FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUG ADVISORY COMMITTEE (ODAC)

Wednesday, February 26, 2020

8:00 a.m. to 12:11 p.m.

Morning Session

FDA White Oak Campus

Building 31, the Great Room

10903 New Hampshire Avenue

Silver Spring, Maryland

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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

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. HOFFMAN: Good morning. I'd first like to remind everyone to please silence your cell phones, smartphones, and any other devices if you've not already done so. I would also like to identify the FDA press contact, Brittney Manchester. If you're present, please stand. Thank you.

My name is Philip Hoffman. I'm the chairperson for this meeting. I'll now call the morning's session of today's meeting of the Oncologic Drugs Advisory Committee to order. We'll start by going around the table and introduce ourselves. We'll start with the FDA to my left and go around the table.

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

DR. KLUETZ: Paul Kluetz, deputy director, Oncology Center of Excellence.

DR. BEAVER: Julia Beaver, director of Division of Oncology 1.

DR. WEINSTOCK: Chana Weinstock, team lead for this application.

DR. AGRAWAL: Sundeep Agrawal, medical reviewer for this application.

DR. GAO: Cindy Gao, statistical reviewer for this application.

DR. RINI: Brian Rini, a GU medical oncologist from Vanderbilt.

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

DR. HINRICHS: Christian Hinrichs, investigator, National Cancer Institute.

DR. KLEPIN: Heidi Klepin, geriatric oncologist, Wake Forest School of Medicine.

DR. HOTAKI: Lauren Tesh Hotaki, designated federal officer.

DR. HOFFMAN: Philip Hoffman, medical oncologist, University of Chicago.

DR. CRISTOFANILLI: Massimo Cristofanilli, medical oncologist, Northwest University.

DR. GARCIA: Jorge Garcia, GU medical oncologist, formerly at the Cleveland Clinic, transitioning to become the division chair at Simon Cancer Center at Case.

DR. HAWKINS: Randy Hawkins, internal medicine and pulmonary medicine, Charles University, consumer representative.

MR. KUNGEL: Terry Kungel with the Maine Coalition to Fight Prostate Cancer, patient representative.

DR. SIDDIQUI: Mohummad Siddiqui, urologist at the University of Maryland and Baltimore VA Medical Center.

DR. HUSSAIN: Maha Hussain, GU medical oncologist, Northwestern University.

DR. MAKAROV: Dan Makarov, urologist, NYU.

DR. SANDLER: Howard Sandler, radiation oncologist, Cedar Sinai in Los Angeles.

DR. WALSH: Patrick Walsh, urologist, Johns Hopkins.

DR. CHENG: Jon Cheng, medical oncology, industry rep, and I also work with Merck.

DR. HOFFMAN: For topics such as those being discussed at today's meeting.

DR. HOFFMAN: 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'll pass it to Dr. Lauren Hotaki, who will read the Conflict of Interest Statement.

DR. HOTAKI: Dr. Song, would you mind introducing yourself for the record, please?

DR. SONG: My name is Daniel Song. I'm a radiation oncologist professor at Johns Hopkins.

Conflict of Interest Statement

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

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

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those founded 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 interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services, which the government may expect from the employee.

Related to the discussion of today's

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

The morning session of today's agenda involves discussion of new drug application 212578 for padeliporfin di-potassium powder for solution injected submitted by STEBA Biotech, S.A. The proposed indication for use of this product is for the treatment of patients with localized prostate cancer meeting the following criteria, stage T1 through T2a; and prostate-specific antigen less than or equal to 10 nanograms per mL; and Gleason's grade group 1 based on transrectal ultrasound-guided biopsy or unilateral Gleason grade group 2, based on multiparametric magnetic

resonance imaging-targeted biopsy with less than 50 percent of cores positive.

This is a particular matters meaning during which specific matters related to STEBA Biotech's NDA will be discussed. Based on the agenda for today's morning session and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting. To ensure transparency, we encourage all 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 the Dr. Jonathan Cheng is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. Dr. Cheng's role at this meeting is to represent industry in general and not any particular company. Dr. Cheng is employed by Merck Research Laboratories.

With regard to FDA's guest speaker, the

agency has determined that the information to be provided by this speaker is essential. The following interests are being made public to allow the audience to objectively evaluate any presentation and/or comments made by the speaker.

Dr. Jim Hu has acknowledged that he is a principal investigator on a Patient-Centered Outcomes Research Institute awarded study, PCORI CER-2019C1-15682, titled Prostate Cancer Comparative Outcomes of New Conceptual Paradigms for Treatment. As a guest speaker, Dr. Hu will not participate in committee deliberations, nor will he vote.

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 our exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial

relationships that they have with the firm at issue. Thank you.

DR. HOFFMAN: Alright. We will now proceed with the FDA's opening remarks from Dr. Chana Weinstock.

FDA Opening Remarks - Chana Weinstock

DR. WEINSTOCK: Good morning. My name is Chana Weinstock, and I am a medical oncologist who is the team lead for this new drug application for TOOKAD.

The proposed indication for TOOKAD is for the treatment of patients with localized prostate cancer meeting the following criteria: stage T1 to T2a; a PSA less than 10 nanograms per milliliter; Gleason grade group 1 based on transrectal ultrasound biopsy; or unilateral Gleason grade group 2 based on multiparametric MRI-targeted biopsy with less than 50 percent of cores positive.

We note that the applicant has included some patients with intermediate risk disease in this proposed indication. As we will review shortly, patients with intermediate risk prostate cancer

were not enrolled on the randomized trial PCM301 submitted in support of this application. The ODAC is therefore asked to discuss only the issues surrounding the enrolled population; that is patients with low-risk localized prostate cancer diagnosed with transrectal ultrasound biopsy.

As we begin our discussion of this application, I'm going to take a moment to reorient your thinking about the data that you're about to review. As this may not be the sort of risk-benefit calculus you may be used to using in evaluating trials of anticancer agents, the objective of most cancer trials is to demonstrate antitumor efficacy of an anticancer agent with the goal of delaying or preventing cancer-related morbidity or mortality.

Endpoints used for this purpose might include progression-free and overall survival. However, the objective of a focal therapy in an active surveillance population is to demonstrate a reduction in the need to undergo a morbid procedure such as radical prostatectomy or radiation, with

results in delay or prevention of procedure-related morbidity such as sexual or urinary dysfunction. Endpoints for this purpose could be the rate of those who subsequently undergo surgery or radiation, rates of pathologic upgrade and safety, and long-term morbidity outcomes.

To provide some context to today's discussion, low-risk prostate cancer patients were often historically treated with prostatectomy or radiation. However, active surveillance has become the preferred management strategy for those with a reasonable life expectancy since it is increasingly clear that some patients with clinically insignificant disease are at risk of over-treatment. However, many patients still undergo prostatectomy or radiation during surveillance, up to 40 percent within the first 5 years.

With these factors in mind, an FDA workshop held in 2018 discussed a novel trial endpoint for focal therapies versus active surveillance in men with localized prostate cancer. The overall goal

would be to decrease pathologic upgrade, and panelists opined that this endpoint might represent clinical benefit if this was also accompanied by an overall decrease in rate of definitive therapy and an overall decrease in long-term toxicity, both physician and patient reported.

The submitted trial, PCM301, was conducted and designed prior to the 2018 workshop. It studied patients with low-risk prostate cancer randomized to TOOKAD treatment plus subsequent surveillance versus active surveillance alone. The co-primary endpoints assessed absence of cancer and time to disease progression. Scheduled biopsies were done at 12 and 24 months. We also, again, note that there were no intermediate risk patients enrolled. We also note that the trial design was open label.

The sponsor added a study extension to collect an additional 5 years of data. However, as biopsy and safety data were not collected in a uniform and rigorous manner, FDA considers only the primary two-year study as the basis for this

application.

The study met its co-primary endpoints with an increase in patients whose biopsies were absence of cancer and a decreased time to cancer progression on the TOOKAD arm at 2 years. Although no alpha was allocated and despite the subjective nature of this endpoint, more patients on the active surveillance arm underwent definitive therapy at 2 years.

FDA will be raising key issues today related to the interpretation of these results. Are the study defined endpoints appropriate to characterize benefit? Is the demonstrated safety profile of TOOKAD acceptable? Do uncertainties around trial data allow for a reasonable overall assessment of benefit and risk?

First, the endpoints. Endpoint A, absence of definitive cancer at 24 months in these patients is inherently difficult to interpret due to the fact that, by definition, all patients managed with active surveillance have cancer at baseline, and without further intervention, none should have

cancer absent.

Point B, decreased disease progression; since pathologic upgrade may trigger clinical intervention, improvement in this endpoint may have clinical implications if use of definitive therapy and resultant toxicity also decrease. However, individual components of this composite endpoint may not be objective clinical triggers for intervention. Additionally, whether endpoint be demonstrated a meaningful benefit in PCM301 is unclear, as overall toxicity rates were high.

The safety profile. If TOOKAD caused as much toxicity as definitive therapy, that would be problematic, as unlike active surveillance, all patients on the TOOKAD arm received this therapy upfront. And although urinary dysfunction was similar between arms in the long term, the rate of unresolved erectile dysfunction at month 24 for TOOKAD was 23 percent; and with a limited follow-up time of only 2 years, the possibility of a compromised cure rate and potential harm for patients needing definitive therapy at some point

after an initial TOOKAD remains unknown.

There are data uncertainties. In terms of efficacy, both co-primary endpoints are based on biopsy data, however, biopsy in this setting may be unreliable. This is illustrated by the 13 percent missing month 24 biopsy data in addition to false negative biopsies, which were 14 percent on the active surveillance arm.

We also note that there was potential for unblinding of the central pathologist due to necrosis on histology specimens in the TOOKAD arm. Additionally, there are other sampling errors and misattributions that could potentially occur in this setting.

In terms of safety, many patients stopped reporting adverse events after undergoing definitive therapy. This disproportionately affects the active surveillance arm versus the TOOKAD arm, 19 percent versus 2 percent overall. This is problematic, as the data uncertainty makes it difficult for an accurate benefit-risk assessment.

There's also a planned trial, PCM306, designed with FDA input that may help to address many of the issues noted in review of PCM301. This will be done in a favorable intermediate risk population and will randomize patients to TOOKAD versus active surveillance.

Initial biopsy will be done using multiparametric MRI. Follow-up biopsies will be scheduled for up to 5 years, providing long-term endpoint data. Longer follow-up will include careful collection of safety and PRO data for all patients, including for those who undergo definitive therapy. Triggers for determining referral for definitive therapy will be prespecified to help reduce the subjectivity associated with this decision. The protocol for this trial is finalized and enrollment is set to begin.

Our voting question is therefore as follows. Do the results of PCM301 represent a favorable risk-benefit profile for TOOKAD in patients with low-risk, early-stage prostate cancer?

Thank you. Dr. Hu will now discuss the treatment landscape for localized prostate cancer.

Guest Presentation - Jim Hu

DR. HU: Good morning. Thanks for the opportunity to the FDA and the committee for giving an update on the current landscape for diagnosis and treatment of non-high-risk prostate cancer. I was just given some general guideposts to aid the discussion today, and this is the outline of the talk that I'll give.

I'll briefly go over prostate cancer epidemiology and discuss the contemporary approach to diagnosis of prostate cancer; how there are precision medicine and other biomarkers that are being used to improve prostate cancer risk stratification; the current treatment options for men with this risk stratification; as well as the challenges to partial gland ablation.

I think this is an important figure to consider given the screening of prostate cancer and the resultant decrease in metastatic disease, and compares mammography for breast cancer as well as

the advent of PSA for prostate cancer screening. One can see that the incidence of metastatic disease dropped precipitously after the advent of PSA in the early 1990s. Additionally, we can compare this recent graphic from the American Cancer Society website that gives the incidence rate of prostate cancer as well as the mortality relative to breast cancer, as far as incidence in lung cancer and breast as far as mortality.

In terms of death rates, we can also see that after the early 1990s, prostate cancer specific mortality also declined. However, when we look at recent statistics from the American Cancer Society, you can see that the incidence of prostate cancer reached a low in 2017 and has recently increased, and we'll see reasons why; as well as the death rate also nadired around 2016-2017 and has recently been going up. The lifetime risk of prostate cancer diagnosis is 1 in 9, and the prevalence is 3 million.

We were fortunate to look at the SEER database, Surveillance, Epidemiology, and End

Results, and determine that the likelihood of metastatic disease at diagnosis was increasing in 2012 and 2013 relative to 2011. There were questions whether this was detection bias and was it use of molecular imaging?

Some of the guideline recommendations, I think, around this time may answer the question of changes in epidemiologic figures that I showed earlier. In 2012, the Preventative Services Task Force recommended against PSA screening regardless of age. 2018, this was revised to a grade C, which is an individualized decision.

This is a recent story from this month from the Harvard Gazette in which a non-urologist comments that in 2020, rates of aggressive prostate cancer are going up. As we've seen from the figures, more men are dying of prostate cancer, and despite better therapeutics, we're not doing a good job in screening.

This is a infographic that the U.S. Preventative Services Task Force puts out, and it gives the relative benefit of PSA screening as well

as the harms of screening. One can see that one of the harms, of course, is the false positive rate as well as the side effects of biopsy, which include pain, bleeding, and infection.

This is a schematic of how most biopsies are currently done in the United States that is through a transrectal approach. Infection rates have been noted to be as much as 7 percent in population-based analyses of Medicare data.

Recently, this randomized trial looked at the use of an MRI-targeted approach; that is patients got an MRI first of the prostate in the figure on the left, and then secondly underwent a fusion with ultrasonography, overlaying the MRI and the region of interest. In this particular study, they randomized roughly 250 men to an MRI for elevated PSA versus going straight to a standard biopsy that I showed earlier.

One can see that 28 percent of men in the MRI-targeted arm avoided a biopsy because they had on the PIRAS 1's and 2's. PIRAS is the classification system for MRI and also the

MRI-targeted approach; that is biopsying only the area of interest led to 12 percent greater detection of clinically significant prostate cancer grade group 2 or higher, as well as a 13 percent decrease in the diagnosis of indolent grade group 1 cancer.

There's also a movement now in our field that I think has been promulgated more in Europe towards a transperineal approach to biopsy. There was traditional dogma that under local anesthesia, a transperineal approach would be too uncomfortable.

One of the purported benefits is that a transperineal approach could also improve sampling of the anterior zone of the prostate. It's been noted by several studies that African American men are more likely to have anterior tumors, and hence, there's a movement towards this approach.

One of the guidelines or paradigms to examine innovations in surgery or techniques is what's called the ideal classification. This is an idea, development, evaluation, and long-term

assessment, and this is now in stage 2A in terms of an MRI-targeted approach to transperineal biopsy under local anesthesia.

I'll just add that I think this is of relevance because for target therapies, that is for partial gland ablation, this will allow an approach in the office, rather than general anesthesia, that I think we'll see upcoming with other applications. In terms of evaluating this approach, I'm fortunate to have other co-investigators, a multi-PI mechanism, from Johns Hopkins, Northwestern, et cetera, and we'll examine whether or not this approach bears out.

In terms of the infographic as well, there's mention that 20 to 50 percent of men diagnosed with prostate cancer have indolent disease. When we look at the NCCN guidelines for low-risk disease, for those with a life expectancy less than 10 years, observation is what's recommended. Then we have our standard treatments, including active surveillance; EBRT, external beam radiotherapy or brachy; as well as radical prostatectomy.

In 2015, it was noted that it used to be that all who have been diagnosed with localized disease underwent definitive therapy, however, half of men now are choosing to monitor the prostate cancer.

Dr. Makarov, who's here today on the panel, nicely did work from the Veterans Administration showing that for men less than 65, as well as those older than 65 in the bottom panel, there's been increased adoption of conservative management, whether that be active surveillance that is monitoring with curative intent or watchful waiting where there's no intervention until there's signs of disease.

When we look at the current landscape in terms of competing treatments for prostate cancer, this again comes from surveillance epidemiology, and results are SEER, showing that there has been an uptake in active surveillance regardless of risk stratification, as well as a decline in definitive therapy. When we look at favorable intermediate risk disease, we can see that those with less than

10-year life expectancy, again, there's observation that's preferred. And even for those with greater than 10-year life expectancy, active surveillance is recommended to be considered as a treatment option.

For unfavorable disease, we can see that there's the addition of androgen deprivation therapy for those who are considering radiation therapy, as level 1 evidence has demonstrated benefit for this. Again, when we break down the CR data by intermediate risk disease, we see upward inflection in terms of adoption of monitoring.

Just to close out the NCCN recommendations, there was actually a statement about the use of biomarkers such as Decipher, Oncotype, Prolaris, ProMark, such that men with lower or favorable intermediate risk disease should consider this to improve risk stratification. This was highlighted in a Wall Street Journal article discussing the use of these biomarkers.

Before I delve into that, I'll just mention that when we look at traditional staging or grading

for prostate cancer, we can see that the Gleason score goes from 6 to 10. This has been revised to grade grouping, however, it was noted in this study from the Martini Klinik that when one looks at the percent of pattern 4, that gives a finer risk stratification, and as such, this has been adopted by most pathologists for favorable intermediate risk disease, giving the percent pattern 4.

When we look at our own targeted-biopsy experience to determine when we target the MRI abnormal areas as well as do systematic biopsies, how are we doing relative to accurate stratification in men who ultimately went to radical prostatectomy, we find that, still, about a third of men had an increase in NCCN risk. When we had the entire radical prostatectomy specimen to examine, 12 percent had a decrease in NCCN risk. There was a 25 percent discordance in terms of upgrading a radical prostatectomy and 22 percent downgrading, and upstaging was found in 29 percent.

This is just a schematic demonstrating the typical resulting of a precision medicine test, and

it just shows that the endpoints there highlighted below our freedom from high-grade disease or freedom from non-organ confined disease; that is pathologic T3 disease. This is scored from 0 to 100, this GPS score, and also takes into consideration conventional NCCN stratification variables, that is PSA Gleason score and clinical stage.

When we look at how this performs in an active surveillance cohort, this comes from UCSF and shows that in those with adverse pathology highlighted here in red, one can see that as the GPS score on the 0 to 100 scale on the Y-axis increased, there is a greater likelihood of the red bars in this waterfall plot. The solid line just indicates the 75th percentile. The median GPS in this cohort was 26.

