was similar to the S-TRAC trial, the placebo group in both trials had a 5-year disease-free survival rate of approximately 50 percent. In fact, I believe the ASSURE trial was slightly lower.

That's not to say that I know why they're different or what that means, just that they're different. And as a renal cell cancer physician, I'm left with that issue to be resolved.

DR. BURSTEIN: Just in follow-up to those comments about the particulars of managing renal cell carcinoma in 2017, again, the community sometimes has a lag time before data are fully digested and things. But as I've read the

guidelines in anticipation of this meeting and I've looked at the existing national registry-type trials and other adjuvant trials, this has not pushed itself into the guidelines. I haven't seen guideline endorsement of sunitinib in this indication.

The current clinical trials, as I broadly understand them, are generally compared against a placebo. There hasn't been a push to make this a control arm in those trials. And that sometimes happens because as we've heard today, there's individual selection factors; not everybody would want to consider this.

I'm wondering why that hasn't sort of percolated a little further along, or is that just simply they're waiting for this in the FDA? Or maybe there's the same kind of uncertainties we've all been discussing already?

When there's a slam dunk, that's not what happens, right? So when you have adjuvant trastuzumab, everybody comes back and says, okay, as of yesterday, the trial that looked reasonable

is no longer reasonable. You have to have a trastuzumab arm or something. I haven't heard that about this, and I'm trying to figure out what, if anything, that means in the way of how this drug is perceived in the consensus community.

DR. PAZDUR: That's somewhat tangential to this whole meeting, okay, what goes into consensus reports. I really want to emphasize that that should not be put in your decision-making, what outside groups do. We have no control over that. I don't know what their meeting schedules are. These are totally extraneous. So let's put that aside.

The other issue I want to reach out to is Lance's discussion of these non-prespecified, non-randomized subgroups that we look at. This is very dangerous territory to go into to start looking at non-randomized populations from another trial and trying to compare it to the results of a randomized population.

We had a great deal of internal debate, whether even or not, to present these issues here,

or these findings here, because it is a non-randomized population, all of these subgroups. So you cannot make any inference as far as treatment effect on these populations. They are at best, if you want to call it, exploratory, ad hoc, hypothesis generating, but I really would not want anyone to be making a definitive decision based on these non-randomized subgroups.

Here again, the whole benefit, remember, of randomization is to take advantage of factors that we don't know about. Here again, I don't think anybody in this room says we know everything there is to know about all the prognostic factors of renal cell cancers. This really precludes the discussion that we're having as far as looking at these non-randomized populations.

The thing also I have to hear from the committee is we've used DFS in multiple adjuvant disease settings of similar magnitude, as was pointed out. If you're planning on voting no or have some qualms about this, I have to know from you what's different about this disease setting

from colon cancer, melanoma, breast cancer, et cetera.

If we could have some discussion on this, is this -- because we have to have a consistent regulatory policy here. We have to know if there's a difference with this disease that would preclude us from using DFS that was seen in a well-conducted randomized trial.

DR. ULDRICK: Thank you.

Any questions or any comments on that? Dr. Bukowski?

DR. BUKOWSKI: I echo what you said regarding these post hoc subset analyses. If it's positive and it matches the S-TRAC trial, well, everybody's happy. It doesn't, but that's not a reason to discard the analysis from S-TRAC. I think it's interesting to look at it, but it's purely speculative, as you say, and we should regard it in the same way as that.

DR. ULDRICK: Dr. Redman?

DR. REDMAN: There's a long discussion about accepting disease-free survival, but let's just

look at S-TRAC. So my interpretation sitting in front of a patient who has had a resected kidney cancer, they want to know is this treatment going to delay or prevent my disease from coming back, not squamous cell carcinoma of the skin, not breast carcinoma in situ being called a disease-free survival event.

At least the data I looked at here and was presented, when you look at kidney cancer specific disease-free survival, there was no difference. So I will accept disease-free survival, and there's always a balance of it. How much toxicity is there versus the benefit?

In this, you can look at it and say, I'm going to give you this drug for a year, and it's going to delay the onset of a disease by a year, give or take a month. Sorry, industry.

DR. ULDRICK: Dr. Srinivasan?

DR. SRINIVASAN: I echo some of Dr. Redman's comments, of course, but I also want to go back to this point of disease-free survival or event-free survival as a reasonable endpoint. I think a lot

is said about its value in colon cancer and breast cancer, but are there other conditions like pancreatic cancer where DFS may not be an appropriate surrogate, and do we know today that it is a good surrogate for kidney cancer?

I'm not sure we know the answer to that. I'd be interested to see what others have to say the general applicability of DFS as a surrogate endpoint across all tumors. And if anybody else has any insights into its applicability in kidney cancer, I'd be very eager to hear about that as well.

DR. ULDRICK: Actually, I just want to follow up on that. You had mentioned DFS as a surrogate. Do you mean as a surrogate for overall survival or a surrogate for something else?

DR. SRINIVASAN: Meaningful clinical benefit in the adjuvant setting.

DR. ULDRICK: Dr. Halabi?

DR. HALABI: I wanted to make a couple of comments on DFS. Similar to what you've heard, no analysis has been done to demonstrate that DFS is a

good surrogate of overall survival in the adjuvant setting. So I think this really remains an important question to be answered.

The other comments I wanted to make is regarding the S-TRAC results and how robust the results are, and I've been struggling with this. The analysis, even though it was statistically significant, is based on 257 events. And even though it's statistically significant, the upper limit of the confidence interval of the hazard ratio goes to 0.98, which someone could say that if you were to repeat the trial again, you may end up with a totally different hazard ratio.

I'm still struggling with those two things. When you're looking at the benefit-risk ratio, I think it is important to look at the robustness of the data. And the fact that DFS has not been shown that it is a good surrogate of overall survival, this doesn't mean it will not be. I think this still remains a very important question.

DR. ULDRICK: Dr. Beaver?

DR. BEAVER: Just to follow up so we have

some clarity, in the other diseases where we have approved based on DFS for regular approval, the majority have not had DFS as a validated surrogate for overall survival.

So I think getting at Dr. Pazdur's point, the question is, is DFS -- and FDA has viewed DFS as a direct measure of clinical benefit supporting regular approval. So the question is, why is that different in renal cell versus other malignancies?

In colon cancer, there was a meta-analysis for 5FU-based therapies that showed it was a surrogate for overall survival but not for other types of therapies. So I think it's important to realize in the context of other approvals, that DFS is not a surrogate for overall survival or maybe to be approved, but has not yet been demonstrated as such.

DR. ULDRICK: Thank you. That's a very important clarification.

DR. BURSTEIN: It's an interesting -- some of this -- I do not have encyclopedic knowledge here, but if you go to breast cancer or colon, the

original relationships between DFS and OS were often seen in studies that were treatment versus placebo or treatment versus nothing. In some of the subsequent iterations of this where there have been tweaks to the regimen or regimens on top of regimens, I think the relationships between DFS and OS have either narrowed or even resolved entirely. That's progress because as people do better and better, there are more drugs out back and so forth.

But I think that what I didn't see here was a strong signal of an OS benefit, which you did see in some of these earlier waves where first-generation treatments versus nothing did in some respects contribute to an overall survival benefit.

The second point I wanted to make in follow-up is the question the panel's being asked to vote for, apropos of the discussion of risk stratification and subsetting, is specifically for a high-risk population because that's how it was defined in the S-TRAC study. But one of the things that we discussed earlier is I don't see that the

outcomes in S-TRAC are actually numerically different in terms of risk than they were in the ASSURE study, which was not a high-risk patient population.

My conundrum is if the risks are the same and there's a positive finding in one and not in the other, you're still left with this question of how are you defining risk, and if they can't use the criteria here to define a higher-risk patient population that shows a clear signal of benefit, I don't know that it's so unfair to look for subsets and question whether you're really seeing a signal when a previous North American-based cooperative group study didn't show that signal when parsed various ways, admittedly.

DR. ULDRICK: Any additional comments or questions? Dr. Pagliaro?

DR. PAGLIARO: I want to try to address the question of why is renal cell carcinoma different. If you look at the history of successful adjuvant therapies in breast cancer, colon cancer, bladder cancer, the common denominator is microscopic

disease curable with chemotherapy, microscopic disease not curable with chemotherapy. We have a number of renal cell carcinoma experts here. I'm not aware of any analogous situation in renal cell carcinoma where micrometastasis somehow has a different sensitivity than macro disease.