Then in multivariable analysis, the UCSF group found that for a 5-unit increase in the GPS score, there was a significant increase in the hazard ratio for both adverse pathology as well as biochemical recurrence in these 215 men who

initially started on active surveillance and then had a delayed radical prostatectomy.

This has also been shown in terms of adding a score of the conventional NCCN to the genomic classifier or the Decipher score. Summing that to a 1 to 5 score led to a better area under the curve in terms of prediction for metastatic disease as shown on the right versus your conventional NCCN risk stratification.

However, a group from the University of Michigan looked radical prostatectomy specimens and asked whether or not these genomic classifiers can differentiate between prostate cancers that have intratumor heterogeneity and/or multifocality.

On panel A, they demonstrate that for grade group 1 through 5, there is an increase in the three of the commercially available RNA expression-based biopsy tests as one would hope to find; then they also looked at in panel C, comparing these three genomic classifier scores of men with a grade group 1 alone on the left of panel C and whether their scores differed from those who

had great group 1 and tumor multifocality.

They found at least that there was no difference in the ability for these genomic scores to pick up on a tumor heterogeneity or a hidden higher grade cancer. They also added that these tests may cost up to $4500 per test, as well as the fact that 70 percent of men diagnosed with prostate cancer may be eligible for these tests. In an aggregate, these tests may cost $250 million annually.

In terms of the harms of treatment for prostate cancer, I would just highlight here that this infographic states that the risk of erectile dysfunction is 50 out of the 80 men treated. It may be mistaken that this is 15 percent and the risk of urinary incontinence is 15 percent, but rather it's about a 60 percent risk of ED as well as a 20 percent risk of urinary incontinence. When we look at the average age now that men are diagnosed with prostate cancer, that's age 66, one has to keep in mind that as men get older, there's a natural increase in the prevalence of erectile

dysfunction.

This is also an example of direct-to-consumer advertising about CyberKnife or SBRT. I think certainly this has increased patient convenience in terms of 5 treatments over 2 weeks rather than the standard daily treatments up to 7 or 8 weeks. When we looked at the likelihood over time, one can see that the use of SBRT is increasing and it's more so used for low-risk disease. Interestingly enough, in the higher risk disease, a androgen deprivation therapy wasn't used as much as the guidelines would advocate for.

In a workshop with the American Neurological Association, as well as the Society for Urologic Oncology, there was a public forum where patients had a chance to express their desire for a focal therapy approach, that this would be, quote/unquote, "a promise from heaven." Men who choose active surveillance, many of them dread the biopsies, and it was stated here that many of them would rather have a partial gland approach.

When we look at, for instance, surgical

treatment for prostate cancer, of course these men oftentimes have no ejaculate or even climacteria. There's a trade-off between cancer control and erectile dysfunction in some cases, as well as urinary continence. The paradigm for partial gland ablation is to perhaps give up a little bit in terms of cancer control but have an increase in the likelihood of preservation of ejaculatory, urinary, as well as sexual function.

This is just a schematic of the different energy modalities that have been described to conduct partial gland ablation. When we look at the current tools -- and I mentioned the MRI as being a very widely used biomarker -- this is a nice study conducted from UCLA where they looked at whole-mount pathology as well as the region of interest.

In panel B, that's an axial image MRI; panel C is a coronal. One can see that compared to the whole mount in red, the MRI in this case underpredicts the tumor border, and it was estimated that this was about 13 millimeters

overall. I think this has led to, amongst those who do focal therapy, the idea of treating beyond the border.

In another paper that looked at the eligibility, the UCLA group again looked at those who were diagnosed with a favorable intermediate risk prostate cancer and looked at the fact that when they went to radical prostatectomy and whole mount, what would be the eligibility, and found that about 39 percent of men who had a targeted biopsy would be eligible for focal therapy.

Furthermore, they found that of those men who were eligible, the biopsy was concordant with whole mount pathology in 75 percent of cases. However, there was a recent study from Europe that demonstrated at 6 months after high intensity focused ultrasound, biopsies were conducted, and 41 percent of these men had clinically significant disease. Yet, when the UCLA group looked at their use of hemiablation in follow-up biopsies, they also found a 21 percent risk of persistent disease.

Going back to the schematic, A shows that

the region of interest was diagnosed there with MRI-targeted biopsy. The follow-up biopsies were performed such that only the half of the prostate that was treated was biopsied. Again, here you can see that there was 21 percent persistent intermediate risk or higher disease.

When we looked at our own partial gland experience with cryotherapy, we looked at some of the MRI characteristics post-treatment. I think this is relevant because it begs the question, how do you conduct your biopsies to get to the endpoint of ablation and success.

Just from this schematic, this is pretreatment versus post-treatment MRI and the red area is the region of interest. One can see there's a little bit of a distortion, as well as loss of volume, which one would expect after partial gland ablation. When one looks at the MRI characteristics here, you can see that there's a change, and there's not a consistent pattern in terms of region of interest changes one can see, as well as the volume reduction.

We also asked our pathologist to grade or assess whether or not there's treatment effect present or absent, and one can see that in the targeted region of interest after treatment where we biopsy, sometimes there's an absence of a treatment effect.

This is just a schematic again that follows longitudinally a patient that went to radical prostatectomy. I think in panel E and G, you can see that we've ablated the right anterior part of the prostate, and you can see that the left side actually bulges over.

Where this is going is the question of how do you consistently conduct a targeted biopsy to determine successful endpoints as far as histology when there's going to be variation in the configuration of the prostate?

As part of the effort to look at partial gland ablation and its safety and outcomes, we've partnered with the FDA, Charlie Viviano, Ben Fisher, Denesed Abnovich [ph]. Michael Gorin is also here from Johns Hopkins who's hosting a REDCap

database. My partner Art Sedrakyan has U01 funding for us to do this. We've looked at developing a coordinated registry network to look carefully at the outcomes of ablation regardless of energy modality, as well as looked carefully at patient selection.

This is a schematic that Dr. Weinstock showed earlier, so I'm not going to belabor this further, but this came out from the July 2018 meeting where primary endpoints of local progression or secondary endpoints delay to definitive therapy were discussed in a randomized trial setting.

Hash Ahmed asked can we deliver randomized trials for focal therapy and prostate cancer, and listed here are 11 randomized trials that failed. One can see that the reason for closure on the right side is largely due to the lack of physician equipoise or lack of patient equipoise. Hence, earlier there was mention of our PCORI grant to look at comparative effectiveness studying SBRT partial gland ablation as well as the traditional

treatments and active surveillance.

I'll just highlight again, going back to this averaged outcome of the harms of treatment, 60 percent ED as well as 20 percent urinary incontinence, when Dr. Scardino, who's here today, looked with Andrew Vickers at the likelihood of erectile dysfunction as well as urinary incontinence after radical prostatectomy, one can see that there is a tremendous variation between 11 surgeons who conducted the operation, with the solid vertical bars there being the median for urinary function on the left and erectile function on the right.

So you can imagine that those population-based estimates -- and again, this was conducted at Memorial Sloan Kettering, those are our community hospitals where the surgeon volume is going to be much lower in this study. As well, it was noted that for surgeons who perform 25 radical prostatectomies a year, the likelihood of achieving both urinary continence as well as erectile function was around 21 percent, and this increased

to 47 percent when the annual surgeon volume was about over a hundred.

Just pointing out, for myself, I think it's important for those who do focal therapy to also be experts at other treatment options for prostate cancer, that is active surveillance and definitive therapy, to decrease the absence of physician equipoise. Fortunately, just to point out, Dr. Walsh is here today, and I'm fortunate to work with him on a technique to decrease the likelihood of urinary incontinence.

In summary, I would say in terms of the randomized trials, again, physician equipoise is critical. When we look at our field currently, I think there is a subdivision of labor in terms of those who -- in Europe, or the UK, there's a labeling of those who do focal therapy as the focalists, whereas the people that do radical prostatectomies are the roboticists. That division of labor I think needs to be solved for there to be fairness to the patient.

Finally, in terms of value, defined as

outcomes over cost by Michael Porter at Harvard Business School, in focal therapy fields up front, we looked at the longitudinal costs of treatment. We see that that's going to increase over time, so consideration to get it right the first time.

In conclusion, we've covered topics talking about the controversies over PSA screening as well as the shift to transperineal biopsy, which I think will also hold promise for focal therapy approaches done in the office. We talked about biomarkers as well as RNA-based expression profiles in MRI to improve risk stratification, as well as the advent of SBRT to increase patient convenience, and the challenges of partial gland ablation in terms of patient selection and identifying endpoints. Thank you.

DR. HOFFMAN: Thank you very much, Dr. Hu.

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

understand the context of an individual's presentation.

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

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

We'll now proceed with the applicant's presentations.

Applicant Presentation - John Rewcastle

DR. REWCASTLE: Good morning. My name is John Rewcastle, and I'm the head of U.S. regulatory

at STEBA Biotech. We are pleased to be here today to present data from our Study 301, a randomized clinical trial supporting a novel therapy for localized prostate cancer.

These data demonstrate that TOOKAD vascular-targeted, photodynamic therapy, TOOKAD VTP, is more effective than active surveillance and less morbid than radical therapy with a positive benefit-risk profile. It is a new option that meets an important need in localized prostate cancer.

TOOKAD VTP is a drug device combination that includes a drug derived from phototropic bacteria and a non-thermal-like delivery system. TOOKAD is administered intravenously and is activated locally within the prostate by illuminating with low energy laser light. Upon activation, TOOKAD rapidly constricts the blood supply only in the illuminated area. This results in necrosis.

TOOKAD VTP can provide a safe and effective treatment for men with localized prostate cancer. It is a minimally invasive ablation of one lobe of

the prostate, or a hemiablation, that preserves surrounding normal tissue and thereby quality of life. Importantly, it reduces the risk of disease progression, which delays or avoids the need for radical therapy and its well-known morbidities. These are important and clinically meaningful endpoints for localized prostate cancer.

Given the relatively indolent nature of early-stage prostate cancer, traditional survival measures are not practical endpoints for clinical trials. This was discussed in detail when in July of 2018, the FDA Oncology Center of Excellence held a public workshop with multidisciplinary experts in attendance. An important conclusion from this workshop was agreement that avoidance of the morbidity of radical therapy is a clinical benefit in the management of localized prostate cancer.

Another outcome of that workshop was general agreement on trial design for registration of a prostate cancer therapy. The primary objective should be demonstrating delay or avoidance of local disease progression. The secondary objectives

should be demonstrating a delay or avoidance of radical therapy as well as a delay or prevention of short- and long-term procedure-related morbidity. The data we'll present today are consistent with these general recommendations.

We are seeking accelerated approval for TOOKAD VTP for the treatment of localized prostate cancer, meeting the criteria listed here. I'd like to point out that our indication allows for both TRUS and MRI biopsy methods. This is important because we know that TRUS biopsy undergrades prostate cancer.

If a low-risk population diagnosed with TRUS biopsy, such as the Study 301 population, underwent an MRI targeted biopsy, a significant portion of that population would be reclassified to have grade group 2 or higher disease. This effectively shifts the risk groups. The population itself is still the same, but more precise biopsy has reclassified them more accurately.

By including a subset of grade group 2 patients who underwent MRI-targeted biopsy, our

indication remains consistent with the Study 301 population, current practice, and the NCCN guidelines. For the remainder of our presentation, when we refer to low risk, we are referring to TRUS biopsy-diagnosed low risk, which is the population of Study 301.

Here's the agenda for the remainder of our presentation. Dr. Peter Scardino will discuss the need that exists in the current management of clinically localized prostate cancer. Dr. Neal Shore will review the TOOKAD procedure, followed by Dr. Henry Boodée, who will review the clinical efficacy and safety data.

Lastly, Dr. Inderbir Gill will provide his clinical perspective on the use of TOOKAD VTP. We also have additional experts with us today to help answer questions. The experts listed on this slide have been compensated for their time and travel to today's meeting. Thank you. I will now turn the lecture over to Dr. Scardino.

Applicant Presentation - Peter Scardino

DR. SCARDINO: Thank you very much,

Dr. Rewcastle.

Good morning. My name is Peter Scardino. I'm a board certified urologist specializing for the last 40 years in the diagnosis and treatment of prostate cancer. I served for more than 20 years as chief of urology, then chair of surgery at Memorial Sloan Kettering. Over the course of my career, I've written hundreds of articles about prostate cancer, treated thousands of men with surgery, and place hundreds of men on active surveillance.

I am here today, an uncompensated advisor to the sponsor and the other companies developing technology for ablation of prostate cancer, because I believe there is a major unmet need for a treatment option that bridges the gap between radical therapy and active surveillance for men with early-stage disease.

Prostate cancer is the most commonly diagnosed non-skin cancer in men in the United States with nearly 192,000 new cases expected this year. High detection rates are due in part to the

widespread use of PSA testing. Additionally, biopsy methods are now more sensitive with MR-guided biopsies targeting visible lesions added to ultrasound-guided transrectal, systematic biopsies of the prostate.

With early detection and more effective treatment, the age-adjusted mortality rate fell 52 percent between 1992 and 2014, but this has been accomplished at the cost of considerable overdiagnosis and overtreatment. This is particularly true for patients with clinically localized disease who make up most of the newly diagnosed cases today.

Detected at an early stage, these cancers grow slowly and progression to metastasis within 10 years is uncommon. It's often been said of prostate cancer that most men die with their cancer rather than of it. Hence, many argue that immediate radical prostatectomy or radiation therapy are unnecessary for many of these men who should be monitored with active surveillance.

The choice of initial management depends in

part on the prognosis of the cancer best indicated by its grade and volume. To assess a patient's risk profile and help identify appropriate treatment options, the National Comprehensive Cancer Network, or NCCN, classifies prostate cancer before treatment into 6 risk groups according to the grade, indicated by the ISUP grade group and the volume of cancer, indicated by the clinical stage; the PSA level; and the amount of cancer in biopsy cores.

For the lower risk groups, the NCCN guidelines recommend two distinct options for initial management, either active surveillance or radical therapy, depending upon the nature of the cancer, the patient's life expectancy, and his personal preferences about the risk and benefits of each treatment option.

Today, about 45 percent of these men choose active surveillance and 55 percent are treated immediately with radical prostatectomy or radiation therapy. There are other alternatives such as cryoablation or HIFU, which have been used to

ablate the part of the prostate harboring the dominant cancer, leaving the remaining prostate intact. But these and other technologies for partial gland ablation have not been tested in randomized clinical trials. None are cleared or approved by the FDA for partial bland ablation of prostate cancer and none are included in professional guidelines.

Active surveillance is now widely accepted for cancers that are expected to grow slowly. Surveillance reduces overtreatment, avoids treatment-related side effects, preserves quality of life, and allows men to maintain normal activities and work schedules. As the name implies, active surveillance requires careful monitoring, which typically include checkups every 6 months and periodic MRIs and biopsies.

But active surveillance also has distinct disadvantages. Some patients find it difficult to do nothing and live with the anxiety that their cancer could spread. If the cancer does progress on active surveillance, it may require more

intensive or multimodal treatment that could be less effective and more damaging to quality of life than if radical therapy had been chosen initially; and there is a low but real risk of dying of prostate cancer on active surveillance, about 3 to 4 percent at 15 years for low-risk cancers and 11 to 12 percent for favorable intermediate risk.

So it's not surprising that many patients with early-stage prostate cancer do not accept and their physicians won't recommend active surveillance, mainly because of their fear that the cancer will metastasize without warning.

While active surveillance avoids radical therapy and preserves important functions initially, about half of the patients who start on active surveillance convert to radical therapy over 10 years. Therefore, while acceptance of active surveillance has increased, it is not the ultimate solution for most men. In fact, three-quarters of them eventually are treated with radical therapy.

Radical therapy refers to whole-gland treatment that is typically accomplished with

surgery or radiation therapy. While radical therapy is generally successful in controlling the disease, it is not always definitive. In those with early-stage disease, the cancer will recur in about 20 percent often requiring additional salvage treatment.

Radical prostatectomy risks damage to the urinary sphincter responsible for continence and the neurovascular bundles responsible for erectile function. Radiation therapy risks damage to the bladder and the rectum, leading to radiation cystitis or proctitis, along with damage to erectile function.

In a large prospective study of self-reported scores on urinary, sexual, and bowel function published in the New England Journal of Medicine, all three functions decreased immediately after radical prostatectomy in red or radiation therapy in blue, most notably erectile function in the middle panel. While some recover function over time, only a fraction of men return to their baseline function. These results have been

confirmed in many other studies and have improved little over the past two decades.

In summary, men diagnosed with early-stage prostate cancer face the possibility that their cancer will progress and require radical therapy later or that it could spread and become incurable in a low but real possibility of dying from their disease. These men have two distinctly different treatment options, monitoring the cancer with active surveillance or treating immediately with radical therapy.

I believe there is an unmet need for a treatment option that fills the gap between active surveillance and radical therapy, an option that can reasonably control the cancer, largely preserve normal function, and safely delay or avoid the long-term morbidity of radical therapy.

Thank you very much. Next, I'd like to invite Dr. Shore to the lectern.

Applicant Presentation - Neal Shore

DR. SHORE: Good morning. Thank you very much, Dr. Scardino. My name is Neal Shore, and I

am the medical director at the Carolina Urologic Research Center. My time and travel have been compensated by the sponsor.

I specialize in treating localized and advanced genitourinary oncology patients. I have performed hundreds of prostate gland ablation procedures, including photodynamic therapy, cryotherapy, brachytherapy, and HIFU. I have proctored several hundred neurologic colleagues on cryotherapy. I have performed over 300 clinical trials, mainly focusing on innovative therapies for prostate cancer. I am also an investigator for the TOOKAD confirmatory study.

TOOKAD VTP is a pharmacological treatment that allows for a hemiablation of the prostate. As mentioned by Dr. Rewcastle, it involves a photosensitizing drug along with a minimally invasive placement of optical fibers in the target prostate lobe. The drug, padeliporfin, is derived from chlorophyll, the most efficient substance in nature for transferring energy from light.

Next, let me walk you through the treatment

procedure. After patient preparation and anesthesia, an ultrasound probe is positioned in the rectum for imaging of the tumor-bearing lobe. A software system called TOOGUIDE provides treatment recommendations such as number, length, and position of the optical fibers in the prostate.

The optical fibers are inserted in the prostate through a perineal template. Next, TOOKAD, at a dose of 4-milligram per kilogram, is administered intravenously for 10 minutes. The drug circulates in the vascular system and remains inactive until the optical fibers are turned on. The fibers provide low energy, non-thermal, near-infrared illumination for 22 minutes and 15 seconds. The drug is activated only in the illuminated lobe.