You see this even in renal cell particularly compared to other tumors. You see macro disease that responds very well despite its size and bulk. I do think there's a difference in the natural history and biology of renal cell carcinoma. Whether that's an ironclad principle that you can use for drug development, it's probably not, but it's an observation that I have made. I think others probably have as well.

DR. ULDRICK: Any further comments, discussion?

(No response.)

DR. ULDRICK: Does anyone want to comment on the safety profile, the concept of the burden of treatment that you brought up, Dr. Pagliaro, after hearing the totality of the data today? Have you

changed your thoughts on that?

DR. PAGLIARO: The burden of the treatment, I think my takeaway conclusion about that is -- it may be similar to Dr. Redman, and correct me if I'm wrong, but it's a year of sunitinib now to avoid a year of sunitinib later. I don't see the net benefit in terms of the number of patient years of treatment to get the same end result.

DR. ULDRICK: Anyone from the FDA want to comment on time to subsequent therapy in relation to this comment?

DR. MAHER: Not at this point, no.

DR. ULDRICK: If there's no further discussion on this question, we will now begin the voting process. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you've entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may

press the corresponding button until the vote is closed.

After everyone has completed their vote, the vote will be locked. The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to.

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

(Voting.)

DR. CHEE: For question 1, we have 6 yeses, 6 nos, and zero abstain.

DR. ULDRICK: Now that the vote is complete,

we'll go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record.

Start with Dr. Bukowski -- I'm sorry. We can start at the end of the table.

DR. SRINIVASAN: Ram Srinivasan. I voted yes. This was one of the most difficult decisions I've had to make, as you can tell from the vote. What really swayed me was the fact that we do have a well-designed randomized study that shows benefit in DFS, an endpoint that, as has been pointed out numerous times, has been the basis for approval for many different agents in many different malignancies in the adjuvant setting.

Seeing the data, it's hard to at least offer physicians and patients the opportunity to discuss these data and then make the choice for themselves as to whether this agent is appropriate or not for them in that setting. So that's really what swayed my vote.

DR. REDMAN: I agree with what's just

stated, but however, my problem is again sitting in front of --

DR. ULDRICK: Can you just state what you voted, please, and your --

DR. REDMAN: Bruce Redman, University of Michigan. No. The problem I have is, again, going back and sitting in front of a patient, being able to digest this data and help them digest this data, telling them that it's going to delay the recurrence of their disease.

The specific disease we're talking about is kidney cancer. I did not see data that supported that. To tell them even that this may delay enough of an onset that we're going to delay the onset of time that you're going to need additional treatment, which is a clinically relevant question, and I did not see the data to support that.

DR. BUKOWSKI: Bukowski. I voted yes. The things that influenced me were the conduct of a study that was well-designed and was positive, and utilizing a drug that has clear benefit in the metastatic disease situation. So to extrapolate

from there to an adjuvant setting with a positive study seems reasonable.

The risk-benefit issue is the side effect profile of Sutent prohibitive to prevent one from using it for a year in a well patient, I think the answer is no. And I thought that this drug should be approved potentially and offered to patients in the adjuvant setting who have a high risk of recurrence.

I think disease-free survival, although not validated in renal cancer, is probably the only endpoint that we have at the present time in this disease in this setting to test a drug. And all of the drugs we're utilizing in the adjuvant trials are utilizing that as the endpoint.

DR. PAGLIARO: Lance Pagliaro, Mayo Clinic. I voted no. The background for this presumed benefit is a standard of care where we can give patients the opportunity to remain disease free without treatment and to target our treatment to the patients who need it, and then to tailor it based on their response. I think that in light of

all the evidence we've seen today, the patients are still best served by taking that wait-and-see approach.

The administration of sunitinib across the board to patients who are both destined to recur and not destined to recur, patients whose disease is responsive and is not responsive results in a net increase in exposure to the therapy and its consequences without a corresponding benefit in terms of cancer mortality or survival duration until death from any cause or burden of therapy. So I'm hard pressed to see how that is a better option that the current status quo.

DR. LUMLEY: I'm Dan Lumley, patient rep, and I voted yes. I wanted to tell you a very brief story as to why I voted yes.

About 17 years ago, my urologist in Kansas City called me and he said, "Dan, we've got the scan back, and you have kidney cancer." He did it nicer than that. I was stunned.

I was so stunned that I said to him, "Doc, is this going to get me?" And he says, "No, I

don't think so." He says, "There's hope."

When my wife came home, I said, "I have kidney cancer, but I'm thinking of Bill Clinton." She said, "Are you nuts? Why are you thinking of Bill Clinton?" I said, "Because he always said he was from a town named Hope, and I have hope that I'm going to survive this."

So I feel this drug provides patients with some hope.

MS. PREUSSE: Courtney Preusse, consumer rep. I'm going to counter what Dan said. And this was a very difficult counter because I did listen to the personal stories from the audience members, and I thank them for standing up and sharing their stories.

I am here to represent consumers of this drug, of drugs that are approved by the FDA, so I take this responsibility extremely seriously. At the same time, I feel that approving this drug -- I voted no, and I did so because I feel that approving this drug would provide false hope to patients.

I feel that the data is immature. I feel that there are still too many questions to be answered regarding overall survival, regarding what sort of patients are benefitting from this type of treatment. And I feel that elevating this drug out of clinical trial status into full FDA approval would somehow elevate it above all the other investigations that are currently ongoing in clinical trials.

I don't feel that it's in a place right now where it can be elevated. It's still too investigational, and it needs to be pursued just like the 200 other trials in clinicaltrials.gov. And until we have more concrete answers, there are options. It may require travel. It may require signing up for a clinical trial. But it keeps everything at the same baseline for further investigation.

DR. NOWAKOWSKI: Greg Nowakowski. I voted no for the reasons partially already mentioned. I think although the S-TRAC study was well-conducted, I think we couldn't shake off this shadow of the

larger ASSURE study, which did not necessarily show this benefit despite all the differences and interpretation difficulties, which we discussed.

Furthermore, disease-free survival, the major benefit of being disease free is delaying the time of next treatment and side effects from next treatment. Although some trend, we did not necessarily see that this was significantly different, and there was no difference in overall survival.

Most of all, the therapy is not benign. It's actually quite toxic for adjuvant therapy. So putting this together, I voted no.

DR. BURSTEIN: Harold Burstein from Dana Farber. I voted no as well. I want to thank as always our public speakers, who did a beautiful job of presenting some of the challenges of renal cell carcinoma. It's an insidious and difficult disease. It's a disease for which we do not have a screening modality, and it's a disease where surgery remains the gold standard of treatment, and that hasn't really changed in decades. So it's not

that there isn't a critical need here.

I voted no because I wasn't convinced that the collective experience I saw suggested that TKIs help prevent recurrence of this disease. The two questions I had coming in were, was there something different about the risk profile of patients in S-TRAC that distinguished the result from the ASSURE trial or the PROTECT trial, and was there a clear signal that the dosing maintenance somehow was accounting for that difference if it wasn't risk.

In the end, I wasn't convinced there was a difference of the populations broadly speaking, and I wasn't seeing a clear signal that maintaining the dose as the effort was done in S-TRAC really could account for that difference in comparison to the ASSURE trial.

The secondary considerations in my own mind were what's already been said, that there was no specific difference in kidney cancer-free recurrence; that there was no difference in the time to initiation of therapy; that the

investigator-reported outcomes tended to be more similar in S-TRAC and of course were the same in ASSURE; and that the related study with an interchangeable drug in a metastatic setting of pazopanib showed no benefit in the adjuvant setting.

I think the toxicity questions in my own mind are harder. Patients will endure god-awful toxicity in the adjuvant setting if they think it will really help them. We used Adriamycin for a long time in breast cancer, which arguably is the worst drug anyone's ever gotten for anything. It makes you feel terrible, and patients happily accepted it if they thought it would provide meaningful benefit.

So I'm sympathetic to the argument that doctors and patients can make those individualized decisions. I just didn't see the clear signal of benefit here.

DR. ULDRICK: Thomas Uldrick, Center for Cancer Research. I voted yes. I thought that this was a well-conducted study. I was convinced by the

argument that the patient selection, specifically around the histology but also the T3/T4 tumors, was convincing.

I do think that the risk-benefit profile has to take into consideration the side effects, but I believe this is something that could be negotiated between patients and doctors. And importantly, it's reversible.