The light-activated drug reacts with oxygen in circulating red blood cells, which then triggers a cascade of events. Vasodilation is immediately followed by vasoconstriction and subsequently blood flow arrest in the target lobe, as you can see in the model shown here. The optical fibers are

removed once illumination is completed. Total operating room time is approximately 2 hours.

Because TOOKAD is a photosensitizing drug, it is important that patients avoid intense infrared light perioperatively. To mitigate this risk, patients are covered with blankets and transferred to a dimly-lit recovery room as they awaken from anesthesia, where they remain for 6 hours until they are ready for discharge. Overall, there is a low potential for phototoxic events, as TOOKAD has a short half-life of approximately 70 minutes.

Here is an example of an untreated prostate. On the right, we see the same patient's prostate 7 days after VTP treatment, where the treated is clearly visible as a result of the devascularization within the treated lobe. The necrosis is contained within the anatomic contour of the gland and is confirmed by biopsy. It is important to note that the ability to biopsy the prostate is not hindered by any treatment effects and histological interpretation is not confounded.

It is easier to see the treatment effect of TOOKAD in other indications. Here is an example of a VTP treatment in an upper urinary tract carcinoma, which is an indication currently under IND investigation. It's important to realize the proximal ureter is a very delicate and thin-walled structure.

The ureteral tumor was treated with TOOKAD VTP on day 0. By day 7, in the middle image, the treatment effect was apparent. By day 30 on the right, there is complete tumor ablation while sparing the surrounding normal tissue. The ureteral lumen and wall completely recover with no scarring or stricture.

In summary, prostate hemiablation with TOOKAD VTP is a non-thermal procedure that can be safely performed at an outpatient surgery setting. Treatment consists of accurate optical fiber placement within the gland, IV TOOKAD administration, followed by light activation and laser illumination within the prostate. This leads to targeted necrosis of the entire tumor-bearing

lobe while preserving the surrounding tissue and organ function.

Thank you very much. Next, I'd like to invite Dr. Boodée to the lectern.

Applicant Presentation - Henri Boodée

DR. BOODÉE: Thank you, Dr. Shore.

My name is Henry Boodée, and I'm a board certified urologist with more than 15 years of clinical practice experience prior to joining industry. I'm currently the head of U.S. medical affairs and clinical development at STEBA Biotech.

I will present the efficacy and safety data from Study 301 supporting our proposed indication, demonstrating that TOOKAD VTP treatment results in clinically meaningful and statistically significant reductions in local disease progression and conversion to radical therapy when compared to active surveillance.

Study 301 is a multicenter, phase 3, randomized, open-label trial conducted in 413 patients. Patients were randomized to either TOOKAD VTP plus active surveillance or active

surveillance alone. Patients were diagnosed using the standard of care at the time, which included TRUS biopsy. Patients were biopsied at both 12 and 24 months, and the primary analysis was conducted after 24 months of follow-up. Patients are being followed long term for an additional 5 years as the study is still ongoing.

Per the protocol, more than one TOOKAD treatment was allowed for patients in the TOOKAD within the 24-month period. The study had co-primary endpoints. The first was to assess the difference in the rate of local disease progression over 24 months. Progression was defined as presenting with at least one of the events shown here.

The second co-primary endpoint was the rate of absence of cancer anywhere in the prostate at 24 months, meaning that the biopsy results all had to be negative or free of cancer in order to be counted toward this endpoint. All biopsies were sent to a central lab and reviewed to ensure consistency of the co-primary endpoint analysis,

but no treatment decisions were made based on their assessment.

The study also included several secondary efficacy endpoints. These were not controlled for type 1 error. In the interest of time, we will focus on key secondary endpoints. First, we evaluated if patients initiated any radical or systemic treatment for prostate cancer. We also assessed the proportion of patients with the extension to clinical T3, metastasis, and prostate cancer-related death.

Next, let's look at study outcomes. Patient demographics were balanced across groups. The mean age was 63 and the majority of patients were Caucasian. Baseline disease characteristics were representative of the target population. Most patients had unilateral cancer with a Gleason score of 3 plus 3.

Next, let's look at the co-primary endpoint analysis. Both co-primary endpoints were met with high significance. The hazard ratio for local disease progression was 0.34, meaning that

treatment with TOOKAD VTP reduced the risk of progression by 66 percent compared to active surveillance. Similarly, patients in the TOOKAD VTP group were significantly more likely to have a negative biopsy throughout the prostate than patients in the active surveillance group.

We acknowledge that our endpoints may be affected by the rate of missing biopsies. The rate of missing biopsy at 24 months is 18 percent in the VTP group and 42 percent in the active surveillance group. If we use the 12-month biopsy result when the 24-month biopsy is not available, the actual rate of missing biopsies is 6 percent in the VTP arm and 9 percent in the active surveillance arm. Hence, this is lower and balanced between the two arms.

In a post hoc analysis to assess the effectiveness of VTP ablation, we analyzed biopsy results in field in the VTP treated lobe or, for active surveillance, the largest cancer-containing lobe. In the VTP group, 25 percent had a positive in-field biopsy compared to 65 percent in the

active surveillance group. Grade group 2 or higher was found in only 10 percent of the VTP group compared to 34 percent in the active surveillance group.

Now, we'll focus on the progression endpoint. TOOKAD was effective against each individual parameter that could define progression with the majority of progression being triggered by Gleason pattern greater than or equal to 4.

Here, we present the primary analysis of local disease progression by treatment group over the first 24 months. This aligns with the recommendation from the 2018 FDA workshop. By the time of the first post-treatment biopsy at 12 months, we can see significant separation between the curves, which is maintained through 24 months. This is consistent with what we observe in the long-term follow-up period, which currently has data available out to 60 months after treatment.

In the active surveillance group, the median time to progression is 13.8 months. In the TOOKAD group, median time to progression has still not

been reached at 60 months. This durable difference between TOOKAD VTP and active surveillance is clinically and statistically significant as shown by the absolute risk reduction of 28 percent by month 60 with a hazard ratio of 0.39.

Now let's move on to the secondary endpoints. There is a link between local disease progression and the decision to convert to radical therapy. This also aligns with the recommendation from the 2018 FDA workshop for a secondary objective. There were substantially fewer patients who converted to radical therapy after TOOKAD VTP than with active surveillance at both 24 and 60 months. At 5 years, the absolute difference was 20 percent. This corresponds to nearly twice the risk of converting to radical therapy for patients in the active surveillance arm.

Overall, TOOKAD VTP reduced the conversion to radical therapy with a hazard ratio of 0.41 and a descriptive p-value less than 0.001. The avoidance or delay of radical therapy implies a clinically meaningful benefit because patients are

not exposed to treatment harm.

We analyzed the data further to determine if there was any difference between the arms and the decision to receive radical therapy given that this was an unblinded study. Although more patients on active surveillance had disease progression, a similar proportion of patients in both groups received radical therapy after progression.

Conversely, while more patients in the active surveillance group received radical therapy, the proportion of patients who develop disease progression before receiving radical therapy remained similar. Therefore, there was no evidence of a difference in treatment decisions between groups.

Looking at severe cancer-related events, there were 4 patients in the active surveillance group for which clinical T3 disease was observed at 24 months. At month 60, there were 2 patients in the TOOKAD VTP group with clinical T3 disease and 7 in the active surveillance group. Metastasis was observed in one patient in each group. As expected

in this patient population, there were no prostate cancer-related deaths.

In summary, TOOKAD VTP increased the probability of a negative prostate biopsy at 24 months and delayed disease progression for men with early prostate cancer. Importantly, treatment with TOOKAD VTP reduced the rate of conversion to radical therapy compared to active surveillance. The durability of clinically meaningful results was supported by long-term follow-up data 5 years from randomization.

Now, I'll review the safety results from Study 301. Overall, 95 percent of patients in the TOOKAD VTP group reported an adverse event compared to 55 percent in the active surveillance arm, which is expected given that they received treatment and the active surveillance group did not. These were mostly mild to moderate and self-limiting. At 24 months, the majority of cases had resolved without sequelae.

Regarding SAEs, these were also mostly mild to moderate, and nearly all the SAEs resolved by 24

months. Across both groups, only 3 patients discontinued due to an adverse event. A myocardial infarction was observed approximately 9.5 months after TOOKAD VTP and was unrelated to the drug, device, or procedure. Similarly, the anaphylactic reaction was temporally related to anesthesia and the patient never received TOOKAD.

Now, let's look at some adverse events of special interest. As we didn't have consistent follow-up after radical therapy, we are presenting this safety data censored at the time of radical therapy. Urinary symptoms were most commonly reported as grade 1 or 2, with the most common being dysuria, hematuria, and urinary retention. No grade 3 events occurred in either arm in more than 2 percent of patients. However, by 24 months, nearly all events had resolved, and this is consistent with the patient-reported data we collected in our study.

We measured IPSS, an internationally recognized voiding symptom tool, as a mean change from baseline over 24 months. While there is an

initial increase or worsening in symptoms, this returns to baseline by 6 months. Because more patients in the active surveillance arm had radical therapy, the numbers of patients were no longer comparable, and the results may be introducing bias. Importantly, by 24 months, there is no meaningful difference in symptom scores between TOOKAD VTP and active surveillance.

Moving next to erectile dysfunction, there is more erectile dysfunction associated with TOOKAD compared to active surveillance. The majority of erectile dysfunction events were grade 1, which is mild dysfunction that does not require any intervention. This means that men were able to continue sexual activity without assistance.

Of particular importance, the rate of grade 3 erectile dysfunction, which is unresponsive to intervention, was low in both groups. Grade 2 erectile dysfunction, in which treatment, including PDE5 inhibitors, is indicated, was reported by 16 percent of the TOOKAD patients and by 2 percent in the active surveillance group.

At 24 months, meaningful recovery of erectile function was observed; 8 percent of men reported grade 2 erectile dysfunction compared to 2 percent in the active surveillance arm. At 24 months, no grade 3 erectile dysfunction was observed in either arm. This low rate of grade 3 events and single-digit percentage of grade 2 events in both arms at 24 months is likely why patient-reported outcomes related to erectile function are largely similar between groups.

Let's look at these. IIEF erectile function scores worsened after the TOOKAD VTP procedure as expected, however, by 24 months, the scores were similar to those in the active surveillance group. Similar to the IPSS data, bias may have been introduced.

Importantly, the literature shows that salvage radical therapy is feasible after TOOKAD VTP if needed. This retrospective study with salvage radical prostatectomy after TOOKAD VTP collected data from 42 patients across the TOOKAD VTP development program. Generally, the outcomes

were similar to treatment-naive patients.

The radical prostatectomy procedure presented no unusual challenges in 69 percent of patients and 88 percent of patients had undetectable PSA levels at 6 to 12 months after the procedure. Only 12 percent of patients had postoperative complications. Therefore, early data suggests that radical prostatectomy remains an option after TOOKAD VTP.

Finally, I'd like to review our confirmatory post-approval Study 306. Study 306 was designed in consultation with the FDA. Eligible patients will include patients with favorable intermediate risk prostate cancer diagnosed with multiparametric MRI-guided biopsy. Study 306 will evaluate objective disease progression and conversion to radical therapy.

This confirmatory study will have more consistent follow-up after conversion to radical therapy to quantify the reduction in harm. The primary endpoint will be evaluated over 30 months, secondary endpoints would be evaluated at 30 and

72 months, and then long-term follow-up would continue for a total of 10 years since randomization, irrespective of progression or conversion to radical therapy, to evaluate overall survival.

Overall, the sample size is 400 patients, which includes approximately 150 patients from the U.S. In the U.S., we are working with the SUO-CTC to ensure efficient enrollment of patients, and in Europe, we are working with the EORTC. The study is ongoing and we are committed to completing it.

In conclusion, TOOKAD VTP safety profile is manageable and typically reversible. The reported adverse events were mostly mild to moderate and self-limiting. More erectile function events occurred after TOOKAD VTP compared to active surveillance, however, patient-reported erectile function was similar between groups.

Salvage therapy with radical prostatectomy is feasible after TOOKAD VTP. In addition, all results will be further evaluated in our confirmatory study. Finally, STEBA will be

providing training for every surgeon using this procedure.

Thank you. I'd now like to invite Dr. Gill to the lectern.

Applicant Presentation - Inderbir Gill

DR. GILL: Thank you, Dr. Boodée.

My name is Inderbir Gill, and I'm the chair of urology at the Keck School of Medicine at the University of Southern California. I am an unpaid advisor to the sponsor. I'm a practicing robotic surgeon, and along with my team have performed thousands of radical prostatectomy surgeries, and I'm discouraged that there has not been any real improvement over the past two decades in erectile dysfunction or urinary incontinence outcomes. Therefore, I am actively searching for a better way to treat patients with early-stage prostate cancer.

First, I would like to take a critical look at the study. As mentioned, the co-primary endpoints rely on accurate and unbiased biopsy collection. This concern was raised due to the number of missing biopsies due to reasons other

than conversion to radical therapy, 13 percent and 15 percent in the VTP and active surveillance arms. However, this analysis considers only the 24-month ITT analysis and not the 12-month data.

When we look at the 12- and 24-month biopsies, only 6 percent of patients in the VTP and 9 percent in the active surveillance arm had a missing biopsy. I believe these are very respectable numbers.

FDA also raised concern regarding pathologic interpretation of biopsy outcomes post VTP. I do not share this concern. The concordance rate between the local and central review was 85 percent for progression and 92 percent for presence of cancer, both well above the 80 percent concordance often used as the consensus threshold in inter-observer variability studies.

Sampling error is inherent in any biopsy method, and this raises the potential issue of false negative results. The 13 percent false negative rate was expected, and in fact lower than the active surveillance literature. Additionally,

this sampling error is symmetric across both arms of the study.

FDA indicates that the decision to convert to radical therapy was subjective. This is true. Aside from pathologic progression, the triggers for conversion were not precisely captured in this study, which could be a source of bias, however, the proportion of men in whom progression was the driver of conversion to radical therapy was similar in both arms.

Study 301 did not specify follow-up for harm after conversion to radical therapy, so it is just not possible to directly compare the ultimate morbidities between the two arms after conversion.

That said, Study 301 did thoroughly characterize the morbidity profile of VTP compared to active surveillance before conversion to radical therapy, and as a surgeon and a clinician, I am very comfortable with the morbidity profile of TOOKAD, nor do I find it surprising. Certainly, it is far less than that of radical therapy. Although Study 301 has some limitations, I find the data

meaningful and reliable.

Finally, I was concerned about repeat VTP treatments and if doing would increase procedural morbidity. The sponsor provided an analysis comparing the adverse events of interest occurring at any time during the surgery in men having only one VTP, shown to the left of the Y-axis, and men having more than one VTP, to the right of the Y-axis.

Reassuringly, there does not appear to be an increase in adverse events with more than one VTP as shown here. Most importantly from my perspective, there is no increased in grade 3 complications, which is what truly impacts my patients. This analysis puts to rest my concerns that repeat VTP might increase procedural morbidity.

In addition to FDA's concerns, there are some limitations of focal therapy in general. First, it may not completely ablate all the cancer. For TOOKAD, 10 percent of the in-field biopsies were positive for clinically significant disease,

but recognize this is a limitation of all ablative therapies. Note, even radical prostatectomy surgery has a 10 percent positive margin rate for organ-confined disease.

TOOKAD has been shown to delay but may not always avoid radical therapy. Also, overuse at either end of the disease spectrum is a concern for me. Having an option like TOOKAD cannot become licensed to treat all men with early-stage disease, therefore, guidelines need to be established to inform surgeons on the appropriate use of VTP. Certainly with literally anything you'd do to the prostate, even a mere prostate biopsy, there are going to be local transient urinary sequelae, such as hematuria and retention.

Now, despite the limitations just discussed, as a surgeon, there are quite a few things I like about VTP. I believe the delicate neighborhood of the prostate, the way it is anatomically ensconced within the neurovascular bundle and its proximity to the sphincter, lends itself naturally to in situ ablation.

VTP is non-thermal and can be targeted with millimeter accuracy. As a result, collateral damage to the external sphincter and neurovascular bundle is minimized. In addition, its non-thermal nature allows all locations within the prostate to be treated, unlike other ablative therapies.

VTP can also be used to retreat. Because it is non-thermal, there is likely to be minimal very prostatic reaction, allowing salvage radical therapy to be performed without undue morbidity. Finally, the technique is a simple outpatient procedure that is easy to learn and well within the wheelhouse of most urologists.

TOOKAD VTP is the missing reasonable bridge between the binary extremes of active surveillance and radical therapy. It is more effective than surveillance in controlling the cancer and causes less morbidity than radical therapy. I believe it should be an option for men who are candidates for active surveillance as defined by the NCCN guidelines and consistent with the proposed indication. I would much rather thoughtfully

provide my patients with an option like TOOKAD VTP and not have to do a radical prostatectomy unless absolutely necessary.

In terms of how I see TOOKAD fitting into contemporary clinical practice, it is a good option for high-volume, grade 1 disease based on transrectal ultrasound biopsy. For lower volume group 1 disease, it would be the selected patient who is at higher risk for progression or someone who has already demonstrated progression. I would also recommend TOOKAD for MR-biopsy detected grade group 2 disease that is unilateral and small volume.

Now let me summarize the positive benefit-risk profile of TOOKAD VTP. VTP significantly reduces disease progression, leading to lower rates of conversion to radical therapy, which is maintained out to 5 years. This represents a major treatment benefit. In essence, we are setting the clock back on the disease by delaying or avoiding radical therapy and its attendant morbidities.

Here is a high-level overview of functional results from a large prospective randomized trial of radiotherapy versus radical prostatectomy, the ProtecT study. In comparable populations, the rate of urinary incontinence is 4 percent with radiation and 19 percent with prostatectomy.

Now, we all know that incontinence is a major issue, one that will get your attention every time it happens, day or night. ED is even higher at 34 percent after radiation and 47 percent after prostatectomy, and this is level 1 evidence.

Now let's look at the TOOKAD data from Study 301 that was presented earlier. The incontinence rate is truly excellent, only 1.6 percent, the rate of ED a very respectable 8 percent with active surveillance at 2 percent. Note that this is adverse-event reporting, which reflects the change from baseline in both studies.