In regards to the question related to disease-free survival in this disease, it seems that this is one of many studies that have looked at disease-free survival as a primary endpoint. Although the natural history of renal cell carcinoma is different than some of the other diseases, I did not hear a convincing argument why it should not be used as disease-free survival endpoint. And again, many other studies in this area have used this endpoint.

DR. SHAW: Alice Shaw from Mass General, and I voted yes for many of the same reasons that we just heard about. I think the main factor swaying me was that this was a large, well-conducted,

randomized study that was positive and that this is really a huge area of unmet need for our patients.

As we just heard, I feel like we cannot say DFS is not an appropriate endpoint in renal cell carcinoma the way it is in other studies in other cancer types. We just don't have the data that can justify saying we can't use DFS. We don't know for certain that DFS will definitely translate, but we also don't have data saying that it won't translate into real clinical benefit and OS benefit.

I would also comment about the safety profile. I think the S-TRAC study was actually reassuring in that we saw a very similar safety signal to what's been reported, that the safety issues that are known to come up with sunitinib are almost always reversible, and they also can often be managed by dose interruption and reduction. But I think it does point out that this is a challenging drug. Patients do really have to be very carefully selected and counseled and managed as well.

Then I would just highlight one final point

about -- and this was mentioned earlier in our discussion, about how important it is for us to do these correlative studies within this S-TRAC study and identify the biomarkers so that we do know which patients will benefit and which ones will not so that we don't expose patients to a toxic therapy. We can do this better hopefully in the future. Thanks.

DR. HOFFMAN: Philip Hoffman from University of Chicago. I voted yes. I don't find any particular flaws about this study and did not feel that we should penalize it because the other study didn't match it. We've heard a lot of discussion about reasons why there may have been differences and so on. And I can't comment so much on the statistical aspects of that, but this was a positive study.

While it is true that we don't have overall survival information, the natural history of kidney cancer is a very long natural history. Late recurrences are fairly common, so I think that this may come and it may turn out that it won't. And

certainly, in the world of oncology, treatments have come and gone, and if in 10 years, this doesn't bear out, it will stop being used for this purpose.

I did find the arguments of Drs. George and Figlin compelling as a clinician myself, that the potential to be disease free, even if the overall survival we don't yet know, is an important point for patients, and it's something that patients strive for. And with appropriate selection and management of toxicity, I think that it's reasonable to approve this.

DR. HALABI: I'm Susan Halabi at Duke University. I voted no, and similar to my peers, I struggled with this vote.

Just to give you a brief background on me, I'm a statistician who has been designing clinical trials in the GU space. So of course, when I see something positive, it's exciting.

Similar to my peers, the signal wasn't very clear, though, and the thing that I was struggling most with was the robustness of the data, if we can

make the decision based on 257 events.

To clarify, I have no issues using DFS as a primary endpoint because similar to other diseases, colon and breast in the adjuvant setting, it has been extensively used. But to base a decision on 257 events when the confidence interval almost touches 1 is troubling. And when you look at the toxicity profile, it looks to me a little bit excessive as expected in the Sutent arm.

Finally, the thing that persuaded me looking at the ASSURE data, I had problems consolidating and compromising the data from the ASSURE trial with that of S-TRAC. Thank you.

DR. PAZDUR: Well, that's the end of the vote. I'm glad we came to a consensus here.

(Laughter.)

DR. PAZDUR: It makes our job infinitely more easier when we have a uniform recommendation from the committee.

Interestingly enough, we have these same debates internally among all of the reviewers here, and that's the reason why we brought this to an

ODAC meeting. I'm somewhat happy to see that we're not isolated in our own questions that we have regarding this application.

Again, we'd like to thank everybody for their discussion here. The points are well made. We've made them ourselves internally.

For the FDA tea leaf readers and the trade press, et cetera, we'll have our definitive decision regarding this application on or before the PDUFA due date.

Thank you very much, and we appreciate your discussion of this application. We realize how complicated and how different opinions can come to bear in making a decision and the difficulty of making that decision. Again, thanks for the consensus. We appreciate it.

(Laughter.)

Adjournment

DR. ULDRICK: Thanks. We will now adjourn the meeting. Panel members, please leave your name badge here on the table so they may be recycled. Please also take all personal belongings with you

as the room is cleaned at the end of the meeting day. Meeting materials left on the table will be disposed of. Thank you.

(Whereupon, at 12:04 p.m., the meeting was adjourned.)