Overall, I am satisfied with the safety profile of TOOKAD VTP for my patients. The side effects are substantially lower compared to radical therapy, making it a great treatment option. I'm

enthusiastic about bringing TOOKAD VTP to my patients, and I truly believe its benefits outweigh its risks. The benefits are an absolute 30 percent decrease in progression and a 23 percent decrease in conversion to radical therapy. The cost is a minimal absolute increased risk of 0.4 percent for incontinence and a 6 percent increase in erectile dysfunction. Thank you for your time.

DR. HOFFMAN: Thank you.

We will now proceed with the presentation from the FDA, Dr. Agrawal.

FDA Presentation - Sundeep Agrawal

DR. AGRAWAL: Good morning. My name is Sundeep Agrawal, and I'm a medical hematologist-oncologist and medical officer on the clinical review team for this new drug application for TOOKAD. The FDA review team additionally consists of the following members of the clinical and statistical teams, division leadership, and project management.

I will discuss the results of trial PCM301 alongside the key review issues which are the

following: Are the endpoints appropriate to characterize benefit? Is the safety profile of TOOKAD acceptable? Do uncertainties allow for reasonable assessment of benefit-risk? I will then summarize the FDA position and read the question for the committee.

The study design of PCM301 has already been discussed. FDA would like to reiterate that the sponsor added a study extension to collect an additional 5 years of data. However, as biopsy and safety data were not collected in a uniform and rigorous manner in the extension study, FDA considers only the primary 2-year study as the basis for this application. I will begin by reviewing the endpoints used in this trial and whether they are appropriate to characterize benefit.

Co-primary endpoint A was defined as the absence of definitive cancer at 2 years. Forty-nine percent of patients in the TOOKAD arm and 14 percent of patients in the active surveillance arm had no cancer on biopsy at

2 years, a rate difference of 35 percent.

Missing biopsies were noted on both arms. Approximately 18 percent in the TOOKAD arm and 42 percent of patients in the active surveillance arm had missing biopsy data. This includes 6 percent of patients on TOOKAD and 27 percent of patients on active surveillance who did not have biopsy data available because they underwent definitive treatment, so no further biopsy was possible.

FDA also notes that in assessing this endpoint, there was a potential for unblinding of the central pathologist due to possibility of necrotic changes on histology specimens in the TOOKAD arm.

FDA notes issues with the utility of this endpoint. The surveillance arm is expected to have a hundred percent rate of cancer given no intervention in these patients. Thus, the utility of comparing this to the absence of cancer in TOOKAD patients is unclear. Additionally, the result of absence of cancer in itself will not

alter clinical management of these patients. Thus, the clinical utility of this endpoint is unclear.

There are also uncertainties in the assessment of the endpoint. Despite not undergoing treatment, 14 percent of patients on the active surveillance arm had a negative biopsy at 2 years. These are presumed to be false negatives, as prostate cancer is not expected to regress without treatment.

Many patients on the active surveillance arm had either a false negative biopsy or missing biopsy data at 2 years. Limitations to biopsy such as false negatives and misattribution of grade have been documented in other series of low-risk prostate cancer patients.

These biopsy issues do not appear to be due to the sponsor's trial conduct, however, these issues make this endpoint difficult to interpret nonetheless. FDA had prior concerns and did not agree to the use of this endpoint for PCM301 and communicated these concerns to the sponsor prior to the start of this trial.

Co-primary endpoint B evaluated time to disease progression. FDA would like to note that the sponsor uses the term "rate of local disease progression," while FDA uses the term "time to disease progression." Progression criteria used by the sponsor to define a progression event is listed on the right-hand side.

This slide provides a Kaplan-Meier plot for co-primary endpoint B where an event was considered as progression to moderate or higher risk cancer at 2 years follow-up. Using a log rank test, the observed differences are unlikely due to chance, and the p-value is statistically significant. The observed hazard ratio is 0.34. Approximately 72 percent of patients on the TOOKAD arm and 42 percent on the active surveillance arm remain progression-free.

FDA notes that since biopsies were only done annually and patients were only followed for 2 years, the trial may not have been able to accurately estimate the median time to progression, including the medians. By design, this trial only

followed patients for 2 years, so most patients without progression events were censored at or shortly after 24 months.

FDA performed sensitivity analyses of co-primary endpoint B, evaluating a modified definition of pathologic upgrade to align with criteria for upgrade to unfavorable risk and/or a higher risk of prostate cancer. FDA also conducted an analysis including patients on each arm missing month 24 biopsies and considered them as having had an event. Results from both of these analyses are consistent with the primary endpoint results.

The table on the left lists the enrollment criteria for PCM301. The table on the right lists the criteria used to define a progression event alongside the percent of patients in each arm who had a progression event by each criterion. The most common criteria met to define a progression event were increase in Gleason score, more than 3 positive cores, or a cancer core length greater than 5 millimeters.

Some patients met multiple criteria for

progression. Any criterion, even minimally greater than the enrollment criteria, defined a progression event for this endpoint. Some progression criteria that contribute to the composite endpoint may not be objective triggers for intervention. Additionally, small incremental changes from enrollment parameters may meet progression criteria. Even if these changes would not change clinical decision making, the rationale for the selection of these criteria is unclear.

Time to disease progression is affected by uncertainties related to biopsy results. Misattribution of grade and false negatives can affect interpretation of biopsy results in addition to other issues. For example, approximately 30 percent of patients in the active surveillance arm had a decrease in positive core number and decrease in core length with cancer despite no intervention. Additionally, the accuracy of biopsy after TOOKAD is unknown. It is possible that post-TOOKAD scarring may affect biopsy samples.

FDA also notes the open-label nature of this

trial. As noted earlier, although biopsy specimens are reviewed by central pathologists blinded to treatment assignments, true blinding may have been difficult due to the presence of characteristic changes on post-TOOKAD specimens. These issues introduce uncertainty into the assessment of the time to disease progression endpoint.

The value of a disease progression endpoint such as co-primary endpoint B is in providing an objective trigger for intervention with a morbid procedure such as radical prostatectomy or radiation therapy. However, in PCM301, approximately 50 percent of patients who progressed by protocol criteria on both arms did not undergo definitive therapy by month 24, and several patients underwent definitive therapy but had no disease progression.

The decision to undergo definitive therapy has an inherent degree of subjectivity based on the patient and physician preference, however, the level of variability noted in PCM301 makes interpreting this endpoint challenging.

Time to definitive therapy was a secondary endpoint. It was not controlled for type 1 error and is considered descriptive only. Time to definitive therapy was improved in the TOOKAD arm compared to the active surveillance arm. At 2 years, approximately 6 percent of patients in the TOOKAD arm and 29 percent of patients in the active surveillance arm went on to receive definitive therapy. The hazard ratio is 0.17.

FDA notes the following limitations of this analysis. The trial was open label. This analysis was not adjusted for multiple testing. The decision to undergo definitive therapy with firm criteria to undergo prostatectomy was not prespecified in the protocol and approximately 50 percent of progressors did not undergo definitive therapy at 2 years.

In summary of efficacy, both prespecified co-primary endpoints were met, however, the clinical relevance of the endpoints is unclear. For endpoint A, absence of cancer does not lead to a change in patient management, and thus the

clinical relevance of this endpoint is unclear. For endpoint B, time to progression, there was limited 2-year follow-up. Correlation with long-term outcomes is not known.

The clinical value of this endpoint is also uncertain as defined, as only 50 percent of progressors subsequently underwent definitive therapy at 2 years. Both endpoints relied on biopsy data, but there are considerable false negatives in sampling errors in this setting that make interpretation of these endpoints difficult, and PCM301 was an open-label trial, which can potentially introduce bias.

I will now review the safety profile of TOOKAD. The sponsor has previously reviewed safety in trial PCM301. This graph depicts adverse events occurring in 10 percent or more of patients in either arm. Ninety-five percent of patients in the TOOKAD arm had an adverse event compared to 55 percent in the active surveillance arm. Grade 3 and 4 events were noted in 22 percent of patients on TOOKAD compared to 10 percent of patients on

active surveillance.

Most acute and subacute toxicities were related to the genitourinary tract and included hematuria, dysuria, and perineal pain. Most of these events resolved, however, long-term adverse events such as erectile dysfunction remained unresolved in a considerable number of patients.

Sexual and urinary dysfunction can impact patients' quality of life after undergoing treatment for localized prostate cancer. A review of published literature demonstrates large discrepancies in prevalence rates of these toxicities after definitive therapy. Discrepant rates are due to several methodologic differences in studies that have been done to assess these toxicities.

In addition, rates varied based on several factors such as age, pretreatment sexual function, and the treatment received. In contemporary series at 2 years after definitive therapy for localized prostate cancer, rates of sexual dysfunction range from 14 percent to as high as 90 percent. Urinary

dysfunction rates range from 10 percent to as high as 70 percent.

In comparing TOOKAD to active surveillance at 2 years, unresolved erectile dysfunction was noted in 23 percent of patients receiving TOOKAD versus 10 percent with active surveillance. Rates of unresolved urinary incontinence were similar to each other between arms, however, many patients stopped reporting adverse events after undergoing definitive therapy.

Of the 64 patients who underwent definitive therapy in the active surveillance arm, 40 of them did not report any adverse event afterwards. This represents 19 percent of patients overall in this arm. In the TOOKAD arm, only 12 patients had definitive therapy and 5 of these patients did not report any adverse event thereafter, representing 2 percent of the patients overall in the TOOKAD arm.

Thus, there was a disproportionate number of patients underreporting adverse events in the active surveillance arm. The true incidence of

long-term toxicities in the active surveillance arm is unknown, and this makes an accurate comparison between arms difficult.

Patient-reported outcomes were exploratory endpoints in this trial. The IIEF-15 and IPSS are instruments that measure erectile function and urinary symptoms, respectively. The EQ-5D is a PRO instrument used to assess quality of life. Because the EQ-5D is a generic tool used for health assessment and was assessed at only two post-baseline time points, the FDA analysis focused on the IIEF-15 and IPSS results.

These questionnaires were administered at baseline 7 days after TOOKAD in patients on the TOOKAD arm, and at months 3, 6, 9, 12, and 24. Compliance rates were greater than 90 percent in both arms early in the trial, but by month 24, compliance rates fell below 80 percent in the active surveillance arm. There was considerable missing PRO data in patients undergoing definitive therapy with disproportionately more missing data in patients on the active surveillance arm compared

to TOOKAD.

These graphs represent mean changes from baseline over time for urinary symptoms on the left and for erectile function on the right. The solid red line denotes TOOKAD and the dotted line is the active surveillance arm. Please note FDA has oriented both graphs so that a higher change from baseline in both graphs represents worsening symptoms.

On the left is the summary score for urinary symptoms. The TOOKAD arm demonstrates increased patient-reported urinary symptoms at the 3-month time point after the procedure, but then this appears to improve. In the active surveillance arm, patient-reported urinary symptoms worsen steadily after month 9. At month 24, results appear to favor the TOOKAD arm.

On the right is the summary score for erectile function. Patients on the TOOKAD arm reported worsening erectile function that does not return to baseline. In the active surveillance arm, erectile dysfunction gradually increases

throughout the course of the trial partially due to some of these patients undergoing definitive therapies with resulting adverse events captured via PROs. At month 24, the TOOKAD arm and the active surveillance arm appear to demonstrate comparable mean changes from baseline.

FDA notes the following limitations in PRO reporting from this trial. Some relevant reported adverse events were not assessed. There were limited assessments of acute and long-term toxicity. There were few assessments from baseline to month 6 to capture acute toxicity and limited long-term follow-up.

There was also considerable missing data. Completion rates were lower on the active surveillance arm compared to TOOKAD at month 24, and many patients stopped reporting after definitive therapy.

PRO analyses were not planned to control for type 1 error and are thus descriptive only. Based on these limitations, there is significant residual uncertainty regarding the difference in the level

of patient-reported symptomatic morbidity between TOOKAD and active surveillance.

In summarizing safety, it is important to again note the context. In the low-risk, localized prostate cancer population, the proposed benefit of TOOKAD is to limit or prevent morbidity associated with definitive therapies. Reducing long-term toxicity is important to characterize TOOKAD's benefit.

Toxicity must be evaluated in the context of active surveillance. Some patients on active surveillance receive definitive treatment with resulting toxicity, but all patients receiving TOOKAD have the risk of toxicity upfront. In PCM301, there was a higher incidence of toxicity on the TOOKAD arm compared to active surveillance with higher rates of all-grade, grade 3 and 4, and erectile dysfunction events.

There was also disproportionate missing safety and PRO data in the active surveillance arm that makes an accurate comparison between arms difficult.

Limited follow-up make long-term outcomes unclear, as there is a potential for compromised cure rates due to treatment delay of definitive therapy and limited data on outcomes of surgery and radiation treatments following TOOKAD.

I will now summarize the uncertainties from PCM301 and whether they allow for a reasonable assessment of benefit-risk. FDA review notes several uncertainties in the data for both efficacy and safety that make an assessment of benefit-risk difficult.

In terms of efficacy, the absence of cancer endpoint and the disease progression endpoint may be affected by unreliable biopsy data. In terms of safety, there were no adverse events or PRO data recorded after definitive therapy for many patients. Thus, the true incidence of long-term toxicities in these patients is unknown. It is difficult to quantify the effect of missing data on study conclusions.

The applicant has discussed plans with the FDA regarding an additional study entitled PCM306,

a randomized trial of TOOKAD versus active surveillance in favorable, intermediate risk, localized prostate cancer. The primary endpoint of this study will evaluate objective progression of cancer. A key secondary endpoint will evaluate conversion to radical, local, or systemic therapy.

There are proposed measures in place to better collect data on this trial and with longer follow-up. PSA testing and biopsy results will be obtained at defined intervals. Patients in both arms will be required to have follow-up, MRI-guided biopsies at 12, 24, 42, and 60 months, which will allow for more long-term outcomes data.

Longer follow-up will include collection of safety and PRO data to better elucidate the long-term safety profile. Given that morbidity is an outcome of interest, PRO and safety data will be critical; and as noted earlier, there will be prespecified criteria for determining referral to definitive therapy, which may help reduce the subjectivity associated with this decision. This in turn will serve to better support the endpoints.

In summary, PCM301 met both of its co-primary efficacy endpoints, however, clinical relevance of these efficacy endpoints is unclear. Progression of disease as defined does not clearly translate into patients subsequently undergoing definitive therapy. Acute and subacute toxicity reported as adverse events and patient-reported outcomes are worse on the TOOKAD arm.

Erectile function at month 24 appears worse with TOOKAD, with 23 percent of patients having unresolved erectile dysfunction. Missing data, false negatives, and other sampling issues make accurate assessment of results difficult. The open-label design of this trial could introduce potential bias into the efficacy assessment, and other measures such as patient-reported outcomes, and long-term efficacy and safety outcomes are unknown.

Our question to the committee is as follows: Do the results of a PCM301 represent a favorable benefit-risk profile for TOOKAD in patients with low-risk, early-stage prostate cancer? Thank you.

Clarifying Questions to Presenters

DR. HOFFMAN: We're a few minutes early, which is good. We will now take clarifying questions for the presenters. Please remember to state your name for the record before you speak, and if you can, please direct questions to a specific presenter. I want to start with two questions for Dr. Boodée.

I'm sorry. If you want to ask a question, try to indicate with your hand up to Lauren, so she'll get a list of who's asking.

One question was, with respect to radical prostatectomy after TOOKAD therapy, feasibility said 69 percent of the radical prostatectomies presented no unusual challenges. I'd like to know about the 31 percent that did present some unusual challenges. The other was that I noted early in the presentation that some patients underwent this procedure more than once, and I was wondering what prompted that. I presume it was in the same lobe both times or however many times that it was.

DR. REWCASTLE: Sure. To start, I think to

discuss the difficulty in prostatectomy that's observed both with a normal prostate as well as what was observed in the literature and reported, Dr. Gill could speak to this quite well.

DR. GILL: Inderbir Gill from Los Angeles. Radical prostatectomy when performed in the salvage scenario is more challenging than when performed in the upfront scenario. Having said that, I don't have any personal experience with post-VTP radical prostatectomy.

That said, I do have a lot of experience with post-radiation failure, radical prostatectomy, post hemi-gland ablation salvage prostatectomy. In general, the hemi-gland or partial gland ablation prostatectomy is significantly easier to do than a whole-gland therapy such as radiation, for example, because the adhesions between the prostate and the rectum are limited to one side.

Therefore, the contralateral side is virtually untouched and allows you to go from known to unknown, thereby being able to do a nice nerve sparing even in the presence of post hemi-gland

ablation. Typically, a salvage prostatectomy after radiation, nerve sparing is typically not an option.

DR. HOFFMAN: And the question about doing this more than once?

DR. REWCASTLE: Sure. Within the trial, you were allowed to have more than one treatment, so there are different classifications. First, you'd have a patient who had unilateral disease and had a unilateral VTP. There are also subjects who had a bilateral initial diagnosis, and they would have had two procedures. So you don't ablate the entire prostate at once; you ablate one side, and then subsequently ablate the contralateral side.

I can show you the breakdown of subjects here. Of the 163 patients who had unilateral VTP, 124 of them, that's all they got, and that was throughout the trial; 29 of them had a contralateral de novo VTP, the results of the 12-month biopsy.

In terms of retreatment, 8 patients had that previously treated lobe treated and 2 had a

bilateral treatment after their initial. Of those subjects, the 33 who had the staged bilateral VTP, 29, that was the total VTPs they received, and then 4 had a unilateral treatment as well.

You asked what the motivation was. It was either an initially prescribed unilateral bilateral or following that 12-month biopsy to guide the treatment decision.

DR. HOFFMAN: Dr. Rini?

DR. RINI: I have a follow-up question, I think, to what Dr. Hoffman did about post-procedure radical or definitive therapy. There were I think 42 patients in the VTP arm who had definitive therapy and I think 47 surveillance patients. Dr. Gill alluded to this, but do you have specific details about the toxicity in each of those populations?

DR. REWCASTLE: We didn't include that specifically. It's in a literature report of 42 subjects. After the break, I could pull the adverse events of that to give you more detail if you'd like.

DR. RINI: Well, you mentioned, again as Dr. Hoffman mentioned, 69 didn't have complications, so you must have data on the complications that did occur. It seems like that's a main point for FDA, if this procedure somehow makes radical more dangerous or something. So that's the nature of the question, if there are details.

DR. REWCASTLE: I can ask Dr. Coeytaux to respond to this, please.

DR. COEYTAUX: Emmanuel Coeytaux, STEBA Biotech. The 69 percent is post-procedural report of the feasibility of the procedure. When we discussed with the experts, they were telling us if you would take naive populations, you would probably have 2 sets that would be considered easy and one activity difficult because of a variety of situations that present.

Then in terms of the safety, the 12-person postoperative complications is something that is also seminal to what you would see in treatment-naive populations.

DR. RINI: I was just asking for any more specific details on what exactly those complications were.

DR. REWCASTLE: So the original trial, which was designed -- we designed a trial in 2010. In 2018, we really got clarity with the multidisciplinary meeting that the FDA hosted, which I think was a great step forward, and really changed our thinking to let's follow irrespective of what happens in the pathway.

We were really, in the design of 301, most closely looking at what happens to the patient in terms of biopsies of binary event progression as well as conversion of radical therapy. In our Study 306, we intend to follow that very closely; and really, nobody's done this in great detail, so I think that will provide better information.

DR. RINI: Thank you.

DR. HOFFMAN: Dr. Song, do you have a follow-up to that part or is it separate?

DR. SONG: I have a different question.

DR. HOFFMAN: Okay. Dr. Hussain.

DR. HUSSAIN: Thank you. I have several questions. I'm going to lump them together. One of them is, with regard to the study design, was there a central path review at baseline required?

The other question is the study design overall. Considering, as was presented, that the standard of care treatment for these patients could be observation or therapy, why was there no active control included? Because at the end of the day, this is a treatment intervention, and to demonstrate efficacy and safety, it would be important to say how does it correlate there. And then, where was this study conducted?

DR. REWCASTLE: First question, if there's a central pathology review at baseline? No, there wasn't. The central pathology review was based on a 24-month biopsy -- or all of the follow-up biopsies. But that information fed the assessment of the endpoints; it was not part of the treatment decision. So uniformly, it was the local biopsy decisions that drove the treatment.

DR. HUSSAIN: Then that could add imbalance

between the arms if you actually did not control for the primary eligibility criteria of the central, of the Gleason score.

DR. REWCASTLE: It could. Nobody has done a trial like this before and randomized to a novel prostate cancer therapy. Having a further delay of your biopsy to reading it, we looked at potential more headwind for patients, so there is a bit of a balance there.

Your second question was?

DR. HUSSAIN: The question was, considering that the standard of care for these patients, what you presented and obviously the FDA officer presented, is either you treat or you observe, why was there not an active treatment control arm?

DR. REWCASTLE: It gets more difficult. As was discussed, a lot of our endpoints are based on biopsy. If we had a radical prostatectomy, you don't have anything to biopse [ph] anymore, and then how would you compare with biochemical markers versus biopsy? So your metric would be different, and as well, the metrics for radiation are

different as well in terms of interpretation of biopsies.

Really, our goal here was to focus against active surveillance and see if we can find the middle ground, but certainly that is an interesting potential design.

DR. HUSSAIN: And when was it conducted? [off mic.]

DR. REWCASTLE: And when was it conducted? It was conducted in 2011 and '12, and it was conducted in Europe at 47 centers.

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: I was hoping for a clarification. In the proposed indication -- sorry, my name. Minhaj Siddiqui. I'm a urologist, University of Maryland, and this is to whoever feels they can best address the question.

The proposed indication has unilateral -- the study we saw was for grade group 1 unilaterally focused, and we saw a lot of data presented on that topic. The proposed indication

also includes unilateral grade group 2. The thing is that one of the primary outcomes, the progression event is defined as presence of grade group 2, so how do you handle this population, which is already grade group 2?

DR. REWCASTLE: In terms of handling that population, it's the difference in the biopsy method that makes a big difference in the interpretation. I think Dr. Gill can speak to this from a clinical perspective.

DR. GILL: Inderbir Gill. The point here is that when transrectal ultrasound diagnoses low-risk prostate cancer, there is potentially a good third of the patients who already have grade group 2 disease; it just was not identified on the transrectal ultrasound biopsy.

In support of that, I will point out the fact that the 24-month biopsy in the active surveillance arm showed a 12- and 24-month and the active surveillance arm showed 34 percent of patients actually had grade group 2 disease. That would be like a confirmatory biopsy that we would

use in clinical practice; 34 percent actually had grade group 2 disease, it just was not identified on the baseline transrectal ultrasound-guided biopsy.

So I guess to answer your question, how would you jive the fact that they already have grade group 2 disease, the contention here is that a third of the patients did have grade group 2 disease at baseline. Even in PCM301, it is the reason that they're asking for the inclusion of that in the indication.

DR. HUSSAIN: My challenge here, though, is that
they have technically already progressed at inclusion, based on the definition. So is there data to support modified progression criteria for this population or how do we handle a progression event in someone who already meeting those criteria?

DR. REWCASTLE: Dr. Coeytaux?

DR. COEYTAUX: I think in Study 306, which will be in patients diagnosed with grade group 2,

this is a key question, and we reviewed the design with the FDA. What we're going to use is the most contemporary definition of progression, which is correlated to the amount of pattern 4.

So we enrolled a subset of grade group 2 with a predefined amount of pattern 4 -- on top of mind, I think 2 millimeters -- and then we have the progression endpoints that look at the total amount of pattern 4 on subsequent biopsy. This has been shown to be correlated with adverse pathologic outcomes, so we think this is a relevant way to mind our progression.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: I have three questions for Dr. Boodée. The first one is I recognize that the study was conducted in a European region, and therefore for 90 percent or so, patients are Caucasian. The first question, is there any data to believe that actually the target could be applicable to a much more heterogeneous patient population like we see in North America, including African American patients?

The second question, which I think Dr. Rini alluded to, is the data that you guys have related to subsequent therapy with radical prostatectomy after target therapy, I think you have a retrospective analysis of 47-plus patients, where safety and/or efficacy of RP doesn't appear to be compromised. But I would argue a significant proportion of patients in North America would also choose SRS, brachy, and/or radiation therapy as local definitive therapy if they were to progress.

Do you have any data as to the safety and efficacy of that subsequent therapy?

Lastly, what was the median number of biopsies done at 12 months and 24 months for those patients who are to receive target therapy compared with active surveillance? You have a range in the protocol looking at 10 to 24 biopsies, but I would argue that if you were to actually do more biopsy sampling for active surveillance, you may be able to pick up more cancer in the active surveillance patient population, or vice versa, compared with the target-treated patients.

DR. REWCASTLE: I'll actually answer them in reverse order. If we can look at slide EP-29, this looks at the number of biopsy cores taken per patient. The average number of cores taken at 12 months was 12.8 versus 13.4; at 24 months, it is 12.6 versus 13.0, and no statistical difference between the two arms. I think that's a pretty standard TRUS biopsy.

You asked about subsequent therapies that were not radical prostatectomy. Eighty percent of the subjects who converted within our trial underwent radical therapy. We don't really have any meaningful numbers on radiation therapy, which was 14 percent of those who converted, however, we did not receive any reports that it was not possible, not feasible. This will be captured much better within Study 306, which is really designed to capture this sort of information.

The last question, which is important, is looking at the ethnic mix of 301. 301 was conducted in Europe in a predominantly Caucasian population. We do have some experience in

Study 202, which was a U.S. study. Forty-seven percent of the gentleman enrolled were African American and 3 percent were Asian. We didn't see a difference in outcomes. For Study 306, we're really going to focus on centers in large metropolitan areas with diverse populations to make sure we capture a much more reflective population here in the United States.

DR. HOFFMAN: Dr. Halabi?

DR. HALABI: Susan Halabi, Duke University. I have two questions and one comment. The first question is to the sponsor. We know that there are 38 patients and 86 patients that were missing biopsies at 24 months, and then we had almost 30 patients that were missing at both time points.

Knowing that the biopsy will affect rate of progression, at least one of the components of this endpoint, how did you deal with the missing data -- this is more of a statistical question -- and were sensitivity analyses done?

Then the other question has to do with biology. In those patients who are at lower risk,

what's the likelihood that the data is going to change in terms of the components of the progression over time? That's my other question. Then the final comment I wanted to make for the record, there's no such thing called descriptive p-value, so I would like people to refrain from using that.

DR. REWCASTLE: One clarity point is the rate of missing biopsy was at the snapshot at 24 months, and that was an ITT analysis at a single time point, whereas progression was a time-to-event analysis. And as discussed, the missing data for that analysis was 6 percent and 9 percent between the two arms.

In terms of the sensitivity analysis we did to test the robustness of the findings, FDA made the comment that they assumed that all of the biopsies that were missing were positive. We actually went a step further, and we said let's assume the missing biopsies in the TOOKAD arm are positive and the missing biopsies in the active surveillance arm are negative.

If we look at EP-32, we have the result of this analysis. The top here is assuming that any missing biopsy is positive. The bottom is assuming a missing biopsy in VTP is positive and one in active surveillance is negative, and we maintain a highly significant result. If we do the same thing for progression, we also maintain a highly significant result. So we actually took our sensitivity analysis another step further, and we still maintain our significance.

DR. HOFFMAN: Dr. Sandler?

DR. SANDLER: Thank you. I had a question maybe best answered by Dr. Gill. It was sponsor slide 77, where sponsor is comparing the toxicity from the ProtecT study to the 301 study. I just wanted to mention that as a radiation oncologist, I'm pretty familiar with the Donovan study. Their conclusion was that there was no increase in urinary incontinence versus active monitoring in that study. So that 4 percent number is a baseline for that age population.

The erectile dysfunction number from the

ProtecT study I would say is non-comparable to Study 301. In that study, for whatever reason, all the radiation patients got androgen ablation therapy, which we know has an impact on erectile dysfunction. For low-risk patients, as in the 301 study, radiation is indicated without the use of ADT, so one would expect erectile dysfunction numbers would be quite a bit better.

I guess my question is the assumption is, for sure, that -- your assumption I think is that TOOKAD is safer than radical therapy, but I'm not sure that I'm seeing data that suggests that TOOKAD is actually safer than radiation therapy as definitive treatment. I was just wondering if you could discuss that, and then briefly discuss the issue with TUR.

Two patients who had a prior TUR was excluded halfway through the study, I think, after there were some adverse events. I was just wondering what's the reason for the adverse events in using TOOKAD after a prior TUR?

DR. REWCASTLE: I think the most important

or appropriate person to answer the question regarding radiation therapy would be Dr. Zelefsky, and as he approaches, I'll address the TUR question. There was one subject who had serious incontinence after VTP, and he had a TUR defect. In an abundance of caution, that's why we backed off on TUR within the study.

I think Dr. Zelefsky can address the radiation therapy questions.

DR. ZELEFSKY: Michael Zelefsky, radiation oncology from Memorial Sloan Kettering Cancer Center. To address Dr. Sandler's point, I think, obviously, it's very difficult to make comparisons like this to the ProtecT trial exactly along the lines that you had mentioned, in particular with the hormonal therapy as a confounding factor for assessing erectile dysfunction, and even longer term follow up in those studies compared to the TOOKAD as well.

In addition, it would be difficult as well to make such comparisons because we are dealing with hemiablation, and the ProtecT trial was

obviously with whole-gland radiation.

I think the point of the comparison is just, certainly in the radiation literature as you know well, the overall risks of erectile dysfunction with whole-gland radiation is generally about 30 percent in the patient populations we treat. So it's hard to say that we would be seeing 10 percent, for instance, erectile dysfunction rates in general with whole-gland radiation.

So I think the comparison was made only to be provocative that we see relatively lower rates than what's been published with whole-gland radiation. I do agree that these kind of comparisons are really impossible because of the different patient populations that were treated.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Thank you. Randy Hawkins, internal medicine. One question is about adverse events and others will follow on Dr. Garcia's question.

To the applicant, for the urinary tract infection adverse events, were any of those

associated with sepsis or hospitalization? Regarding the follow-up on Dr. Garcia's inquiry, there's some evidence that African Americans have a higher mortality in these low-grade prostate cancers, so there'd be a desire to get that group into this study, and we understand why perhaps that didn't occur in Europe.

You've stated that one approach to increase numbers would be in the U.S. metropolitan areas. I would suggest it would take more than just the location. I talk to you a little further about how you've got to market to the African American urologists, et cetera. And the third would be, with 306, the duration, do you anticipate any drop off given the number of biopsies that are required for this length of time?

DR. REWCASTLE: The first question regarding UTIs in sepsis and hospitalization, the answer is no. They're all managed and resolved. Regarding the number of biopsies, we've designed the trial to be consistent with active surveillance, so I don't think the burden on the patient is really more than

what they'd be getting in active surveillance. So we don't anticipate subjects dropping off but, Dr. Gill, if you can talk about the other questions

DR. GILL: Inderbir Gill. I just want to make sure I understand your question correctly. Are you asking whether TOOKAD could potentially be equally applicable to the African American population as the Caucasian?

DR. HAWKINS: No, not in 301, but as you anticipate 306, if I can ask about that. It really was a follow-up on Dr. Garcia's question. How will you reach out to increase the number of African Americans enrolled in the study beyond what you stated already?

DR. GILL: As Dr. Rewcastle mentioned, in the 202 study, another study that the sponsor is doing, there is about a 47 percent prevalence of African Americans in that study already, although very small numbers. But how would one increase and make sure that there is adequate representation of African Americans? It would be the things that John mentioned, which is go to centers that already

have a significant proportion of African Americans, number one. Number two, reach out to African neurologists and include those centers in the multi-institutional trial.

I feel confident that given that this trial will be accruing in about 15 centers in the U.S., we would have about a good 20 percent or so African Americans in this patient mix.

DR. REWCASTLE: Correct. And, Dr. Hawkins, I'd like to follow up. If you've got some lessons learned that you can give to us after this, I'd like to hear them because it's important to us that we get a good representative sample.

DR. HOFFMAN: Dr. Makarov?

DR. MAKAROV: Thank you. Dan Makarov from NYU. My question sort of dovetails with some of the other comments that were made before, Dr. Siddiqui and Dr. Garcia. When you look at the failure rate for the co-primary endpoint B progression in the active surveillance arm, 58 percent at 2 years is extraordinarily high. And I'm guessing that the reason for that, as you've

discussed the biopsy data, is that there is no confirmatory biopsy that was done, at least not routinely, and probably MRI was not done routinely to screen these patients out.

Do you know if it was done off protocol in certain patients? Was it done somewhere along the line or would that definitely have been captured? And if not, regardless, what do you think the data would look like if you performed this trial in the United States in the carefully preselected with confirmatory biopsy or MRI; what would the results of this same trial look like here?

DR. REWCASTLE: So to answer the first part of the question with the progression rate, if we look at slide E-12, because we looked at this as well, is what we found consistent with the literature? Your progression rate is going to be driven largely by the intensity of follow-up in the biopsy, and their progression rates are different. So it's hard to compare studies, but what is easy to compare is the conversion of radical therapy rates. We did a complete review of the literature

and found the studies that had two planned biopsies in the first years, and looked at their rates of conversion of radical therapy, and our rate within Study 301 is consistent with this.

DR. MAKAROV: When you look at the Hopkins cohort -- I'm not so familiar with some of the others -- I think at 15 years, they have like 30 percent progression, pathologic end-stage progression, I think; definitely not 58 percent at 2 years.

DR. REWCASTLE: Again, what's easy to compare is the conversion rate.

DR. MAKAROV: So what do you think it would look like if you did it in the United States?

DR. REWCASTLE: Well, that's what we're going to find out. Dr. Coeytaux?

DR. COEYTAUX: Emmanuel Coeytaux. So I think this is exactly what we want to do with the Study 306 patient population diagnosed with highly sensitive biopsy technique, MRI-targeted biopsy. We expect the rate of progression is going to be much lower than in 301. We looked extensively for

what it would be and never found any good literature on that, so we've done an adaptive design in this study to accommodate actually for all that uncertainty. We think it will be lower, and we think that the difference with TOOKAD is still going to be there. The effect will be lower.

DR. MAKAROV: But 306 is an intermediate risk, not low risk, right? So it should in theory be higher, active surveillance and an intermediate risk cohort.

DR. COEYTAUX: It's higher risk diagnosed with a more sensitive biopsy technique. So we're going to remove some of the reclassification. And you're right, there is reclassification, so we show that we've effectively treated disease that was just not properly detected in the beginning, but that was the situation when we conducted the trial. I totally agree with that.

DR. MAKAROV: I definitely believe that focal therapy has a role in treatment of prostate cancer. I just worry about looking at a low-risk cohort and declaring victory so soon, you know?

DR. COEYTAUX: I think we agree with that, that's why we emphasize its lowest diagnosed with TRUS biopsy. We know the world is shifting to better diagnosis techniques, and that's what we tried to take into account in the indication we proposed. I think a lot of urologists would argue that it's the lowest from yesterday diagnosed with TRUS biopsy and all of the intermediate risk of today diagnosed with MRI-targeted biopsy, but that's a reach.

DR. HOFFMAN: Mr. Kungel?

MR. KUNGEL: Terry Kungel. The question is to Dr. Rewcastle, and it's a follow-up from Dr. Makarov.

If we look at 100 percent of the people that were on active surveillance that went to definitive treatment, can we say of that 100 percent what percent actually were progressing and what percent were not progressing, and making a decision probably rated on the basis of anxiety?

DR. REWCASTLE: Correct. If we can get those slides that we presented in the core that

shows the proportional rate of progressing?

So what we did, while this slide is coming up, is we looked at the proportion of those who had progression and subsequently underwent radical therapy. FDA's analysis said it was only half of those met, but that's if you stopped the analysis at 24 months. When we continued to follow, we captured some of those conversions which were occurring; because it takes a while, after a positive biopsy or progression, to then make a decision to be treated and for that treatment to happen.

We found 67 percent of those who progressed went on to radical therapy in both arms. So proportionately it was similar. We also looked at, for those who had radical therapy, what percent had actually progressed, and it's about 80 percent in both arms.

I'd like to show you quickly on --

MR. KUNGEL: So 20 percent made an anxiety-based decision, not a medical decision.

DR. REWCASTLE: Correct. And what I want to

show is DB-19, which is a study of 10,000 men who underwent prostatectomy, and I'll try to quickly explain.

This is the probability of being in a different situation. You have a progression in a treatment or you have a progression without a treatment, which is the purple.

If you look at the purple to the red, throughout the study, it's approximately 80 percent. That's the one we just talked about, which is those who have a treatment without a progression. Our study of 200 men is consistent with this study of 10,000 men, so we think we're very consistent with what we found here.

MR. KUNGEL: But when we were saying that TOOKAD beat AS in terms of moving to definitive treatment, some of that was a function of guys being anxious.

DR. REWCASTLE: Correct.

Dr. Scardino, could you talk about the decision process a bit of men? Because it's not always a definitive biopsy-based decision.

DR. SCARDINO: The decision to convert to radical therapy for a patient on active surveillance can be motivated by a variety of things, including a rising PSA level that today we know is not significant, an insignificant but a measurable change in tumor volume going from 3 to 4 cores.

In this study there was that 20 percent of patients who had some reason, and in addition to that, they just worried about it; and some family member or friend had surgery or radiation and was very happy, so they changed their mind. I think 20 percent of patients are going to decide when they're watching their cancer; they've decided they want to get treatment even though they may not have a very good, meaningful change, a meaningful change in the nature of their cancer.

MR. KUNGEL: One quick question, though, is 50 percent of the people that were known to progress chose to do nothing.

DR. SCARDINO: Yes. Well, these men were enrolled on a study where active surveillance was a

50/50 chance that they would get enrolled, so they were accepting of active surveillance. They'd been on it for a while. Now something changes that meets your objective criteria for progression, they feel perfectly fine, and they don't want to go through radical therapy.

DR. REWCASTLE: Correct. And just to clarify again, at 24 months, 50 percent of the men haven't taken action, but if you look farther out, 67 percent of those who do have progression do convert. That's just the cutoff of the follow-up.

DR. HOFFMAN: Dr. Walsh, do you have a follow-up?

DR. WALSH: Well, I wanted to follow up on what Dr. Makarov said because I was also struck by that progression rate. In the sponsor's presentation that they sent to us, on page 14 they say that in the PROMIS trial, on men who underwent MRI-targeted biopsy, 70 percent of the men who were grade group 1 were converted to grade group 2 or greater.

I think there's a real difference in the

European population and what you're going to find in the United States. I asked Dr. Epstein what our experience is in patients with very low-risk cancer who undergo radical prostatectomy. Only 15 percent have grade group 2 or greater, and in men with low risk, it's 30 percent.

So I think it's going to be an entirely different progression rate in the United States because the disease is different, and because there's so much screening, people are picked up so much earlier.

While I'm talking, I am a bit concerned about the definition that is used on targeted biopsy using the word "50 percent of cores positive." I couldn't find that that had ever been confirmed, and I think if one's going to use that as a criterion in 306, that you would want to have confirmation on what that actually told us. There is a recent article published in Urology looking at targeted biopsies, and it was length of core that predicted severity, not number of cores.

DR. REWCASTLE: Within Study 306, we've

actually built that in. We're using the millimeters of pattern 4 as inclusion as well as for the progression. We're trying to be contemporary as we go, and there's only so much you can do for that.

DR. WALSH: Well, I think you ought to do what Epstein did in 1993 in JAMA. He took patients who had undergone radical prostatectomies, and then looked at percent of cancer. They defined what would be insignificant cancer, and then made the criteria.

There are a number of patients now in the United States that have undergone targeted biopsies that had negative systematic biopsies, and it would be easy to collect; you don't have to wait for PSA failure. It's easy to collect the pathologic findings in those patients to see whether or not there is a criterion like he developed in 1993 that would be based upon actual data and not just speculation.

DR. REWCASTLE: Okay.

Dr. Scardino, can you speak to this?

DR. SCARDINO: I think that's a very reasonable suggestion. The better data we have, the more accurate we can do the biopsies. The better we can stage the patients, the more appropriately we can treat them. The greater than 50 percent positive biopsy came from NCCN guidelines. Although it's in the guidelines, it's not as convincing in the literature.

DR. HOFFMAN: Dr. Song?

DR. SONG: My question was previously addressed.

DR. HOFFMAN: Dr. Hinrichs?

DR. HINRICHS: I have two questions. The first relates to the toxicity. The applicant presented a slide titled, Most Assays were Transient and Resolved, and it really has just two data points. One is whether the toxicity occurred and the other is if it resolved at 24 months. Transient might mean different things to different people.

What was the duration of these toxicities that occurred?

DR. REWCASTLE: We presented the resolution at 24 months specifically because at that last assessment in the primary portion of the trial, there's a specific visit where every AE was reviewed and has it resolved or not.

Most of the adverse events that occurred with the trial were perioperative. Interestingly on SAEs, the most common one, which was 8 percent urinary retention, was actually an artifact of management.

In Europe, if you present urinary retention, you tend to have a catheter placed and you're admitted, whereas in the United States, you'd be put in outpatient treatment, so you wouldn't have that trigger for having a serious adverse event due to hospitalization.

DR. HINRICHS: So can you trust the data on the time to resolution of these events?

DR. REWCASTLE: For the urinary retention it was 10 percent -- sorry; 10 days was the median time to resolution.

DR. HINRICHS: One question is to

characterize the toxicity of the intervention. Just whether the events occurred and whether they were present at 24 months is very limited characterization. Do you have some data to characterize it further?

DR. REWCASTLE: We can look at which additional data we have and maybe get some additional resolution after the break. But I would like to say in Study 306, we've worked hard with the FDA to really capture a lot more in terms of not only the adverse events but also the PROs who are moving to the CTCAE PRO assessments, and we should have a better capture of these data.

DR. HINRICHS: I have one other question also.

DR. REWCASTLE: Sure.

DR. HINRICHS: The study was designed to compare active surveillance to a treatment, to an intervention, but it seems that active surveillance is a changing practice, and it's changed a lot since the study began, now MRI-targeted biopsies being an important part of that. How do we

interpret this data given that the active surveillance that was studied is not the active surveillance that's practiced now?

DR. REWCASTLE: I think a clinical perspective from Dr. Scardino or Gill would be good, hearing the differences in active surveillance now versus when the study was conducted, and if that impacts the interpretation.

DR. SCARDINO: Thank you very much. Peter Scardino. Well, active surveillance for low-risk cancers that were planned for the 301 study was essentially the standard of care. Although many patients were getting treated, it was becoming the standard of care, and it was advocated by academics and leaders in Europe, and it was the right thing to compare this kind of partial gland ablation to.

In the United States, active surveillance is a moving target. There are programs that have only focused on very low-risk cancer. Most programs focus on low risk. There are some that have included favorable intermediate risk and mixtures of all those. So there isn't a uniform agreement

about what is the ideal population for an active surveillance and what is the ideal workup, although we agree today, MR-guided biopsies supplementing systematic biopsies is certainly a minimum standard of care with a baseline MRI.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Thanks. Heidi Klepin, Wake Forest. I have a comment and two related questions. The comment is just reorienting us as we just did.

One of our key questions here that we're grappling with is whether or not the TOOKAD procedure has fewer adverse events than potentially a prostatectomy or radiation, as was suggested on slide 77 and discussed earlier; rather, in this low-risk population, many of whom are older who have some multiple chronic conditions, who have this guideline-based option of active surveillance, what is the trade off for them in taking on some earlier short-term risk and what's the benefit in that? Because the risk of active surveillance, we saw the data, and the risk is lower in the short

term.

So the questions around that, one relates to the idea that active surveillance might actually reduce the anxiety -- I mean, that the early treatment would reduce anxiety. This was brought up earlier. I don't see that we have any data in this study around anxiety specifically. Is that correct?

DR. REWCASTLE: That's correct.

DR. KLEPIN: Then related to that, there was a comment around anxiety in active surveillance associated with repeated biopsies, which makes sense. We see that with our patients. If this treatment were approved, would the recommendations following treatment with TOOKAD continue to require and recommend biopsies on a regular basis? Would patients be in a similar follow-up paradigm as far as repeated biopsies as they would be on active surveillance?

DR. REWCASTLE: When a man is diagnosed with prostate cancer, they basically are entering into a surveillance phase for the rest of their life.

Really, with active surveillance, the follow-up and the schedule of biopsies will be similar to what we'd be doing post-TOOKAD.

Dr. Coeytaux, do you have additional?

DR. COEYTAUX: One thing on the anxiety, we're going to actually measure anxiety in the confirmatory Study 306, so we'll have that data from that new study.

I think one point I wanted to clarify, we have to remember that active surveillance doesn't mean no treatment forever. We have 50 percent of these patients that do convert to radical therapy at some point. In our mind, the point is can we improve that? That's really what TOOKAD is aiming at, and can we reduce that risk of future conversion to radical therapy; not to say we want just to treat patients earlier.

DR. HOFFMAN: Dr. Sandler, did you have another question?

DR. SANDLER: I did. Thank you for letting me ask another question, and it's Howard Sandler.

I was just wondering if the sponsor could

discuss -- one of the components of the composite progression endpoint was a PSA greater than 10 on three separate occasions. I just think that that's a biased endpoint in a study where you're doing an ablative therapy because you allowed PSAs up to 10, so people could have a PSA of 9.9.

So it wouldn't be surprising that over two years, some people's, on active surveillance, PSA would go up over 10, whereas the ablative treatment should lower the PSA by a certain amount, and I didn't hear what that was. So you're going to have this difference in post-treatment, so to speak, PSAs that would lead to a bias against the active surveillance. I was wondering if you could comment on that.

Then second, related to that, I didn't see any data on medications that patients may have used. Were you capturing 5-alpha reductase use in these patients, and was there any difference in 5-alpha reductase use, which could affect PSA between the two arms of the study?

DR. REWCASTLE: Dr. Coeytaux?

DR. COEYTAUX: Your question on the PSA is a very good one. Actually, we went through exactly the same question during our EMA approval. Yes, PSA is entered [indiscernible] by the therapy. After the fact, we realized that this was probably not the most appropriate criterion. Nevertheless, we were very reassured there are very few, actually, patients that had a PSA progression.

We can maybe show the slide with the different criteria of disease progression that was shown in the core presentation. Most of these patients had a progression that was also due to other criteria. So although potentially biased, we were happy to see that it didn't impact the study results.

DR. SANDLER: And the 5-alpha reductase use?

DR. HOFFMAN: Dr. Siddiqui, did you have another question?

DR. COEYTAUX: So on the --

DR. HOFFMAN: Oh.

DR. COEYTAUX: -- alpha-reductase use, we captured, obviously, all medication used during the

study. I must admit that we've not conducted a specific analysis on the alpha reductase use, so I cannot answer directly your specific question here.

DR. SIDDIQUI: Thank you. I had two follow-up questions. These are specific slides actually. Slide 41, it demonstrates the in-field biopsy recurrence rate in TOOKAD versus active surveillance. Specifically, was there any further analysis done to understand why a quarter of TOOKAD patients had in-field biopsy recurrence?

Specifically, I'm particularly interested in understanding that with ablative therapies, there are a couple things that can happen. You can have a true failure of the ablation, where within the zone that was considered to be appropriately treated, the cancer somehow survived and grew back, as opposed to technical features, such as an incomplete ablation or learning curve within the institution. So one could imagine a learning curve improving over time, whereas a biological reason not improving. So that's my first question.

The second is going to be on slide 57 with

the patient-reported outcomes. We learned that -- one is just clarification. I know that for adverse events, we learned that 40 out of 64 active surveillance patients and 5 out of 12 TOOKAD patients who went on to definitive therapy had missing data on adverse events.

Was that a similar number for the patient-reported outcomes or was there no information on patient-reported outcomes for patients who underwent treatment? Because I think with such a disparity in the patients that are getting treatment and the fact that patient-reported outcomes are probably much worse in treatment patients rather than non-treatment patients, that could really shift the way that these curves look, making currently active surveillance look a lot better than it actually is in reality.

DR. REWCASTLE: Correct. Again, I'll answer the second question first because this slide is still up. The graphs we presented for IIEF as well as IPSS, we censored at the time of radical

therapy. Our goal here is to really clearly show the adverse event profile of active surveillance in TOOKAD side by side without the influence of the conversion of radical therapies. If we had kept those in, active surveillance looks worse because you have more patients converting over.

So we're kind of showing you -- or we're biasing -- we're keeping the pure results, where if you looked at more, it would be a different value; and that's because we don't have great follow-up after patients went to radical therapy, which was a shortcoming of this study. So these graphs, just to be clear, are censored at the time of radical therapy, so it's the pure view.

Dr. Coeytaux, you can speak to the other question, which is in regards to slide 41.

DR. COEYTAUX: On the failure rate of the TOOKAD therapy, when we have recurrence, what we've seen is mostly recurrence at the margin. Remember, this study was conducted in 47 centers. That's a lot of learning curves, so what we've seen is mostly learning the procedure and the ability to

treat up to the cap shown [indiscernible].

DR. HOFFMAN: Okay. Let's now take a 12-minute break. Panel members, please remember that there should be no discussion of the meeting topic during this break amongst yourselves or with any member of the audience, and we'll resume at 11 o'clock. Thank you.

(Whereupon, at 10:48 a.m., a recess was taken.)

Open Public Hearing

DR. HOFFMAN: Alright. Let's reconvene, please.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the

committee of any financial relationships that you may have with the sponsor, its product, and if known, it's 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 this meeting.

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

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions.

One of our goals today is for this open public hearing to be conducted in a fair and open

way, where every participant is listened to carefully and treated with dignity, courtesy, and respect. Therefore, please speak only when recognized by the chairperson. I thank you for your cooperation.

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

DR. GORIN: Good morning, and thank you to the FDA and the committee for the opportunity to speak at this morning's open hearing. My name is Michael Gorin, and I'm a urologist at Johns Hopkins University School of Medicine, where within the Department of Urology I direct the program in localized prostate cancer.

In this role, I oversee our department's active surveillance programs for men with low-risk prostate cancer. This program is among the largest and oldest in the world, having been started by my mentor and predecessor, Dr. Ballentine Carter, more than 25 years ago at Hopkins.

I do have a relationship with the sponsor in that I'm an investigator for the upcoming 306 trial. I come today, however, as an uncompensated independent expert wishing to express my views in favor of the approval of TOOKAD vascular-targeted, photodynamic therapy for the partial gland ablation of prostate cancer.

While there is little doubt that active surveillance is the preferred management strategy for men with low-grade prostate cancer, that is grade group 1 or Gleason 6 disease, considerable challenges have historically existed in correctly identifying men with true low-risk disease. This is evident by the fact that the risk of disease reclassification on surveillance has historically been in the range of 30 to 50 percent over as little as 5 years.

It is important to realize that the vast majority of patients on surveillance who are reclassified do not do so because of disease progression -- that is true biologic transition from grade 1 to grade 2 disease -- but rather do so

due to errors in sampling the gland with the use of transrectal ultrasound-guided biopsy. Thus, there has historically been the need for serial biopsies to correctly classify men.

These multiple biopsies place men at risk of complications, including sepsis, bleeding, and sexual dysfunction. Thankfully, in the last several years, there has been considerable progress in our ability to correctly classify men at the time of initial diagnosis with the adaptation of multiparametric MRI.

Evidence for this is evident from our institution, which was recently published, demonstrating a 75 percent reduction in disease reclassification at 24 months and a 50 percent reduction at 4 years among men with a negative MRI at the time of surveillance enrollment.

As the point has been made several times earlier today, a major consideration when evaluating data from the 301 study is the fact that the study cohort was defined with the use of ultrasound-only biopsies and not with the modern

tools of multiparametric MRI. Thus, to call men in this study low risk is not an accurate statement by current standards.

Indeed, the authors observed a 60 percent rate of disease reclassification, which has decreased considerably with the use of TOOKAD. In my view, this was achieved with little in the way of perioperative risks and an acceptable side effect profile in terms of urinary symptoms and erectile dysfunctions, especially when one considers the historical rate of these complications in large published series such as the ProtecT trial.

So in summary, my read of the available data is that the 301 study showed an excellent rate of in-field cancer control in a population highly enriched for intermediate risk disease, a group of patients in need of treatment. This was achieved with an acceptable risk profile and this treatment greatly reduced disease reclassification. In addition, it spared treated men the potential harms of serial biopsies had they remained on

surveillance.

Again, while use of this treatment is inappropriate for most men with true low-risk disease, it would be an error to call the study cohort a modern active surveillance population and to in turn deny men, who meet the inclusion criteria of this study, the potential benefits of this minimally invasive and low morbidity treatment. We must do better for our patients, and TOOKAD appears to be an excellent option for men with high-volume grade group 1 or grade group 2 disease. Thank you.

DR. HOFFMAN: 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.

MR. FORTIN: Good morning. I'm John Fortin, and I'm a patient who has had focal therapy for prostate cancer. I represent no organization, only patients. Only my travel expense, not time for this meeting, is being reimbursed by STEBA. Thank

you for allowing me to share my experience.

Please note that my treatment, while focal, is not the therapy you're evaluating today, and please do not interpret any comments by me as pro or con in regard to TOOKAD. By training, I'm a healthcare actuary, so I have an in-depth understanding of mortality and morbidity data.

I've evaluated, in depth, prostate cancer studies, oncologic, and functional outcomes. Now retired, I've been a fellow in the Society of Actuaries for 45 years. I attend numerous clinical conferences as a reporter for UroToday. Also, the AUA has asked me to fill a volunteer position, patient advocate liaison representing all urological patients in the United States.

I was diagnosed with prostate cancer in early 2014 with what NCCN now classifies as intermediate favorable disease. Numerous doctors all told me that I was not eligible for active surveillance and needed treatment. I studied level 1 evidence and concluded that definitive, quote/unquote, "whole-gland treatment" would have

little, if any, impact on my longevity; yet, urinary incontinence and other side effects are problematic and underreported due to multifactorial biases.

Informed patients worry about months, or years, of incontinence at work, while asleep, while laughing, playing golf, or during intercourse. For ED, when drugs don't work, syringes and implants are theoretically effective, but in practice, romance and QoL often deteriorate. As you know, whole-gland treatment risks include harm from anesthesia, hospital acquired infections, retention, penile shortening, Peyronie's disease, hernia, rectal damage, secondary cancers and retrograde ejaculations, and more.

Often patients are uninsured or underinsured. In Georgia and some other States, if you can't get back to work fast, you might be looking for a new job, so definitive treatment entails significant medical and financial toxicities. My strategy was to find a safe, precise focal approach that more than likely would

destroy MRI-visible lesions, minimize side effects, and preserve all future treatment options. I tried to find a good focal trial, but no luck. Fortunately, docs at two academic medical centers offered focal laser therapy, and after considerable study, it appeared to meet all of my criteria.

Yes, I am now 72. Six years later, I've no evidence of disease and no permanent side effects. Fast forward to today, I still take my PSA tests and things are still not proven, but my story is anecdotal and I'm not a typical patient. But let's try to take a broader look at patients.

Helping patients have become my calling and I've learned a lot. Each patient's different, but allow me to generalize. Docs' job, number one, is saving lives, and we're grateful. Patients want to balance length of life and quality of life, but they have zero objective, comparable oncologic and functional data by treatment; none.

So what is the big picture in the real world? My crystal ball's a little cloudy, but it appears to me, fairly soon, procedures that have no

specific label for focal are likely to be widely used for focal treatment. Patients will assume that these have been fully blessed by regulators. On the supply side, many leading clinicians are embracing focal and will be using many flavors of focal in their practice. I empathize with you as regulators. We're trying to wrap your heads around very complex issues as discussed today.

In closing, I hope and pray that, soon, regulators will have sufficient, while not perfect, evidence to endorse new and improved focal therapy that will reduce overtreatment. Thank you.

DR. HOFFMAN: Thank you.

Will speaker number 3 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. PREST: Hello. My name is Peter Prest. STEBA Biotech supported my travel to this meeting as I offered to share my experience; however, I am not compensated for my time

Today I'm here to tell my story of diagnosis

and treatment for my prostate cancer and why patients like me need options for their cancer treatment. After seeing increases in my PSA over several years during my routine annual physical, my primary care doctor suggested that I get a consult with a urologist at Northwestern Hospital in Chicago.

After additional blood work and an MRI, Dr. Kent Perry conducted a biopsy and informed me of my cancer diagnosis. He insisted a radical prostatectomy was the best option due to my age, overall health, and the availability of his schedule the following week.

I was concerned with Dr. Perry's insistence on a radical prostatectomy and about a complete recovery due to the side effects of such an invasive surgical procedure. Thus, my wife and I looked for other treatment options, including consideration of watchful waiting.

We have a young daughter, and I did not want to compromise my job security, my financial productivity, and lifestyle while she is growing

up. We found Dr. Coleman at Memorial Sloan Kettering through a search of prostate cancer treatment options; and after our consult with Dr. Coleman and several other physicians at Memorial Sloan Kettering, my wife and I decided that the TOOKAD treatment was the best option for me at this point in my life.

Other than the inconvenience of a dark-room requirement and a catheter overnight, there were not any significant side effects as a result of the procedure. The pain was minimal and did not require prescription analgesic. I realized the gold standard for my diagnosis is a radical prostatectomy, but not having to deal with a bag for 5 weeks and other common side effects of incontinence and impotence is a great relief to me. I was back on my feet following the TOOKAD procedure, doing what I needed to do.

So now I am cancer free, and I feel the same as I did before I had the initial diagnosis. I'm able to run, play golf, and enjoy my wife and daughter without any difficulties. I'm going to be

60 in 3 weeks and I have a 3-year-old daughter; and now I have the expectation of having a productive life for many years. While my wife and I do not plan to have more children, avoiding the radical prostatectomy gives me the opportunity to live a productive life with my family for many years.

This procedure is convenient for men that need to work, need to be productive with their life, and should be an available option to patients who want to live a life like I have today. Thank you for your time, and please let me know if you have any questions.

DR. HOFFMAN: Thank you.

Will speaker number 4 step up to the podium and introduce yourself? Please state your name and any organization you're representing for the record.

MR. MORSE: Thank you very much for allowing us the opportunity to speak today. My name is David Morse, and I have no financial relationship with TOOKAD. My whole presence here today came as a result of discussing the fact that it was an

occurrence. I gathered information through several peers that led me in this direction, and I said what a great opportunity to talk about something very near and dear to my heart.

As I said, my name is David Morse, and for the past 5 years I have run a support group at Sarasota Memorial Hospital in Sarasota, Florida. This support group is one of the very first support groups that was ever founded way back 25 or 30 years ago, and it has continued in existence to this day.

The result is that we've seen many, many hundreds of men each year because of the rotating nature of our presentations and the fact that we have new doctors, new oncologists, we have urologists come in and speak, and we have a pretty strong following at these meetings.

Men are very difficult to reach, as we all know, and one of the offshoots of this Men to Men program at Sarasota has been the formation of a nonprofit called the Sarasota Prostate Initiative, which we hope to use to expand the horizons of what

Men to Men has done over the years and try to increase the awareness of options for men in both treatment and diagnostic methods.

Again, I really appreciate the opportunity to speak with you. When I heard about TOOKAD, and it was only a few months ago, I immediately saw this as a real option for a vitally significant group of men who receive a cancer diagnosis and are afraid of the choices they're being given.

In the first place, they're afraid and fearful right from the start of being told they have cancer, and then when they hear about all the options that are out there, many of which provide less than adequate lifestyle consequences, they get even further afraid.

They're afraid on one side to watch and wait, which is very, very hard for men to make a decision about. Most men react, "Let's get this out right now," but watch and wait has proven to be a very, very vital treatment plan for people.

In my case, for example, I was diagnosed with a Gleason 6 score and 2 cores in 2011, and my

doctor urged removal. He was a urologist, and he urged that I remove this. He then allowed that maybe I should see a radiation oncologist, so he was willing to bend a little bit. But the final analysis I said, "No, absolutely not." I had done a considerable amount of research prior to this decision, and we ended up parting ways later on. It was a friendly departure, but nonetheless, I was determined that I would follow a course of active surveillance.

There were no other real options for me I didn't think. The radical prostatectomy and radiation of 38 days, or whatever, were not options I was looking forward to. Had TOOKAD been on the scene at that point, it might have made a significant difference for me. I don't know a lot about TOOKAD; I'm learning as I go. As I say, it was only 3 or 4 months ago that I heard about it, but when I did hear about it, I said, "Wow. This is something that can really affect a tremendous number of men."

My PSA has remained at zero since 2015, so I

feel great at this point. I guess I'm running out of time, but thank you so much for letting me present today. Thank you.

DR. HOFFMAN: Thank you.

Will speaker number 5 step up to the podium and introduce yourself? Please state your name and any organization you're representing.

DR. ZUCKERMAN: Sure. I'm Dr. Diana Zuckerman. I'm president of the National Center for Health Research. Our center does not accept money from pharmaceutical or device companies, so I have no conflicts of interest. Our center analyzes scientific and medical data to provide objective health information to patients, providers, and policy makers.

My own perspective is as a researcher previously at Harvard and Yale, and also, because we've done a lot of work with prostate cancer patients at our center, providing information and patient booklets for them, and that's vetted with experts from the National Cancer Institute.

The American Urological Association, as you

know, recommends active surveillance for most patients with low-risk prostate cancer, but you also know that some patients don't feel comfortable with active surveillance. Treatment can be a reasonable choice if there's clear evidence that the benefits outweigh the risks, but that's not true with the data that we've heard today. I think the FDA has done an excellent job of expressing their concerns, and I just want to briefly go over the five main issues.

Number 1, there was only one clinical trial, and given that there are other effective treatments, we think that one flawed clinical trial is not sufficient since replication is the key to scientific evidence.

Number 2, there were only 5 nonwhite patients; 5, not 5 percent, 5, and that's just not acceptable. You already know that prostate cancer is a more serious issue for African American men, and they should have been included in this study. It's not sufficient to promise to try to do better in postmarket studies. They should be done in

premarket studies.

Number 3, the accuracy of the biopsies, you've already heard about that.

Number 4, too much missing data, you've heard about that. You can't draw conclusions about evidence when you have so much missing data.

Number 5, the trial was open label, and that introduces a lot of bias, as you know, and that should not have been done. This is the kind of procedure that could have had a blinded trial, but it didn't.

The FDA held a workshop in September of 2018 to discuss issues related to clinical trials on prostate cancer, localized prostate cancer, and they concluded that novel treatments could be good if the new therapy was less likely to result in subsequent treatment such as surgery; if there was an overall reduction in adverse events; and if there was no reduction in long-term cancer control. But, unfortunately, those criteria weren't met here in this trial, and the 95 percent with adverse events I think speaks for itself. We're also very

concerned with the long-term complications of the treatment, and how that might be affected by subsequent treatment is unknown.

In summary, I would say that it's really important that these kinds of issues be resolved in premarket studies. It isn't sufficient to wait for postmarket studies. You've heard today how people get very excited about a new treatment that seems less invasive and how that can be very misleading.

In this case, we don't have the data to really support saying that this is a product that's ready to be approved by the FDA and how important it is to have more than one trial really well-designed without the missing data; and just to say that the company was told by FDA what they wanted and what kind of research they thought was needed, and the company did not comply. There's no reason to think they're going to comply in postmarket study if they didn't do it in the premarket study. Thank you.

DR. HOFFMAN: Thank you.

Will speaker number 6 step up to the podium

and introduce yourself? Please state your name and any organization you're representing for the record.

DR. LEPOR: My name is Herbert Lepor. I have no relevant financial disclosures and have supported my own travel to be here today. I have served as the Martin Spatz chair of urology at NYU School of Medicine for the past 26 years.

In 1981, my mentor, Dr. Walsh, hypothesized that men were rendered impotent following radical prostatectomy due to iatrogenic injury to the neural innervation of the penis. My work showed that the nerves mediated the erections course immediately adjacent to the prostate, thereby validating the anatomic splint principles, leading to the anatomic nerve-sparing RP.

I was privileged to be a co-author on the first paper describing the nerve-sparing RP. Since 1986, I performed approximately 5,000 of these procedures and published hundreds of original manuscripts focusing on improving surgical outcomes. While we have come a long way from the

time virtually all men were rendered impotent following radical prostatectomy, thanks to Dr. Walsh, the impact of the surgical procedure on sexual function, even in the hands of experienced surgeons, remains problematic due to penile shortening, penile curvature, and urinary incontinence with orgasm.

Since urology residency and training at Hopkins in the early 1980s, I've been actively engaged in scholarly clinical activities, advancing the screening, detection, and treatment of prostate cancer. Together with our innovative faculty at NYU, we have led the way in developing detection pathways that reliably identifies the location of clinically significant cancers within the prostate, which really opened the door to focal ablation of prostate cancer.

We have investigated at our institution HIFU, cryo, photodynamic therapy, laser, and radio frequency as energy sources to ablate prostate cancer. We routinely perform focal therapy as an outpatient procedure, technical complications are

rare, and men are back to work with unrestricted activities in a few days.

In almost a thousand cases at our institution, less than 1 percent of our patients have experienced incontinence and rectal function was preserved in over 90 percent. In the short term, our biopsy results, which we just submitted for publication, to the targeted area have confirmed complete ablation of cancer in over 90 percent of patients. The immediate and long-term oncologic outcomes are under active investigation.

Since the life expectancy and treatment priorities of men with prostate cancer are highly variable, it's not surprising that the AUA guidelines recommend active surveillance, radical prostatectomy, and radiation therapy as options for low intermediate risk disease. If the guideline-approved spectrum of management strategies for these patients range from no treatment to radical prostatectomy, then it stands to reason that a treatment aimed at destroying the

index lesion followed by active surveillance of the untreated gland should also be an option for low intermediate risk disease.

Unfortunately, there are no randomized studies investigating the risks and benefits of focal therapy for intermediate risk prostate cancer. I believe this is the sweet spot for focal therapy. Ablating the index lesion would provide significant clinical benefit by reducing progression to cancer, thereby reducing the need for radical therapy.

Today I offer men with intermediate risk prostate cancer active surveillance, focal ablation, radical prostatectomy, and radiation therapy. In the absence of level 1 evidence, men make visceral and not evidence-based decisions. Approving the clinical pathway for TOOKAD will enable men to make more informed treatment decisions.

Why did I take time from my clinical and academic responsibilities to attend this ODAC meeting? I wanted members of the panel to hear the

perspectives of a long-standing and continued advocate of the nerve-sparing radical prostatectomy, who firmly believes focal therapy/ablative therapy should be a treatment option for selected men with prostate cancer. I therefore enthusiastically recommend that the FDA embrace the clinical pathway for TOOKAD. Thank you.

DR. HOFFMAN: 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 turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comments. Panel members should not state what their vote will be, but a discussion of the topic can now occur before we break for the vote.

DR. REWCASTLE: [Inaudible - off mic] -- for question to give after the break, just an additional resolution on adverse event resolution.

DR. HOFFMAN: Okay.

DR. REWCASTLE: Okay. I'll do it quickly because I know we are limited on time.

First off, with the discussion of the subjects who had a radical prostatectomy, we did discuss this with Dr. Scardino. The impression is that the difficulty is similar to the treatment of a treatment-naive prostate.

Within the study, different criteria were explored for potential increase in difficulties such as unilateral versus bilateral VTP and also which side a positive margin was on afterwards, and there was no apparent increase in difficulty. Continence and erectile dysfunction were determined to be similar to the literature. It wasn't a randomized comparison, but there was no red flags that this was a hugely morbid procedure.

In terms of adverse event resolution, I can provide a little more information. Any infections, including UTI, median duration to 21 days. Incontinence for those whom had incontinence, 72 percent of those with incontinence resolved within 63 days median. Perineal pain was reported in 23

subjects. It was only grade 3 in one subject at 35 weeks post-procedure. It manifested, and then 35 weeks subsequent it resolved. Prostatitis, which was 3.7 percent of the patients, one grade 3 occurred 4 days after VTP and resolved within 31 days. Thank you.

Questions to the Committee and Discussion

DR. HOFFMAN: Thank you.

We'll now proceed with the questions to the committee and panel discussions. I'd like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel. The question to the committee is, do the results of PCM301 represent a favorable benefit-risk profile for TOOKAD in patients with low-risk, early-stage prostate cancer?

Are there any comments or issues about the wording of the question itself? Yes?

DR. MAKAROV: I do have a question about the scope of what we're looking at. Is that fair to address now?

DR. HOFFMAN: Yes. The FDA -- yes.

DR. MAKAROV: My issue is with this low-risk cohort, which is actually somewhat a heterogeneous cohort, and it's a different cohort than what we've got now. If one believed that there is a utility for this treatment for some patients within this cohort but not for all patients in this cohort, would one be in favor or opposed to the question?

DR. WEINSTOCK: First of all, thank you for your question and for clarifying the intent of our voting question. We're asking about all the patients who were included on PCM301 to evaluate the included patient population as a whole. So whether there were patients who may now be considered to have favorable intermediate risk disease or whether there were very low-risk patients, we're looking at the cohort of patients enrolled as defined by PCM301. I hope that clarifies.

DR. HOFFMAN: Dr. Sandler?

DR. SANDLER: Just a clarifying question. This question, FDA is asking, I think, the panel's

opinion to this question, but the sponsor is asking for an indication for use that includes grade group 2 patients. Should we be considering grade group 2 patients as we're addressing question 1 or should we not be including grade group 2 when we're talking about question 1?

DR. WEINSTOCK: So again, we're looking for you to vote on the patients who are included in PCM301, and those are low-risk patients. Gleason grade group 2 at diagnosis would not have been included in this patient population.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Randy Hawkins. Does FDA have a protocol -- say the vote is yes and this product is approved, is there an established protocol? Does FDA have a protocol for use?

DR. WEINSTOCK: We would have a label that would describe the trial conduct, and the appropriate use would be based on what was done on the trial and based on proper conduct. There would be training involved, and the applicant can expand on that in any center that would be opening this

because, obviously, there's a learning curve involved.

DR. HAWKINS: Would it include the same timing, biopsies, follow-up, et cetera, exactly as this study was? That's what I'm asking.

DR. WEINSTOCK: We would probably describe the way the trial was conducted, and that would be the -- I mean, labeling is an ongoing issue, but we generally describe the way the trial was conducted and we give the indication statement.

DR. HOFFMAN: Okay. Do you have a question about the question? Okay.

MR. KUNGEL: Sorry. Not to harp on this too much, but just to really clarify, because it's very important to me, too; in the FDA slides, on slide 2, the proposed indication lists both grade group 1 and grade group 2, but then all the data and what you said is more focused on trial 301. So we're really just mainly talking actually about the patients who fit the inclusion criteria of trial 301 in reality.

DR. WEINSTOCK: That's correct.

MR. KUNGEL: Thank you.

DR. HOFFMAN: Okay. If there are no further comments about the wording of the question, we'll open the question to discussion among the panel.

DR. HOTAKI: This is your thoughts on the question in general and not giving your vote yet, but just bouncing ideas off each other and generating a robust discussion around the question.

DR. HOFFMAN: Dr. Hawkins?

DR. HAWKINS: Thank you. Randy Hawkins. The question for the applicant, really, is availability and training. Is this essentially going to be something available at tertiary centers because of the devices that are required and equipment that's required? That's a legitimate question.

DR. HOFFMAN: I think we've concluded the questions to the sponsor. I mean, it's a reasonable question. I suspect that if this is approved -- actually, I think they did comment that they were planning to conduct training at the various institutions where this would be available.

DR. BEAVER: Hi. Julia Beaver. If you think it would be helpful to hear briefly about the plans the applicant has, I think that that would be okay.

DR. HOFFMAN: Can we have a comment about that?

DR. REWCASTLE: Certainly. We're going to put into place a robust training program that really mirrors what we did in Europe, and we know that it works because we had good consistent results. That training program is going to be a phase 1, classroom, didactic video, et cetera training. We've got a slide on this, and hopefully that comes up.

You'll learn who are the right patients. It will be a hundred percent consistent with the labeling that we do with FDA to make sure that people aren't straying, to the best of our abilities. To graduate to the second phase, you have to pass a knowledge test. Phase 2 is proctored cases, so at your institution, if you're the new physician, you'd have a proctor come and

help you over your shoulder, and you do a minimum of 5 cases and you get a certification. Once that proctor is satisfied that you've demonstrated the skill to do this, it is not a difficult procedure for urologists because, as Dr. Gill mentioned, the skill set is really in the wheelhouse of a lot of procedures.

Just an additional comment on here is, in terms of risk mitigation, we're not going to be sending or delivering any drug to a center that cannot provide a training number of a physician who's been trained and gone through the program. Hope that helps.

DR. HOFFMAN: Other comments among the committee? Yes?

DR. MAKAROV: I don't know how my fellow committee members feel about it, but I'm really struggling with this decision for a number of reasons. I do think that the trial, with due respect to the sponsor, was not very well designed and executed, and I do have concern about this product hitting the market and then every very

low-risk prostate cancer patient who really should be on active surveillance receiving this therapy.

Because it is easy to do and it is relatively well tolerated, I'm also thinking that among that very low-risk cohort, which is more favorable today than it was there, even within today's low-risk cohort, going through a process of shared decision making and everything, there are patients in whom treatment would be appropriate.

Dr. Gill had a slide listing what the potential indications for this might be, and I think that this product could have a lot of utility in that group. Unfortunately, the trial was not designed around that group and doesn't quite answer that question, so I don't quite know what to do with my vote. And I would love to hear other people's opinions of my thinking, shoot it down, or whatever.

DR. HOFFMAN: Dr. Garcia?

DR. GARCIA: I just had a comment. I think for most patients -- not being a patient myself, it's hard to discuss that, but I think cancer is

cancer, regardless of the risk that one may have. When you look at the data, if you look at actually what PCM306 intends to do with regard to long-term follow-up data, I think in many ways I would have loved to see that data play out in 301.

Also, I think it's nihilistic to believe that the prespecified criteria for definitive therapy in 306 is going to be less subjective when we know in the United States some people will undergo RP and some people will have radiation therapy, so I'm not sure how -- even in 306, you will not be able to demand what would be your local definitive therapy.

Also, if you look at active surveillance and you look at target therapy, it appears to me that the intensity, the frequency of intervention, and the follow-up doesn't appear to be any different than those patients undergoing active surveillance.

Dr. Klepin mentioned early on we are paying attention to lower tract urinary symptoms, PROs related to sexuality, and incontinence, but when you're living with cancer and not knowing if target

actually was able to address your disease, or not locally, those PROs were not captured in this 301 trial. I think fundamentally that part of quality of life may be as relevant and important as lower tract urinary symptoms.

DR. HOFFMAN: Dr. Siddiqui?

DR. SIDDIQUI: I want to feed off actually what Dr. Makarov was just saying. There are a couple of thoughts that I've been trying to just wrap my head around as we've been going through this morning.

One is, I am really, as a urologist, happy to see this expansion of focus from the FDA on outcomes to examine when we're looking at localized prostate cancer, because I couldn't agree more that in this population, the traditional metrics of cancer-specific mortality and whatnot are prohibitive for any kind of realistic progress and may not be applicable as the metric of interest to this patient population, given such high survival rates almost regardless of what you do. So a transition of focus to a more morbidity-centric

approach and to early proxies of possible mortality benefit I think are very beneficial here.

From that perspective, although I am generally opposed to the thought of treating Gleason grade group 1 prostate cancer, I know just from my own real-world practice, being a staunch advocate of active surveillance, that it's hard to convince many patients to go down that route. Most patients will, but there is a good proportion of people who will not.

So there's that, and then there are just lots of things that come along that take people off active surveillance such that even with someone who is being very proactive as a practitioner to keep someone on active surveillance, a 20 to 30 percent rate of treatment at 5 years out is probably a good number; and I'm not sure in the community, with people who are not prostate cancer specialists, if that number is not much higher. It probably is. So something like a 50 percent fall off from active surveillance in the real world is probably real, I would venture to say.

I personally thought that the data on adverse events related to the domains of erectile dysfunction were interesting in that they reflect the fact that active surveillance itself is not completely without its morbidity and that these patients also over time have decreased rectal function. That's not even taking into account that 20 percent, or 19 percent I guess, of that population had much worse outcomes because they underwent treatment.

So I think that, unfortunately, the patient-reported outcomes and the adverse events after treatment were not collected, and that's such a big lost opportunity because I think it would have given a lot more insight into the comparison of a person on active surveillance versus a person who gets this treatment and then does a modified version of active surveillance, an augmented version, whatever you want to call it, would encounter.

Those are the main things I wanted to share in terms of what's influencing my decision here.

DR. HOFFMAN: Dr. Klepin?

DR. KLEPIN: Thanks. Heidi Klepin, Wake Forest. I also wanted to reflect on the discussion, particularly the idea of having an informed discussion, patient and provider, around the risks and benefits and what your trade-offs are in the short term. I'm thinking again about a patient who's considering active surveillance versus this therapy in particular. We know from the trial that there's a potential short-term trade-off that's a negative, so some increased risk of side effect in the short term.

We don't really know fully what the long-term trade-offs might be. We think that there's benefit, potentially, although the primary outcome -- or it's not a primary outcome, but the outcome of moving on to definitive therapy is subjective and has some limitations to it, and biased in this particular study.

We don't have information that's, I think, robust at all around the consequences of having this procedure and how does that complicate a

future therapy, which is something that a patient would want to know, and the longer term side effects is certainly something a patient would want to know in that conversation.

Then the other piece that we've talked about a little bit is the lack of knowing who really would benefit from this. I think there's been discussion around not everybody. We seem to be talking about the fact that a lot of people included probably aren't the right patients for this procedure, yet who is? So we don't know, really, from the standpoint of biomarkers and biology from this trial, nor do we know from the standpoint of their patient characteristics.

A patient with some multimorbidity maybe isn't going to benefit. We have none of those data. Then we don't have data that tells us that the quality of life was better in any way, which is partly I think due to a lack of collecting some of those data later on and not collecting some of the data that we talked about earlier that we'd like. So we are missing, I think, big pieces of having

that informed discussion, which is a challenge.

DR. HOFFMAN: Dr. Walsh?

DR. WALSH: I see a lot of patients for second opinions, and I'm very confident low-risk disease was offering active surveillance because of the data we have at Hopkins. For over 18 years and 1800 patients in men with low-risk disease, 0.6 percent developed metastasis and 0.1 percent died. Contrary to that, many patients come to me frightened to death by their doctor who tells them that they have cancer and they need to be treated.

I think if we, on less than good evidence, approve this, this is something that could cause more harm than good. They will be told -- and I thought the presentations by the sponsor today were spot-on an excellent. I thought the analysis by the FDA was excellent, but what is statistically significant? Like Gertrude Stein, "for a difference to be a difference, it must make a difference."

I think that most of these patients won't be told that at 2 years, half of the men will still

have cancer, and in 28 percent it will be progressing. So if I said to a patient right now, "We don't have to do anything right now; this is fine; right now we don't think you have a cancer that needs to be treated and we're going to follow you," or "We're going to give you some treatment, and in 2 years there's 50 percent chance you're still going to have cancer and 28 percent it's going to be progressing," they might say, "Maybe we should keep an eye on it."

But I don't think that that's what they will hear. I think there were many doctors out there who are in business, and this will be an opportunity that will be misused. I think that the thing we can't do is speed up the time clock today. We have 2-year data, and I don't think the 2-year data are enough to permit so many patients out there who do not need treatment to have a treatment that we don't know whether or not it's working well.

DR. HOFFMAN: Dr. Hussain?

DR. HUSSAIN: Thank you. Hussain,

Northwestern. I want to share the comments, and I think I'm almost echoing Dr. Walsh's comments. I'm a medical oncologist. I sit on the other side of the aisle, and I tend to be a tie-breaker sometimes when patients are seeking local therapy versus active surveillance and they seek a medical oncologist. I've also seen the other side of the aisle situations where a patient is on active surveillance and, one way or another, 2 years later, they pop up with pelvic lymph nodes.

So there are a lot of problems, clearly, and there's no question that there's going to be a population that this therapy may be appropriate.

With all due respect to the sponsor, I have a problem with the way this study was designed and how it was conducted and lots of limitations. I, in fact, identified 9 different points there. That to me makes it problematic at this moment.

Consequently, I fully share the sentiment that putting this on the market will lead to wide utilization and perhaps inappropriate use of this for the right population. A 2-year follow-up is

incredibly short. It's just not enough, and not having proper control arms is a problem. So, again, there are multiple issues there.

DR. HOFFMAN: Alright. Dr. Halabi?

DR. HALABI: Susan Halabi, Duke University. I also wanted to share my thoughts with the committee because I'm mostly struggling to interpret this endpoint. While this endpoint was clearly defined and specified in advance, my concern is this endpoint is not capable of being ascertained as completely as possible as we can, as we did see from the data in all patients, and it's definitely not capable of unbiased estimates.

My concern here is we may be giving an impression that this endpoint does reflect tangible clinical effect to the patient and give them this security when, in fact, it may not. Now, it may translate to clinical benefit to the patient, but I think I agree with the sentiment here that two years of follow-up is not sufficient. Thank you.

DR. HOFFMAN: Okay. I think we should proceed with the voting process. We're going to 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 have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we'll go around the room and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did if you wish to. So please proceed with the vote on your microphone that's flashing.

(Voting.)

DR. HOTAKI: The vote for the record is 2 yes; 13 no; and zero abstentions.

DR. HOFFMAN: Okay. Could we go around the room and indicate how you voted, please, and if you

wish to make any comments. We'll start with Dr. Walsh, right?

DR. HOTAKI: Dr. Cheng, if he wants to comment at all.

DR. HOFFMAN: Oh, okay.

DR. WALSH: I voted no.

DR. HOFFMAN: I'm sorry. State your name.

DR. WALSH: Patrick Walsh. I voted no.

DR. HOFFMAN: I think we probably heard why --

(Laughter.)

DR. HOFFMAN: -- during your comments.

DR. SANDLER: Howard Sandler. I voted no as well. I think for true low-risk patients who are eligible for the 301 study, I strongly prefer active surveillance as their treatment. For patients who, for whatever reason, don't want to do active surveillance, I think they should have proven anticancer therapy with surgery or radiation.

I'm not sure that a treatment that has some risk of morbidity is an ideal option for someone

with a cancer that doesn't need any treatment. Like some of the others, I'm wrestling with this a little bit as well because I think there's something, I believe, that's real and effective going on. But I think for true low-risk patients, as the question was framed by FDA, I'm comfortable with my no vote.

DR. HOFFMAN: Dr. Makarov?

DR. MAKAROV: Dan Makarov, NYU. I voted no. I was highly, highly ambivalent and on the fence until the last few minutes. For me, I think this is a reasonably good technology, and it would be great to offer this to patients, but not the patients in this group.

I think that the study sponsors, the way that the trial was designed and executed, it doesn't demonstrate the -- I don't think it demonstrates a favorable risk in this population, and I know that for sure, as Dr. Walsh was commenting, when you let the genie out of the bottle, this is going to be definitely misused.

I think before we do that, I think we need

just stronger data, but I'm really on the fence because I could see how this would be beneficial to some patients but not the ones in this study as was demonstrated here.

DR. HUSSAIN: Maha Hussain, and I voted no, and I articulated some of my concerns. The part that I struggled with is how do you justify saying to a patient, "By the way, I don't think you really need a treatment, and we really should watch you but, by the way, I'm going to give you a sprinkle of a treatment"? That to me is one big area in terms of the struggle there.

I also think that the data, because of the problem in the study design and conduct, it's subject to flaws and interpretation. I think some proper, stronger, very well-controlled trial is going to be necessary.

DR. SIDDIQUI: Minhaj Siddiqui, and I voted no. As I mentioned, I'm actually very encouraged by the direction things are going. I really think that there is an important space here that will benefit patients greatly. I just felt that with

this particular indication, knowing what the focal therapy community in general is talking about when we're debating the topic of who should get focal therapy, or at least subtotal gland therapy, it's never really unilateral Gleason 6 prostate cancer that's low volume, and that's, I think, not the right direction to take things.

So I'm encouraged by the future plans for trials to do Gleason grade group 2 patients, and it would be wonderful to see data longer than 2 years with complete data collection in the future to hopefully see how that turns out.

MR. KUNGEL: Terry Kungel. I voted no. But let me start by saying that one of the things that I think this panel was addressing was when we were all talking in 2018 about trying to develop new endpoints, that's something that is critically important to the patient community because overall survival and progression-free can take so long that we won't be able to really get effective information as soon as we need it.

So I think trying to approach this from the

standpoint of different new endpoints, terrific. I don't think we actually delivered on an effective way to define those endpoints. I think there are great issues about whether, as described and defined, they're actually useful. I think in terms of the final vote, we've got too many adverse events that were not reported.

I would make the argument that for 306, we absolutely, positively need to move to MRI. The standard TRUS biopsies are producing too many false reports. We need to get 306 using MRI and MRI only.

I would like for 306 to look at measuring depression and anxiety because that's a big piece of what prostate cancer patients are going through. And if we don't know what's going on with the patients in that regard, I don't know that we can properly interpret the data.

The other thing I was going to say, we had essentially 350 men in 47 different sites. I've got a question about how you ever manage consistency and the quality of that data, so that

was the decision to give a no.

DR. HAWKINS: Randy Hawkins. I voted no; concerns about the duration of the study, a short duration. I really wanted to see more objective quality-of-life information. I had real concerns about unknown complications of salvage and just the population limitations.

DR. GARCIA: Jorge Garcia. I voted no, similar comments as the group before; specifically the study design and conduct; the lack of long-term follow-up; and the lack of understanding and whether or not it's worth it for you to embark on potential side effects when at the end of the day, you can still achieve cure by undergoing a late radical prostatectomy or radiation therapy.

DR. CRISTOFANILLI: Massimo Cristofanilli. I voted no. There are a number of reasons. There were some articulated already. First of all, the clinical trial, we were trying to interpret the primary endpoints that were clearly explained and there were some issues with that, the methods, the biopsy, and the safety, the long-term safety.

Also, I think what was important, especially from the expert, was this low-risk group that was not clearly defined, and it's changing every day. The surveillance in this group seems to suggest that, obviously, there is much less risk with what has been studied in the European patients, so I think it would not apply. Besides, the population who are going to be using this with African Americans is not represented.

DR. HOFFMAN: Philip Hoffman, University of Chicago. I voted yes. I was very much torn and on the fence, as well, as I think a number of my colleagues here, but I eventually came down on the positive.

Despite the flaws that had been very well articulated in the analysis, the endpoints, and so on, I noted that I thought there was more positive than negative in the sense that the study did meet its endpoints. I think that the focal therapy does represent potentially an important option for many men with prostate cancer.

So despite the flaws and the expectation

that the next study should address many of those flaws, I thought, on balance, it could still be available for patients as an option.

DR. KLEPIN: Heidi Klepin. I voted no for all the reasons that were articulated. I do think this is a promising therapy, but I don't think the data that was presented in this study clearly showed a clinically meaningful benefit that outweighed the risks for all the limitations that were already mentioned.

I do have concern, as was articulated, that because of the nature of how this could be applied if it were approved, the use would be much more, in some ways, indiscriminant from the standpoint of affecting patients, where we would see a significantly worse adverse event profile in patients who otherwise would have done very well with active surveillance alone.

DR. HINRICHS: Christian Hinrichs. I voted no. It's hard for a study to recover from problematic endpoints. I think that this study began with that, and it didn't recover. It's

deeply flawed for a number of reasons that were articulated by other members of the committee. The real-word implications for this were well articulated by Dr. Walsh. I think that what he said is true and very troubling, and that's why I voted no,

DR. HALABI: Susan Halabi. I voted also no. I think it's often more challenging to determine what's clinically significant. The question that I struggled most with is whether we have sufficient data to approve this drug based on one trial when the scientific and the regulatory community do not have experience with that.

On the other hand, I think we all recognize that there is a clear need to identify acceptable endpoints, and this is something that it's good that the FDA is pushing in the right direction.

The other reasons why I also voted no and other contributing factors were limitations in the design and conduct and the representation of the patients on the trial because I'm not sure that the results would be applicable to the U.S. patients.

DR. RINI: Brian Rini from Vanderbilt. I voted yes. I agree with everyone in terms of the uncertainties and limitations of the trial. I think a lot of this and the reason we're probably here today is that this area is fraught with uncertainty, and it's been a moving target over a decade in terms of how do we biopsy, how do we ascertain, how do we treat these people, and what's the protocol for active surveillance?

So I'd actually like to give the company credit for doing a randomized trial in this setting when, to my knowledge, none of the other focal therapies, which are uncommon, have done. I feel like they're being penalized a little bit for doing the trial in an era when a lot of this wasn't decided, and TRUS was the standard of care and active surveillance was done a certain way, et cetera, et cetera.

Again, I think it was a reasonable effort. Despite those uncertainties, I understand the limitations of the endpoints, which is, again, I think just the limitation of the field. But to me,

the magnitude of benefit, even despite those limitations, was compelling.

To me it really comes down to what we do in medical practice every day, where we're trading off exposing a higher number of patients to a set of risks and hoping to avoid a higher set of risks for a subset of patients, and that's just what shared decision making is about. So that's why I came down on the side of yes.

I would just say I agree with everyone that long-term follow-up data in the 306 study plan hopefully will solve some of these issues, but my guess is we could be sitting here in 3 to 5 years discussing that study and how the field has moved on from that study. So some of this is just limitations of this area that I don't think are going to go away.

DR. SONG: Daniel Song. I voted no. I share the concerns that have been well expressed by other members of the committee. In particular, what Dr. Siddiqui pointed out was the high biopsy positivity rate in the treated areas. It's not

like the treatment is even completely effective, and how does that affect patient's perceptions in follow-up? Some of the patients didn't come for their follow-up biopsies. One can imagine that perhaps maybe they had their 3- or 6-month PSAs and saw maybe it wasn't going up.

So it was not a blinded trial and unfortunately you can't control for that. I do share the enthusiasm for focal therapy. I think it's going to find a place in the treatment of prostate cancer in the future, but I don't think with 2-year data that we have in this study, that we are ready to approve it for general use.

I really look forward to the results of the 306 study. I sympathize with the public comments that it would be great to offer focal therapy as sort of a niche between active surveillance and treatment, but there are other focal therapies which are currently being practiced.

Now, those were approved, I believe, under a 510(k) mechanism, yet this would not be the only player in the focal therapy arena. I believe focal

therapy in general should remain investigational.

Adjournment

DR. HOFFMAN: Okay. Well, I thank everyone for their comments. I think, obviously, the vote is negative, but I have the sense that we've all somewhat shared the fence sitting about some of the positives, potential positives, of focal therapy for a disease that prior to recently hasn't had much focal therapy; but recognize that the limitations of this study, some of the not uncertainties but variability of the biopsy reports or surprising results of some of the biopsies, despite the therapy and so on, I think led the majority of people to vote no.

I think that it may well be that in the coming years as more data accumulates, including potentially on the plan study 306, that the vote may completely turn around as there is more clear data about this.

I thank everyone for their thoughtful comments and anxiety over this. We'll now adjourn the morning session and break for lunch. We'll

reconvene in this room in an hour, at 1:15, at which time we'll begin the afternoon session. For those of you who are only here for the morning session, I thank you for your participation.

(Whereupon, at 12:11 p.m., the morning session was adjourned.)